

2009 in Review

Advancing Medicine in Anesthesiology

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WELCOME to another year in review, highlighting articles that the Editorial Board believed exemplified the mission of ANESTHESIOLOGY, "to advance the science and practice of perioperative, critical care, and pain medicine through the promotion of seminal discovery." This year we chose 12 articles with an equal distribution in the three current sections of original investigations: Perioperative Medicine, Critical Care Medicine, and Pain Medicine. In most cases, these 12 articles have already been highlighted through editorials, cover art, press releases, or placement on the home page of the Journal's Web site. We hope that a brief synopsis at the end of each year is useful for you, either to remind you of important work published this year or to encourage you to look at them for the first time.

Bateman BT, Schumacher C, Wang S, Shaefi S, Berman MF: Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: Incidence, risk factors, and outcomes. ANESTHESIOLOGY 2009; 110:231-8

This study analyzed the Nationwide Inpatient Sample database and estimated that acute ischemic stroke occurs in 0.7, 0.6, and 0.2% in patients undergoing hemicolectomy, lobectomy/segmental lung resection, and total hip replacement, respectively, with increasing risk

with advanced age after each of these procedures (fig. 1). This study is important and interesting in many respects. First, it draws attention to a severe complication responsible for premature death, handicap, and loss of autonomy in elderly patients. Moreover, the incidence of acute ischemic stroke reported here is greater than that usually perceived by the anesthesiology community caring for these patients. Second, it emphasizes the need for us to extend our vision beyond the operating room, a topic of an editorial series in 2009. Third, this study exemplified the use of a very large administrative database to address patient safety issues in real-world conditions. Last, we are caring for more and more elderly people, and the 0.2% incidence of acute ischemic stroke during total hip replacement in this study emphasizes the frailty of these aged patients, although age is clearly not the only important variable.

Waisel DB, Lamiani G, Sandrock NJ, Pascucci R, Truog RD, Meyer EC: Anesthesiology trainees face ethical, practical, and relational challenges in obtaining informed consent. ANESTHESIOLOGY 2009; 110: 480-6

As anesthesiologists, we interact with patients and their families for a brief but intense period of time, needing to rapidly and effectively communicate much information to each other and to understand each others' needs and limitations. This article describes an educational program for anesthesiology trainees and uses narrative research methods to identify key challenges they face in the informed consent portion of this intense interaction. The results are, on the surface, not surprising to trainees or their teachers: mistrust, misunderstanding, information overload, and conflicts between patient and family wishes and medical judgment. The authors were struck with the amount of angst reported by these trainees but reflected that each of us has experienced and continues to experience such ethical, practical, and relational challenges in our practice. High-fidelity simulation may help us to respond quicker and better to rapidly changing problems in the operating room or to facilitate our learning of procedures. This article suggests that we have important educational opportunities to improve the communication between patients and trainees as they evolve into mature physicians.

Alkire MT, Asher CD, Franciscus AM, Hahn EL: Thalamic microinfusion of antibody to a voltage-

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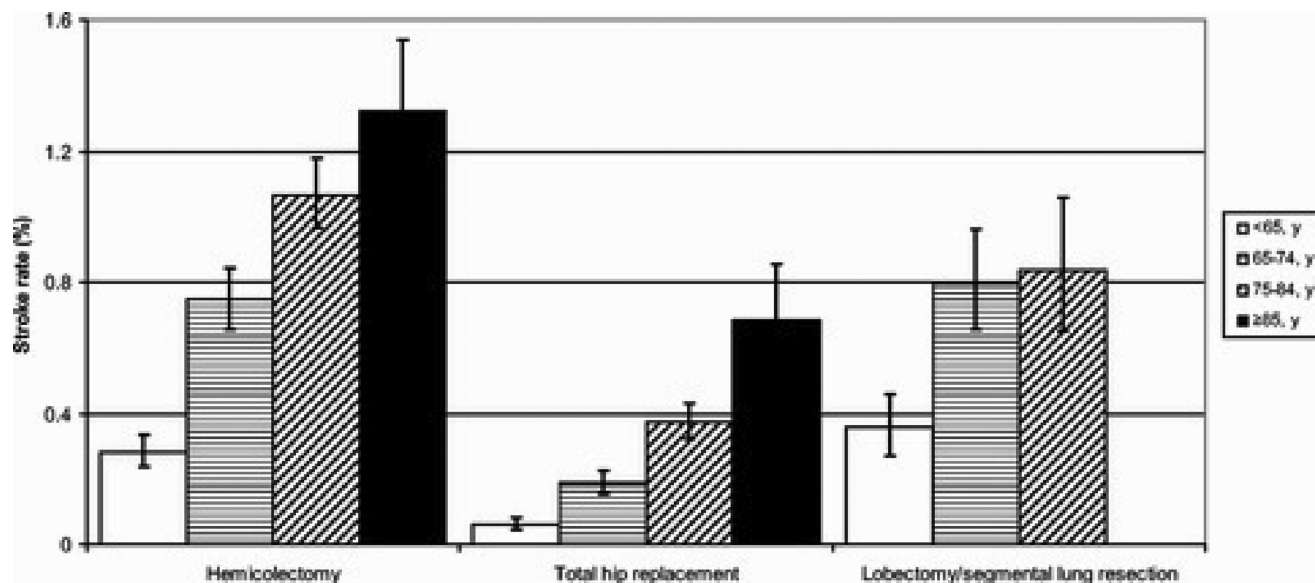


Fig. 1. The rate of perioperative acute ischemic stroke by surgery and patient age group. The rate of perioperative acute ischemic stroke is shown with 95% confidence intervals for each patient group. Figures for the 85 yr-old and older age group cannot be shown for the lobectomy/segmental resection group as it contains less than 10 patients, in accordance with the rules governing the use of the Nationwide Inpatient Sample dataset. Reprinted with permission from Bateman BT, *et al.* ANESTHESIOLOGY 2009; 110:231–8.

gated potassium channel restores consciousness during anesthesia. ANESTHESIOLOGY 2009; 110:766–73

Our understanding of neurologic mechanisms involved in anesthetic-induced unconsciousness has made substantial progress over the past years, with recent evidence suggesting a primary cortical site for anesthesia. The thalamus represents the primary relay station for ascending sensory information and descending motor output from the brain, and these authors previously showed that cholinergic stimulation just to the central medial nucleus of the thalamus reversed sevoflurane-induced loss of righting reflex in both receptor- and site-specific manners. They concluded that thalamic acetylcholine receptors regulate the “on switch” controlling arousal, and that anesthetics, by blocking this switch, cause unconsciousness.

In this study, Alkire *et al.* present additional evidence that thalamic structures are involved in producing anesthesia. Because nicotine is also known to block a variety of potassium channels, Alkire *et al.* hypothesized that anesthetic-induced unconsciousness might be related to a block of a subset of potassium channels (Kv1.2 channels) in the central medial thalamus. Rats were exposed to either desflurane or sevoflurane, and a Kv1.2 antibody was administered to the central medial thalamus *via* a microinfusion through an indwelling cannula. No effect was seen in 30% of animals, partial arousal was seen in 13.4%, and full return to consciousness was seen in 16.5%. This study shows that when the potassium channel antibody was infused very close to the medial thalamic nucleus, it induced a transient level of consciousness with restored mobility during desflurane or sevoflurane anesthesia (fig. 2). The arousal response was

seen in 75% of animals when the needle tip was located within the central medial thalamus. These findings support the view that this subcortical area is an important relay station for regulation of anesthetic-induced unconsciousness and/or arousal phenomena, and that voltage-gated potassium channels are involved in mediating effects of volatile anesthetics producing unconsciousness *in vivo*. The results of this exciting investigation can be taken as one step further in the search for structures and

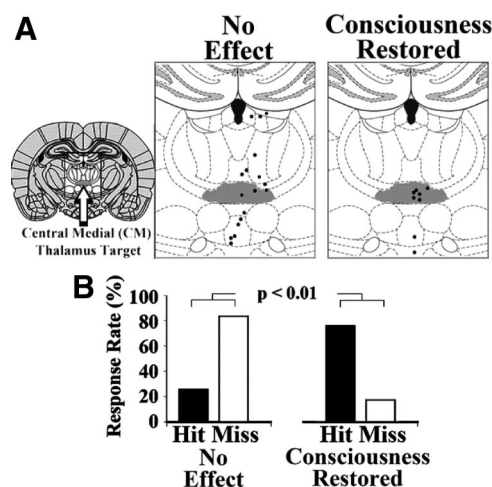


Fig. 2. The return to consciousness effect found with antibody infusion during desflurane anesthesia is site-specific. (A) The central medial thalamus target is shown on rat atlas figure (arrowed), located to the left. Expanded insets show infusion sites (black dots) for the infusions that had no-effect versus those that restored consciousness. (B) The return to consciousness response is significantly associated with infusions that hit the central medial thalamus (gray highlighted area in, A) versus those that missed. Reprinted with permission from Alkire MT *et al.* ANESTHESIOLOGY 2009; 110:766–75.

mechanisms controlling anesthesia and may be used as a background for further work to identify primary targets for anesthetic-induced unconsciousness.

Nouette-Gaulain K, Dadure C, Morau D, Pertuiset C, Galbes O, Hayot M, Mercier J, Sztark F, Rossignol R, Capdevila X: Age-dependent bupivacaine-induced muscle toxicity during continuous regional analgesia in rat. ANESTHESIOLOGY 2009; 111:1120–7

The growing popularity for the application of regional anesthesia has led to a wider use of continuous infusion of local anesthetics through perineural catheters to improve postoperative pain management. Initially these techniques were applied specifically to adults, then to children, and more recently to newborns. Complications associated with the application of local anesthetics, including myotoxicity, have been observed in adults. However, whether the severity and the long-term consequence of this toxicity are, as compared with adults, similar, less, or worse in very young children is unknown. This question has been investigated by Nouette-Gaulain *et al.* A group of young (3-week-old) and adult (12-week-old) rats were randomly assigned to receive seven injections of either 0.25% bupivacaine or isotonic saline during an 8-h period. The authors found that bupivacaine caused both a decrease in mitochondrial adenosine triphosphate synthesis rate and ultrastructural damage in rat muscles. This is *per se* not new, but the finding that young rats showed an age-dependent impairment of mitochondrial bioenergetics and a significant increase in myofibrillar disruption and z-line streaming is new and worrisome. Although local anesthetic myotoxicity does not seem to be clinically relevant in adults outside of ophthalmology, this study raises concern regarding the application of these techniques in very young children. It is hoped that this study will prompt clinical investigation to determine whether continuous application of local anesthetics is safe in our very young patients.

Thiele RH, Pouratian N, Zuo Z, Scalzo DC, Dobbs HA, Dumont AS, Kassell NF, Nemergut EC: Strict glucose control does not affect mortality after aneurysmal subarachnoid hemorrhage. ANESTHESIOLOGY 2009; 110:603–10; and Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G: Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. ANESTHESIOLOGY 2009; 110:611–9

In the early 1980s, reports emerged from laboratories that acute central nervous system injury is dramatically augmented by hyperglycemia. This is true in numerous species. The anesthesiology community rapidly assimilated this knowledge by eliminating dextrose from routine intraoperative intravenous solutions. Subsequently, many human studies were performed looking for an association between hyperglycemia and outcome from stroke, cardiac arrest, and traumatic brain injury. Almost

Table 1. Results of Multivariate Analysis on the Risk of Hypoglycemia Developing

	Odds Ratio (95% Confidence Interval)	P Value
Therapy: intensive vs. conventional insulin therapy	8.941 (4.947–16.157)	< 0.0001
Sex: female vs. male	0.866 (0.536–1.400)	0.5579
Age (as a continuous variable)	1.014 (0.995–1.033)	0.1482
SAPS II (as a continuous variable)	1.000 (0.987–1.013)	0.9782
Diabetes: yes vs. no	0.547 (0.229–1.308)	0.1752
Hypertension: yes vs. no	1.034 (0.456–2.341)	0.9369
Coronary artery disease: yes vs. no	1.851 (0.733–4.673)	0.1923
Overweight/obesity (body mass index >25): yes vs. no	2.790 (0.676–11.516)	0.1560
Blood glucose values at the time of enrolment (as a continuous variable)	0.996 (0.988–1.004)	0.3609

SAPS II = simplified acute physiology score II.

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all studies found a strong correlation between hyperglycemia and worsened outcome. To date, however, the precise mechanism to explain this has been elusive, although the preponderance of data points to enhanced intracellular acidosis secondary to anaerobic glucose metabolism in the absence of oxygen. Later work in rats showed that controlling glucose with insulin could abate the adverse effects of hyperglycemia. Independent from concerns related to central nervous system injury, it has been reported that strict glucose control provides better outcome in a general intensive care unit (ICU) patient population. Although these results have been difficult to replicate, it seems logical to extend rigid glucose control to neurosurgical and neurocritical care patients who would seem at high risk for exacerbation of central nervous system injury.

The articles by Theile *et al.* and Bilotta *et al.* provide important lessons regarding glucose management in neurocritical care patients. Theile *et al.* examined medical records collected between 1995 and 2007 from 834 patients with aneurysmal subarachnoid hemorrhage. Beginning in 2002, strict blood glucose control was practiced from admission to discharge, with the goal being maintenance in a range of 90–120 mg/dl. Outcomes were compared between patients treated before glucose control *versus* those treated after glucose control had been instituted. Glucose control was effective in decreasing the incidence of hyperglycemia. However, there was no effect on hospital mortality. This was, at least in part, attributed to an increased incidence of hypoglycemia in the glucose control group (table 1). Hypoglycemia events were associated with greater chance of death.

Bilotta *et al.* performed a prospective randomized analysis of strict glucose control (79–110 mg/dl) *versus* conven-

tional care in 483 patients during their ICU stay after brain surgery. The incidence of substantive hypoglycemia episodes was nearly tripled in the strict control group. Glucose control decreased ICU duration of stay and the incidence of infections, but there was no effect on 6-month Glasgow Outcome Scale scores or mortality. Each study has limitations, but cumulatively, these two studies make a major advance in our appreciation of the role of glucose management in neurocritical care patients. Although both studies found that strict glucose control protocols decreased average glucose concentrations, the magnitude of reduction was modest. At the same time, hypoglycemia was more frequent, and this plausibly stressed the injured brain. We now know that a systematic intervention designed to strictly control blood glucose during ICU stays can present hazard that may outweigh benefit. This should be considered when treating these patients. A different result may be found if the target range is allowed to be higher. In most laboratory studies, the threshold for hyperglycemia-augmented ischemic/traumatic brain injury seems to be approximately 180 mg/dl.

Santoni BG, Hindman BJ, Puttlitz CM, Weeks JB, Johnson N, Maktabi MA, Todd MM: Manual in-line stabilization increases pressures applied by the laryngoscope blade during direct laryngoscopy and orotracheal intubation. ANESTHESIOLOGY 2009; 110:24–31

Application of manual in-line stabilization (MILS) is recommended to minimize pathologic cervical spine injury during direct laryngoscopy or other intubation procedures in patients with known or suspected cervical spine instability. However, MILS also worsens the laryngeal view and prolongs time required for tracheal intubation, potentially resulting in hypoxemia during the intubation procedure. There has therefore been a recent reconsideration of the clinical practice of MILS. This research group previously reported significant subluxation at the site of unstable cervical spine during direct laryngoscopy with MILS in the cadaveric injury model. Santoni *et al.* extended their previous work and added new convincing evidence suggesting disadvantages of MILS application during direct laryngoscopy. Using a sophisticated new technology for measuring distribution of laryngoscopic forces along the laryngeal blade, they clearly demonstrated that direct laryngoscopy with MILS doubled the forces compared with that without MILS, and degradation of glottic visualization and intubation failure occurred despite the increased laryngoscopic forces. The authors concluded that secondary increase of laryngeal forces with MILS application in the presence of cervical instability and impaired glottic visualization has the potential to increase pathologic craniocervical motion. The work from this team and others questions the benefit of MILS during direct laryngoscopy.

Payen J-F, Bosson J-L, Chanques G, Mantz J, Labarère J: Pain assessment is associated with de-

creased mechanical ventilation in the intensive care unit: A *post hoc* analysis of the DOLOREA study. ANESTHESIOLOGY 2009; 111:1308–16

This study, in the current issue, is a *post hoc* analysis of a large database obtained in 44 French ICUs, which includes 1,381 mechanically ventilated patients. The authors show that patients assessed for pain on day 2 were more likely to receive sedation level assessment, nonopioid drugs, and dedicated analgesia during painful procedures and to receive fewer hypnotics. Moreover, patients with pain assessment had a shorter duration of mechanical ventilation (8 *vs.* 11 days; $P < 0.01$). Using a propensity score adjustment, these patients were weaned from the ventilator and discharged from the ICU earlier than those without pain assessment. This study is observational and thus causality cannot be definitely demonstrated and the interaction between analgesia and sedation is complex. However, this study should be considered as a cornerstone study on pain and its consequences in the ICU for the following reasons. First, this research concerns our three main domains of interest: anesthesia, critical care, and pain. Second, few studies addressed pain control in the ICU, and fewer implicated pain assessment as a factor in the outcome of critically ill patients. Third, there is an increasing interest in pain, comfort, and behavior of critically ill patients because they impact long-term outcome. This study illuminates the methodologic difficulties associated with this new research topic. It is remarkable that only 42% of critically ill patients were assessed for pain on day 2 in the DOLOREA study. What about your ICU?

van Dorp ELA, Kest B, Kowalczyk WJ, Morariu AM, Waxman AR, Arout CA, Dahan A, Sarton EY: Morphine-6 β -glucuronide rapidly increases pain sensitivity independently of opioid receptor activity in mice and humans. ANESTHESIOLOGY 2009; 110:1356–63

Although morphine is the benchmark analgesic drug, use of this drug causes adverse effects. Some of these adverse effects include respiratory depression, nausea, analgesic tolerance, physical dependence, psychological dependence, and hyperalgesia. Most of these beneficial and adverse effects have been attributed to the parent drug, morphine, but it is well-known that morphine metabolites such as morphine-6-glucuronide and morphine-3-glucuronide are biologically active in patients.

Recently, the morphine metabolite morphine-6 β -glucuronide has been shown not only to have analgesic properties but also to increase pain sensitivity. In this study, van Dorp *et al.* completed a translational study using mice and human subjects. The investigators and tested the effect of morphine-6-glucuronide for its analgesic and antianalgesic properties. Administration of morphine-6-glucuronide produced analgesia in normal mice but produced hyperalgesia in opioid receptor

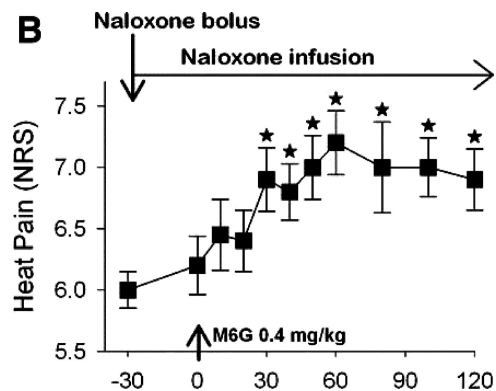


Fig. 3. Influence of 0.4 mg/kg morphine-6 β -glucuronide (M6G) on experimental heat pain responses in human volunteers during background exposure to naloxone. During a naloxone background infusion, M6G causes an immediate and persistent hyperalgesic response. Naloxone was given as an intravenous bolus of 0.043 mg/kg (down arrow), 30 min before M6G injection (up arrow), followed by a continuous infusion of 0.043 mg/kg per hour. Values are mean \pm SEM; symbols indicate different groups of 10 subjects. Significant main effects: M6G-naloxone, $P < 0.001$. *Post hoc* comparisons: * $P < 0.05$ versus $t = 0$. NRS = numerical rating pain scale. Reprinted with permission from van Dorp ELA, *et al.* *ANESTHESIOLOGY* 2009; 110:1356–63.

knockout mice. Hyperalgesia was also produced when receptor antagonists blocked opioid receptors.

In humans, administration of morphine-6-glucuronide increased pain sensitivity even after opioid receptors were blocked (fig. 3). Because morphine-6-glucuronide can accumulate with prolonged administration of morphine or in patients with renal disease, these effects of morphine-6-glucuronide may contribute to the drug's adverse effects. Therefore, the metabolite morphine-6-glucuronide may not only contribute to analgesia but also may counteract the analgesia by producing hyperalgesia independent of opioid receptors.

Cohen SP, Bogduk N, Dragovich A, Buckenmaier CC, Griffith S, Kurihara C, Raymond J, Richter PJ, Williams N, Yaksh TL: Randomized, double-blind, placebo-controlled, dose-response, and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. *ANESTHESIOLOGY* 2009; 110:1116–26

Anesthesiologists are frequently asked to provide pain relief for patients with radiculopathy caused by herniated intervertebral disk. Epidural steroid injections have been used to provide short-term pain relief for sciatica for many years. Recent scientific work indicates that tumor necrosis factor produced by herniated disk material may contribute significantly to radicular pain and sciatica caused by herniated intervertebral disks.

Drugs interfering with tumor necrosis factor have been developed to treat a variety of inflammatory disease states, such as rheumatoid arthritis and psoriasis. Cohen *et al.* proposed that epidural administration of drugs that interfere with tumor necrosis factor may be useful for the treatment of radiculopathy and sciatica caused by herniated intervertebral disks and thus may be an alter-

native to epidural steroid injections. They undertook a safety study to determine whether etanercept, an antitumor necrosis factor agent, caused neurotoxicity. Epidural administration in beagle dogs did not produce any clinical signs of neurotoxicity. Histopathologic examination also revealed no evidence of neurotoxicity caused by epidural etanercept administration.

For safety evaluation in humans, epidural etanercept injections were performed in patients with radiculopathy. This portion of the study revealed no toxicity based on clinical assessment and imaging. This study indicates that clinical trials of epidural administration of etanercept should be undertaken for evaluation of efficacy in the treatment of radiculopathy caused by herniated intervertebral disks.

Binshtok AM, Gerner P, Oh SB, Puopolo M, Suzuki S, Roberson DP, Herbert T, Wang C-F, Kim D, Chung G, Mitani AA, Wang GK, Bean BP, Woolf CJ: Coapplication of lidocaine and the permanently charged sodium channel blocker QX-314 produces a long-lasting nociceptive blockade in rodents. *ANESTHESIOLOGY* 2009; 111:127–37; and Ries CR, Pillai R, Chung CCW, Wang JTC, MacLeod BA, Schwarz SK: QX-314 produces long-lasting local anesthesia modulated by transient receptor potential vanilloid receptors in mice. *ANESTHESIOLOGY* 2009; 111:122–6

Remarkable progress continues to be made in developing long-acting and selective blockade nerve block building on recent advances in the neuropharmacology of nociception. This marks the third consecutive year for the appearance in this review of an article examining the utility of impermeant Na⁺ channel blockers to inhibit nociceptors by entering through capsaicin-activated transient receptor potential vanilloid 1 (TRPV1) channels. This year, two publications allay concerns of possible neurotoxicity and pain due to capsaicin by showing that the impermeant local anesthetic QX-314 (*N*-ethyl-lidocaine) can produce analgesia in the absence of capsaicin. Binshtok *et al.* extend their findings by showing that capsaicin is not necessary to facilitate QX-314 action if coapplied with lidocaine, which can also activate TRPV1 channels. Indeed, perineural injection of the combination of lidocaine and QX-314 prolonged the selective nociceptive block relative to lidocaine alone, an effect that was attenuated, but not eliminated, in TRPV1 knockout mice. Ries *et al.* showed long-acting sensory blockade by high concentrations of QX-314 alone. Even in the absence of capsaicin or another exogenous TRPV1 activator, QX-314 was effective. This was due in part to endogenous activation of TRPV1 channels as the nerve blocking effect was reduced by the TRPV1 antagonist capsaizepine (and potentiated by capsaicin), but evidence is also presented to suggest that TRPV1 is not the only mechanism for QX-314 entry. Together these studies move us a step closer toward long-lasting, nociception-selective regional anesthesia.