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This article describes activities of the Food and Drug Administration's Anesthetic and Analgesic Drug Products Advisory Committee since 2017. Six new drug applications are highlighted to demonstrate how the national opioid crisis impacts analgesic approvals.

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**ON THE COVER:** Body habitus, pneumoperitoneum, and Trendelenburg positioning may each independently impair lung mechanics during robotic laparoscopic surgery. In this issue of ANESTHESIOLOGY, *Tharp et al.* examined the effects of increasing body mass index, pneumoperitoneum, and Trendelenburg positioning on atelectasis, driving pressures, and lung elastance. In an accompanying Editorial, *Bao and Vidal Melo* provide perspective on how the new study results can be used to provide protective mechanical ventilation in obese patients undergoing robotic assisted laparoscopic surgery. Cover Illustration: A. Johnson, Vivo Visuals.

- *Tharp et al.*: Body Habitus and Dynamic Surgical Conditions Independently Impair Pulmonary Mechanics during Robotic-assisted Laparoscopic Surgery: A Cross-sectional Study, p. 750
- *Bao and Vidal Melo*: Lung Mechanics of the Obese Undergoing Robotic Surgery and the Pursuit of Protective Ventilation, p. 695

## Perioperative Medicine

### CLINICAL SCIENCE

-   **Body Habitus and Dynamic Surgical Conditions Independently Impair Pulmonary Mechanics during Robotic-assisted Laparoscopic Surgery:**

 **A Cross-sectional Study**

*W. G. Tharp, S. Murphy, M. W. Breidenstein, C. Love, A. Booms, M. N. Rafferty, A. F. Friend, S. Perrapato, T. P. Ahern, A. E. Dixon, J. H. T. Bates, S. P. Bender* .....750

Obese patients demonstrated increased driving pressures and decreased mean end-expiratory transpulmonary pressures. Pneumoperitoneum and Trendelenburg position further accentuated these differences. The optimal positive end-expiratory pressure was greater than set positive end-expiratory pressure in most subjects at all stages, ranging from 0 to 36.6 cm H<sub>2</sub>O. Intraoperative positive end-expiratory pressure settings should account for dynamic changes in transpulmonary driving and end-expiratory pressures related to these factors. How best to accomplish this clinically remains uncertain. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-   **Volatile versus Total Intravenous Anesthesia for Cancer Prognosis in Patients Having Digestive Cancer Surgery: A Nationwide**

 **Retrospective Cohort Study**

*K. Makito, H. Matsui, K. Fushimi, H. Yasunaga* .....764



Among more than 190,000 patients who had cancer surgery, overall and recurrence-free survival were comparable in patients who had propofol-based total intravenous and volatile anesthesia. Selection of anesthetic approach should be based on factors other than putative effects on cancer recurrence. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-   **Granger Causality of the Electroencephalogram Reveals Abrupt Global Loss of Cortical Information Flow during Propofol-induced**

 **Loss of Responsiveness**

*R. M. Pullon, L. Yan, J. W. Sleight, C. E. Warnaby* .....774

In healthy adult volunteers, propofol anesthesia-induced loss of consciousness was associated with an abrupt, substantial, and global decrease in connectivity. These changes are comparably reversed at regain of consciousness. These observations suggest that information flow is an important indicator of wakefulness. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-   **Cost-effectiveness Analysis of Preoperative Screening Strategies for Obstructive Sleep Apnea among Patients Undergoing Elective Inpatient Surgery**

*A. Sankar, P. R. Dixon, L. Sivanathan, S. G. Memtsoudis, J. R. de Almeida, M. Singh* .....787

In a Canadian single healthcare payer model, the cost-effectiveness of preoperative obstructive sleep apnea screening differs depending on time horizon. Preoperative screening with STOP-Bang followed by immediate confirmatory testing with polysomnography is cost-effective on the lifetime horizon but not the perioperative horizon.

-   **Mepivacaine versus Bupivacaine Spinal Anesthesia for Early Postoperative Ambulation: A Randomized Controlled Trial**

*E. S. Schwenk, V. P. Kasper, J. D. Smoker, A. M. Mendelson, M. S. Austin, S. A. Brown, W. J. Hozack, A. J. Cohen, J. J. Li, C. S. Wahal, J. L. Baratta, M. C. Torjman, A. C. Nemeth, E. E. Czerwinski* .....801


In this randomized, three-arm study involving 154 patients, more individuals in the mepivacaine spinal group ambulated 3 to 3.5 h after injection than did individuals in either the isobaric or hyperbaric bupivacaine group. Likewise, more patients in the mepivacaine group achieved same-day discharge than patients in the other experimental groups.

### BASIC SCIENCE


**Neonatal Isoflurane Anesthesia or Disruption of Postsynaptic Density-95 Protein Interactions Change Dendritic Spine Densities and Cognitive Function in Juvenile Mice**

*M. L. Schaefer, P. J. Perez, M. Wang, C. Gray, C. Krall, X. Sun, E. Hunter, J. Skinner, R. A. Johns* .....812


Disruption of PDZ2 domain-mediated protein-protein interactions or a 4-h-long isoflurane anesthesia in 7-day-old mice induced comparable lasting deficits in synaptogenesis and cognitive function, and these effects were prevented by administration of the nitric oxide donor molsidomine. These experimental observations suggest the involvement of a pathway involving the NMDA receptor, postsynaptic density protein-95, and nitric oxide signaling in isoflurane exposure-induced cognitive impairment in mice.

-  **Volatile Anesthetics Activate a Leak Sodium Conductance in Retrotrapezoid Nucleus Neurons to Maintain Breathing during Anesthesia in Mice**  
*Y. Yang, M. Ou, J. Liu, W. Zhao, L. Zhuoma, Y. Liang, T. Zhu, D. K. Mulkey, C. Zhou* .....824

Isoflurane increased neuronal activity of chemosensitive retrotrapezoid nucleus neurons in brain slices of neonatal mice. Genetic ablation of the voltage-independent sodium leak channel from retrotrapezoid nucleus neurons decreased respiratory rate and ventilatory response to carbon dioxide upon isoflurane and sevoflurane but not after propofol exposure. These observations suggest that the voltage-independent sodium leak channel in retrotrapezoid nucleus neurons of the medulla is a target of volatile anesthetics to activate respiratory activity. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-  **Mitochondrial Complex I Mutations Predispose *Drosophila* to Isoflurane Neurotoxicity**  
*Z. P. G. Olufs, B. Ganetzky, D. A. Wassarman, M. Perouansky* .....839



Isoflurane but not sevoflurane exposure increased mortality in *Drosophila* carrying homozygous mutations in mitochondrial complex I, and hyperoxia increased mortality associated with isoflurane administration. In heterozygous flies, carrying mutations in mitochondrial complex I, age, and hyperoxia rendered flies susceptible to mortality after exposure to isoflurane. These observations raise the possibility that heterozygous carriers of mitochondrial mutations may be more susceptible to perioperative complications after isoflurane exposure. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

-  **Androgenic Modulation of the Chloride Transporter NKCC1 Contributes to Age-dependent Isoflurane Neurotoxicity in Male Rats**  
*G. A. Chinn, J. M. Sasaki Russell, N. A. Yabut, D. Maharjan, J. W. Sall* .....852

Blockade of androgen receptors in 7-day-old male rats protects against isoflurane anesthesia-induced behavioral deficits. Androgen receptor blockade results in a premature transition in the developmental expression profiles of chloride transporters NKCC1 and KCC2. These observations suggest that regulation of specific chloride transporters, determining functional modalities of  $\gamma$ -aminobutyric acid-mediated neurotransmission, by androgens is a critical component for developmental anesthetic neurotoxicity. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*


## Critical Care Medicine

### CLINICAL SCIENCE

-   **Prevalence of Complete Airway Closure According to Body Mass Index in Acute Respiratory Distress Syndrome: Pooled Cohort Analysis**  
*R. Coudroy, D. Vimperc, N. Aissaoui, R. Younan, C. Bailleul, A. Couteau-Chardon, A. Lancelot, E. Guerot, L. Chen, L. Brochard, J.-L. Diehl* .....867


In a *post hoc* analysis of two cohort studies of respiratory mechanics in adult respiratory distress syndrome, the authors compared the prevalence of complete airway closure stratified by body mass index and its effects on respiratory mechanics. Complete airway closure was present in 41% of patients, increasing with body mass index tercile (65% in the highest). Driving pressure and respiratory system elastances (lung, chest wall) were higher when complete airway closure was not adjusted for. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

### BASIC SCIENCE

-    **Assessment of Right Heart Function during Extracorporeal Therapy by Modified Thermodilution in a Porcine Model**  
 *K. F. Bachmann, L. Zwicker, K. Nettelbeck, D. Casoni, P. P. Heinisch, H. Jenni, M. Haenggi, D. Berger* .....879


In 16 healthy pigs that received veno-arterial extracorporeal membrane oxygenation support *via* central cannulation, a novel adaptation of thermodilution cardiac output assessment provided reliable estimation of right ventricular cardiac output and right ventricular function. Future studies appear warranted to determine whether this method of modified thermodilution can be used to accurately assess right ventricular output and function during veno-arterial extracorporeal membrane oxygenation support. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

### CLINICAL SCIENCE

-  **Differential Ventilation Using Flow Control Valves as a Potential Bridge to Full Ventilatory Support during the COVID-19 Crisis: From Bench to Bedside**  
*M. A. Levin, A. Shah, R. Shah, E. Kane, G. Zhou, J. B. Eisenkraft, M. D. Chen, for the Mount Sinai HELPS Innovate Group* .....892

Custom three-dimensional printed inspiratory flow control valves designed to allow individualized setting of tidal volume and airway pressure were evaluated using high-fidelity simulator mannequins with similar or different lung compliance and were found to perform as expected with stable tidal volumes delivered to each mannequin. The system demonstrated stable performance when tested for 1 h in two pairs of volunteer COVID-19 patients with acute respiratory failure. Continuous assessment of tidal volume and peak airway pressure in each patient during the study allowed for dynamic alteration of tidal volume in response to respiratory acidosis. This study suggests that custom-designed flow control valves may facilitate the use of split ventilation techniques in a surge setting. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

## BASIC SCIENCE

-  **Death-associated Protein Kinase 1 Mediates Ventilator-induced Lung Injury in Mice by Promoting Alveolar Epithelial Cell Apoptosis**  
*Y. Wang, Y. Yang, L. Chen, W. Xiong, L. Song, B. Li, T. Zhou, L. Pei, S. Yuan, S. Yao, Y. Shang*.....905

In mice, high tidal volumes increased cyclic stretch, DAPK1 expression, and epithelial cell apoptosis. Inhibition of DAPK1 appeared to be protective against lung injury, reducing lung injury, inflammation, and apoptosis. DAPK1 triggers alveolar epithelial cell apoptosis and mediates ventilator-induced lung injury in mice. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

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