Jean Mantz, M.D., Ph.D., Editor

Perioperative Medicine

Mechanisms of disease: Purinergic signaling during inflammation. N Engl J Med 2013 [Epub ahead of print]

In this review article from the *New England Journal of Medicine*, Dr. Eltzschig from the Department of Anesthesiology at the University of Colorado—together with Drs. Sitkovsky and Robson from Harvard Medical School—discuss the therapeutic functions of purinergic signaling during inflammatory diseases. Research over the past decade has implicated purinergic signaling, particularly in the form of adenosine triphosphate and adenosine signaling, as an important regulatory mechanism in a wide range of diseases and biologic functions. There are many instances in which signaling events through adenosine P1 *versus* adenosine triphosphate receptors of the P2 type have opposing effects in biological systems, and shifting the balance between purinergic signaling seems to be an important therapeutic concept in dampening inflammation and promoting healing. Studies in models of acute lung injury, or ischemia and reperfusion implicate therapies that terminate adenosine triphosphate signaling and enhance adenosine receptor activation in a regulated manner. Several drugs that alter purinergic signaling, such as adenosine, caffeine, clopidogrel, or dipyridamole, are already used in patients. Moreover, implications from experimental studies provide an expanding field of therapeutic indications for selectively targeting purinergic signaling mechanisms in patients. Many of these therapies have important applications in preventing organ injury during the perioperative period, for example during major surgeries, or solid organ transplantation.

Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. Circulation 2012; 126:207–12.

This study describes the relationship between perioperative cardiovascular events and perioperative bleeding in a large cohort of surgical patients prospectively assembled by the National Surgical Quality Improvement Program. Major perioperative hemorrhages, defined as bleeding requiring more than four units of packed red blood cells, were associated with a two-fold increase in the frequencies of postoperative myocardial infarction and postoperative stroke. These postoperative cardiovascular complications are recognized to cause significant morbidity and mortality, but the mechanisms remain controversial. As a matter of fact, the relative impact of thrombosis and of imbalance between oxygen needs and supplies is not known.

These results support the role of bleeding in the pathogenesis of these postoperative complications, which would be in favor of the role of mechanisms related to imbalances. Nevertheless, because of the definition of major hemorrhage, neither can the impact of bleeding and of transfusion be differentiated nor can the impact of preoperative hemoglobin be taken into account. Despite these limitations, these results continue to be of major importance, because they demonstrate the need for large randomized controlled trials to define optimal strategies for the management of antiplatelets during the perioperative period.

Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics 2012; 130:e476-e485. doi: 10.1542/peds.2011–3822

This interesting cohort study directly examined the neuropsychological consequences of exposure to anesthesia before the age of 3 yr using an appropriate battery of tests measured at the age of 10 yr. Deficits were found in abstract reasoning and language after exposure. Interestingly, an association between tests scores and exposure to anesthesia was also been reported in Block's study in the September issue of ANESTHESIOLOGY (ANESTHESIOLOGY 2012; 117: 494–503). However, the interpretation of observational studies related to the possible long-term neurotoxicity of exposure to anesthesia in the infancy is limited by a significant amount of methodological issues (see the accompanying editorial: Flick RP, Warner DO: ANESTHESIOLOGY 2012; 117: 459–61), making additional efforts to clearly identify the factors responsible for these observed associations necessary.

Obstructive sleep apnea and diabetic neuropathy. A novel association in patients with type 2 diabetes. Am J Resp Crit Care Med 2012; 186:434–41.

Perioperative management of patients with obstructive sleep apnea is a challenge because of an increased risk of organ complications. This study highlights a novel association between obstructive sleep apnea and diabetic peripheral neuropathy, and found that the severity of nocturnal hypoxic episodes correlated with severity of obstructive sleep apnea and neuropathy (table 1). The hypothesis that obstructive sleep apnea complicating type 2 diabetes may aggravate glucose toxicity and favor diabetes complications deserves further investigation.

Table 1. The Relationship between OSA and DPN

Clinical Characteristics	OSA+ Patients	OSA – Patients
	Older Longer Duration DM Higher Systolic BP Higher Obesity Measures Sleepier	—
DPN prevalence, %	60*	27
Foot insensitivity, %	50*	15
Neurological abnormalities		
Skin hypersensitivity, %	33*	13
Open sore on the foot, %	27*	7

*$P < 0.001$.

BP = blood pressure; DM = diabetes mellitus; DPN = Diabetic Peripheral Neuropathy; OSA = Obstructive Sleep Apnea.

Critical Care Medicine

Tight glycemic control *versus* standard care after pediatric cardiac surgery. N Engl J Med 2012. doi: 10.1056/NEJMoa206044

Glucose in the ICU: Evidence, guidelines and outcomes. N Engl J Med 2012 Sept. 7. [Epub ahead of print] doi:10.1056/NEJMe1209429

The pioneer article by Van den Berghe *et al.*, Belgium, 2001, showing a 30% reduction of postoperative mortality by tight glycemic control in cardiac surgical patients has been the cornerstone of recommendations for clinical practice supporting that tight glycemic control could save lives in critically ill patients. The recent prospective randomized trial conducted by Agus *et al.* in pediatric cardiac surgical patients demonstrates that tight insulin-based glycemic control (4.4–6.1 mM) can be achieved with a low hypoglycemia rate (3%), but has no impact on infection rates in the cardiac intensive care unit (primary goal), or on secondary outcomes including mortality, length of stay, or measure of organ failures, even in high-risk patient subgroups (fig. 1). These results are to be considered together with those of the major Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial published in 2009, which was conducted in critically ill adult patients. In a very clear, elegant, and incisive accompanying editorial, B. Kavanagh concludes that if the door is open to studying glucose homeostasis in the critically ill, it should be closed to routine normalization of plasma glucose in critically ill adults and children. It is fascinating how long it takes for guidelines to be implemented into clinical practice, and also how quickly guidelines are sometimes formulated based on modest data, then need to be hastily revised or reversed, as pointed out in Kavanagh's editorial.

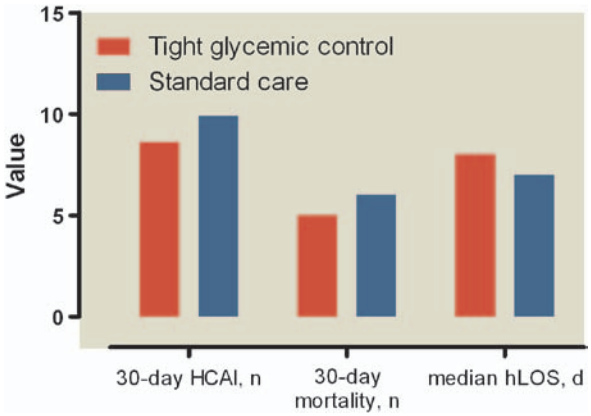

Fig. 1. Study outcomes and adverse events. d = days; HCAI = health care-associated infections (number of infections per 1,000 patient-days in the cardiac intensive care unit); hLOS = hospital length of stay.

Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: A prospective sequential analysis. Crit Care Med 2012; 40:2543–51.

Whether fluid loading should be preferentially performed using colloids or crystalloids in patients in the intensive care unit who have severe sepsis remains a matter of debate and investigation. A recent evidence-based Scandinavian randomized controlled trial concluded that patients with severe sepsis who received hydroxyethylstarch 130/0.4 for fluid resuscitation had an increased risk of death at 90 days and were more prone to require renal-replacement therapy in comparison with those who received Ringer acetate (Perner A *et al.*, *New England Journal of Medicine* 2012; DOI:10.1056/NEJMoa1204242). This novel before–after study conducted on a large sample of consecutive patients in the intensive care unit with severe sepsis found no difference to time of shock reversal (defined by lactate less than 2.2 mM and cessation of vasopressor use) between colloid and crystalloid fluid resuscitation. This study suggests that the rapidity of restoration of hemodynamic status and proper oxygen organ delivery may have a greater impact on outcome than the nature of the fluids used for resuscitation.

Pain Medicine

The relationship between pain and depressive symptoms after lumbar spine surgery. Pain (2012). http://dx.doi.org/10.1016/j.pain.2012.06.026.

This prospective study characterized the relationship between pain and depressive symptoms after lower back surgery. Two

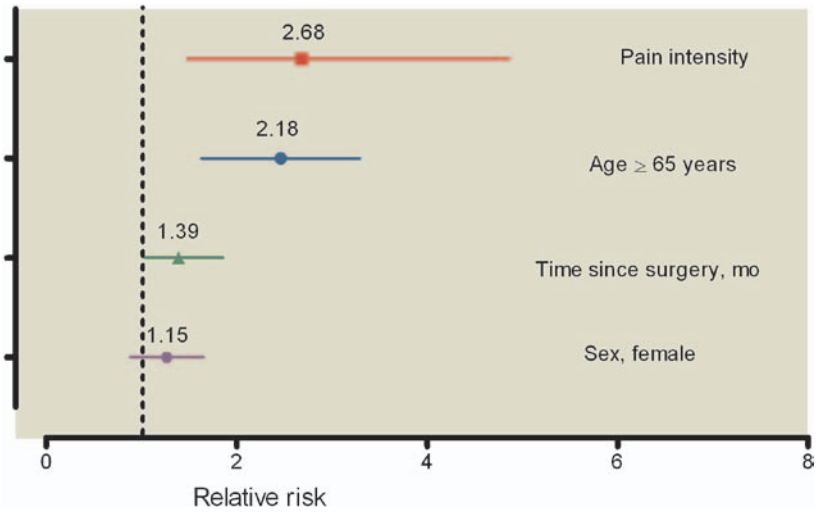

Fig. 2. Relationship between change in pain intensity and improvement in depressive symptoms in the study population (n = 260) at 6 months.

hundred and sixty patients were examined preoperatively and postoperatively at 3 and 6 months. The average preoperative pain intensity and depressions scores were 5.2 and 5.0, respectively. At 3 months, patients with at least a 2-point (or 30%) reduction from the preoperative level were no more likely to experience a reduction in depression (odds ratio 1.07) than patients who did not experience relief from surgery (fig. 2). At 6 months, patients who experienced a reduction in pain were much more likely to experience a reduction in depression (odds ratio 1.93) than those who experienced no pain relief.

Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu1 gene: Evidence of a sex and genotype interaction. J Neurosci 2012; 32:9831–4

This study examines the association of pain and radiculopathy after lumbar disc herniation with μ-opioid receptor genotype. Approximately 50% of the patients underwent surgery for disc herniation. There was a significant effect of μ-opioid receptor genotype and pain intensity during the

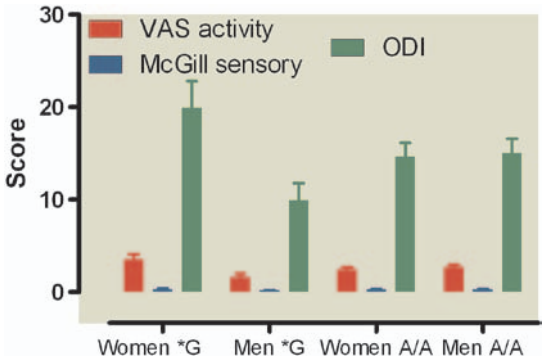

Fig. 3. Pain and disability ratings at 12 months. The figure shows the 12-month visual analogue scale (VAS), McGill, and Oswestry Disability Index (ODI) scorings for the patient groups by sex and A118G genotype. Mean ± SE of the mean are shown. *G or A allele.

12-month period for women (fig. 3). These data suggest that the mu opioid receptor G allele increased the pain intensity in women 1 yr after disc herniation. This is one of several studies to associate genotype and chronic pain after an acute injury like lumbar disc herniation.