Anesthesiology 2010; 113:464–9

Timothy J. Brennan, Ph.D., M.D., Editor

Perioperative Medicine

J. Lance Lichtor, M.D., and Joseph F. Antognini, M.D., Editors

Variation in the 4q25 chromosomal locus predicts atrial fibrillation after coronary artery bypass graft surgery. Circ Cardiovasc Genet 2009; 2:499–506

Atrial fibrillation (AF) occurs in 27–40% of cases after cardiac surgery. AF is associated with increased risk of complications and increased healthcare resource utilization. In ambulatory patients, four single-nucleotide polymorphisms (SNPs) within the 4q25 chromosomal regional were identified, and clinical and genetic predictors of AF have been validated. Their role in postoperative AF is unknown.

This multicenter prospective study assessed whether the genetic variants in the 4q25 chromosomal region are independently associated with postoperative AF after coronary artery bypass graft (CABG) surgery using two prospectively collected cohorts of patients undergoing CABG with cardiopulmonary bypass and with or without concurrent valve surgery. Clinical and genomic multivariate predictors of postoperative AF were identified by genotyping 45 SNPs encompassing the 4q25 locus in the discovery cohort (n = 959 patients; 30.1% had postoperative AF). Validation of three SNPs were then assessed in a separately collected cohort (n = 494 patients, 30.6% had postoperative AF).

Older patients and patients with prior AF were at higher risk for postoperative AF, whereas postoperative "statin" use reduced the risk. After adjustment for clinical predictors of postoperative AF, and multiple comparisons, seven SNPs independently predicted postoperative AF in the discovery cohort. Additive odds ratios for the seven associated 4q25 SNPs ranged between 1.57 and 2.17 (P = 0.0008.0–0.000034). The rs10033464 SNP associated with AF in ambulatory patients was not observed for postoperative AF. Association with postoperative AF were measured and replicated for rs2200733 and rs13143308 in the validation cohort.

Interpretation

Atrial fibrillation remains a significant complication after coronary artery bypass surgery. Patients who have single nucleotide polymorphisms at the chromosome 4q25 region have increased risk for developing atrial fibrillation after bypass surgery. Further research is needed to determine whether preoperative testing for this genetic alteration can lead to early treatment and prevention of atrial fibrillation.

Delirium after coronary artery bypass graft surgery and late mortality. Ann Neurol 2010; 67:338–44

Delirium is common after many surgeries, especially CABG, and its presence increases postoperative morbidity and mortality in the short term (3–12 months postoperatively). However, the impact of a transient postoperative delirium episode on long-term outcomes is not well understood and may be underestimated.

The primary objective of this prospective observational study was to determine whether patients with delirium after CABG surgery have higher long-term out-of-hospital mortality compared with CABG patients without delirium. Consecutive patients (n = 5,034) undergoing CABG surgery at a single institution over a 10-yr period were assessed, and patients with delirium were followed for 3 yr.

Delirium occurred in 6% of all patients. Patients with delirium had increased mortality, (hazard ratio [HR] = 1.65) after adjustment for risk factors.

	With Delirium (n = 304)	Without Delirium (n = 4,748)	*P* Value
Median survival, yr	10.6	>10	
Death rate, per 100 person-yr	16.0	7.0	<0.0001
Postoperative length of stay, days	15.3	7.3	<0.0001
Risk of death up to 10 yr postoperatively	HR = 1.65		

Interpretation

This study shows that delirium can increase morbidity even 10 years after bypass surgery, especially in younger patients and those without prior stroke. These data further underscore the seriousness of postoperative delirium and invite more research on treatment and prevention.

A method to attenuate pneumoperitoneum-induced reductions in splanchnic blood flow. Ann Surg 2005; 241:256–61

Pneumoperitoneum, insufflating the peritoneal cavity with gas, is commonly used during the millions of laparoscopic abdominal procedures performed annually. However, insufflations with carbon dioxide may significantly reduce organ blood flow, resulting in tissue ischemia and postoperative morbidity and mortality. To determine whether adding ethyl

nitrate to the insufflation admixture would attenuate pneumoperitoneum-induced decreases in organ blood flow, an *in vivo* experiment in pigs was conducted.

Laser-Doppler flow probes were placed on the liver and right kidney of anesthetized pigs. After a baseline recording period, animals were insufflated to a final intraperitoneal pressure of 15 mmHg with either carbon dioxide (standard practice) or carbon dioxide plus ethyl nitrite (ENO). Insufflation was maintained for 60 min and then the abdomen was manually deflated; monitoring was continued for another 60 min.

Inclusion of ENO increased heart rate and decreased pressure in a dose-related manner; however these changes were moderate. Based on these dose finding studies, 100 ppm ENO was used in subsequent experiments. The addition of ENO was found to increase hepatic blood flow. Renal blood flow was not changed.

	CO_2 (n = 5)	CO_2 + ENO (n = 6)
Heart rate	NC	NC
Liver blood flow	↓ 50% of baseline	10% of baseline
20 min	↓ Remained low	Similar to baseline
60 min	—	14.3 U/min × higher*
Adjusted model		
Kidney blood flow	NC	NC†

* $P = 0.0454$; † $P = 0.6215$.
CO_2 = carbon dioxide; NC = no change.

Interpretation

As an increased number of more complex laparoscopic surgeries are being performed, further refinement of the technique is warranted. In this study of a porcine model of laparoscopic surgery, the addition of ENO to carbon dioxide improved splanchnic but not renal blood flow. Further studies are warranted to determine whether the addition of ENO to carbon dioxide reduces adverse events associated with reduced visceral blood flow in humans undergoing laparoscopic surgery.

The volume-mortality relation for radical cystectomy in England: Retrospective analysis of hospital episode statistics. BMJ 2010; 340: c1128

In England, although many healthcare services have been centralized, numerous studies have demonstrated conflicting data on outcomes in high-volume *versus* low-volume institutions and/or surgeons. To address the differences, this retrospective study was designed to investigate the relation between volume and mortality after adjustment for case mix for radical cystectomy in the English healthcare setting using improved statistical methods, taking into account the institutional and surgeon volume effects and institutional structural and process-of-care factors.

Hospital episode statistics were analyzed, with the use of multilevel modeling, for patients with a primary diagnosis of cancer, undergoing an inpatient elective cystectomy in English hospitals between 2001 and 2007. Institutional and surgeon volume were defined by number of cystectomies per year: institutions: low (more than 2 but less than 10), medium (at least 10 but less than 16), or high (16 or more); surgeons: (at least 1 but less than 5), medium (at least 5 but no more than 8), or high (8 or more).

Overall, the number of radical cystectomies increased from 1,120 in 2000 to 1,296 in 2006 ($P = 0.005$), whereas mortality decreased from 3.5% in 2000 to 2.1% in 2005. Compared with low volume institutions, the odds of 30-day in-hospital (odds ratio [OR] = 1.72; $P = 0.05$) and total mortality (OR = 1.82; $P = 0.02$) were higher in medium-volume institutions after adjustment for structural and process-of-care factors. The odds of in-hospital mortality were lower in high-volume institutions (OR = 0.67; $P = 0.03$) after adjustment for patient case mix. High surgeon volume resulted in lower odds of in-hospital mortality (OR = 0.67 and 0.64; $P = 0.03$ and 0.01 after no adjustment or adjustment for patient case mix, respectively).

Interpretation

In this retrospective analysis of cystectomy patients in England, 30-day in-hospital and total mortality were lower in low-volume compared with medium-volume institutions. The findings were surprising and seemed to be related to institutional structure and processes of care.

Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. Br J Surg 2010; 97:485–94

Preoperative fasting may reduce the metabolic preparation needed to attenuate postoperative insulin resistance. Preoperative carbohydrate (CHO) treatment may lead to reduced insulin resistance and improved clinical outcomes.

This is the first placebo controlled, double-blind, randomized study to assess the effect of CHO administration on clinical outcome of patients undergoing elective colorectal surgery or liver resection. Patients (n = 142) received either oral CHO or placebo drinks to be taken on the evening before surgery and 2 h before induction of anesthesia.

The groups were well matched with respect to surgical procedure, epidural analgesia, laparoscopic procedures, fasting period before induction, and duration of surgery. Postoperative fatigue score were higher than baseline for all patients but did not differ between the groups. However, the CHO-treated group returned to baseline levels faster than the placebo group (by day 6 in CHO group). The median hospital stay length of stay was also similar between groups (7 *vs.* 8 days in the CHO and placebo groups, respectively).

Median time to oral intake and the rate of postoperative infectious complications were also similar between groups ($P = 0.968$ and $P = 0.387$, respectively). Preoperative and postoperative discomfort scores were also similar between groups. It is noteworthy that no significant differences were observed in glucose, insulin, or cortisol response protein (CRP) levels between groups on any study day. However, insulin and CRP were attenuated on day 1 in the CHO group.

Interpretation

In this study, nondiabetics undergoing major abdominal surgery received oral carbohydrate drinks or placebo both the evening and 2 h before surgery. Patients who received the carbohydrate drinks had more side effects, including nausea, bloating, and headache; there was no benefit on fatigue or length of hospital stay. Insulin and cortisol response were attenuated in the CHO group.

Critical Care Medicine

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

Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 2010; 36:444–51

An early acute kidney injury (AKI) biomarker may facilitate timely interventions to ameliorate downstream effects of AKI. Several studies have demonstrated the potential utility of serum and urine neutrophil gelatinase-associated lipocalin (NGAL) for early detection of AKI, specifically in children. However, its generalizability to adults is not yet known.

To estimate the diagnostic accuracy of plasma NGAL (pNGAL), this prospective observational study of patients admitted consecutively to a general medical-surgical intensive care unit was conducted. Of 301 enrolled patients, the most common reasons for intensive care unit (ICU) admission were neurologic, respiratory, cardiovascular, traumatic, or gastrointestinal illness. Almost half (44%) of all patients had AKI during their ICU stay; 68% of cases occurred within the first 24 h). The median length of ICU stay was 7 days.

The first median pNGAL level was significantly higher in study patients than that observed in healthy adults (117.0 *vs.* 61.2 ng/ml, respectively; $P < 0.001$). pNGAL values were significantly higher among patients with AKI at the time of first measurement ($P < 0.001$) and in patients who developed AKI within 48 h ($P < 0.001$). Plasma NGAL was a good diagnostic marker for AKI development within the next 48 h (area under receiver operating characteristic curve [ROC], 0.78), and for the need for renal replacement therapy (area under ROC 0.82; 95% confidence interval [CI], 0.70–0.95). Peak plasma NGAL concentrations increased with worsening AKI severity ($R = 0.554$, $P < 0.001$).

Interpretation

This prospective observational study confirms and extends previous findings by showing that pNGAL is a good predictor of acute kidney injury development early after ICU admission and also predicts need for renal replacement therapy. This suggests that there is utility for the use of pNGAL at the bedside in ICU patients as a diagnostic and prognostic biomarker of acute kidney injury.

The impact of experimental hypoperfusion on subsequent kidney function. Intensive Care Med 2010; 36:533–40

There has been a lack of progress in understanding and treating AKI, a complication of critical illness that may lead to death. Animal models that more closely mimic the human condition are needed to fully understand the mechanisms of AKI.

To investigate the short- and medium-term renal hemodynamic and functional responses to both short and sustained hypoperfusion, 11 conscious sheep were monitored in a prospective observational study after unilateral nephrectomy with a vascular occluder and flow probe implanted on the remaining renal artery. In five animals, renal blood flow (RBF) was reduced by 25, 50, and 75%, respectively, with the use of acute vascular occlusion for 30 min at weekly intervals. In another 6 animals, RBF was reduced by 80% for 2 h.

Two hours after occlusion (25, 50, or 75% renal hypoperfusion for 30 min), RBF returned to baseline values, urine output was normal after 24 h and remained normal for 3 days. Creatinine clearance was normal 24 h after occlusion. During 2 h of 80% hypoperfusion, urine output decreased from 80 to 17 ml, and creatinine clearance from 32 to 3 ml/min., In addition, plasma creatinine increased from 103 to 132 μM, and fractional excretion of sodium and urea increased. Release of occlusion induced brief hyperemia. Subsequently, all measured variables returned to normal within 8 h and remained normal for the subsequent 3 days. Kidneys were histopathologically normal.

Interpretation

Renal ischemia and reperfusion are usually recognized as the main factors leading to AKI and tubular necrosis in hemodynamically unstable patients in the ICU. This experimental study indicates that even a profound and long lasting reduction of renal perfusion is followed by restoration of baseline function and flow. This suggests that severe renal hypoperfusion by itself cannot induce persistent AKI. Rather, AKI likely occurs when additional factors (*e.g.*, inflammation, toxic factors) are present.

The impact of crystalloid and colloid infusion on the kidney in rodent sepsis. Intensive Care Med 2010; 36:541–8

Up to 64% of patients with septic shock have sepsis-related acute renal failure. However, the ideal fluid substitution in these patients remains unclear. Crystalloids are preferred in North America, but crystalloid/colloid combinations are used in European intensive care units.

The impact of crystalloid and colloid solutions on kidney function was investigated in a rodent model of abdominal sepsis induced by cecal ligation and puncture (CLP). Rats were anesthetized and underwent either the CLP procedure or were sham-operated. Septic animals were treated with 0.9% sodium chloride (NaCl), a balanced crystalloid solution, hydroxyethyl starch (HES), or gelatin solutions, and kidneys were harvested after 24 h for histopathologic studies.

Septic animals exhibited a mortality rate of 19% after 24 h; all rats in the sham group survived and had no signs of critical illness. The highest rate of mortality was in rats treated with 0.9% NaCl (50%) compared with HES (25%), gelatin (25%), and balanced crystalloid solution (0%) groups. Total injury scores were higher in rats treated with colloids (HES, 6%; gelatin, 4%) but were not significantly different in the crystalloid groups compared with sham control animals. The histopathologic observations revealed that gelatin- and HES-treated animals showed vesicles within epithelial cells of the renal tubules and overall increased injury. In contrast, total injury scores in groups treated with crystalloids (0.9% NaCl or balanced crystalloid solution) were not significantly different compared with sham-operated animals.

Interpretation

Volume expansion is a pivotal treatment of sepsis in ICU patients. Renal toxicity of colloids remains a matter of debate. This study indicates that gelatin and HES adversely affected kidney function in an experimental sepsis model. It is noteworthy that gelatin was more harmful than HES.

Suggested by: Laurent Jacob, M.D., Ph.D.

Comparison of dopamine and norepinephrine in the treatment of septic shock. N Engl J Med 2010; 362:779–89

To correct hypotension, dopamine and norepinephrine are the most frequently recommended first-line vasopressor agents in the treatment of shock. Secondary stimulatory effects on α-adrenergic, β-adrenergic, and catecholamine receptors may result in unwanted side effects.

Patients were randomized in this blinded multicenter trial to assess whether first-line norepinephrine could reduce the rate of death among patients in shock. Adult patients (n = 1,679) in shock (arterial pressure less than 70 mmHg or systolic blood pressure less than 100 mmHg despite adequate fluid administration, and no signs of tissue hypoperfusion) received either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure.

	Dopamine (n = 858)	Norepinephrine (n = 821)	*P* Value
Baseline characteristics			
Age, median yr	68	67	—
APACHE II Median, %	20	20	—
Required medications, %			
Open-label norepinephrine	26	20	<0.001
Open-label epinephrine	3.5	2.3	0.10
Vasopressin	0.2	0.2	0.67
Mortality, %			
28-day	52.5	48.5	0.10
In ICU	50.2	45.9	0.07
During hospital stay	59.4	56.6	0.24
Follow up*	NS	NS	NS
Length of stay, median days			
ICU	5	5	0.12
Hospital	11	12	0.22
Adverse events, %			
Arrhythmias	24.1	12.4	<0.001
Myocardial infarction	2.2	3.0	0.29
Discontinuation due to arrhythmias, %	6.1	1.6	<0.001

* Not significantly different after 6 or 12 months' follow up.
APACHE = Acute Physiology and Chronic Health Evaluation; NS = not significantly different.

A subgroup analysis showed that, compared with norepinephrine, dopamine was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1,044 patients with septic shock or the 263 with hypovolemic shock ($P = 0.03$ for cardiogenic shock, $P = 0.19$ for septic shock, and $P = 0.84$ for hypovolemic shock).

Interpretation

No difference in mortality rates at day 28 was observed in patients with septic shock treated with either dopamine or norepinephrine. After subgroup analyses, there was an increased incidence of arrhythmias and greater mortality in patients with cardiogenic shock treated with dopamine. These results suggest that the recommendation of the American College of Cardiology-American Heart Association be revisited to evaluate whether dopamine should be the first vasopressor used in patients who develop hypotension as a result of acute myocardial infarction.

Pain Medicine

Timothy J. Brennan, Ph.D., M.D., Editor

Randomized controlled trial of integrated care to reduce disability from chronic low back pain in working and private life. BMJ 2010; 340:c1035

Current clinical guidelines focus on prevention of work disability rather than treatment for pain in patients with chronic low back pain. Integrated care programs with patient-directed and workplace-directed focus have been shown to be cost-effective in patients with subacute low back pain.

This population-based, randomized controlled trial evaluated the effectiveness of an integrated care program, including prevention of work disability and pain treatment interventions, for patients with chronic low back pain (n = 134) in primary care (10 physiotherapy practices, 1 occupational health service, 1 occupational therapy practice, and 5 secondary care hospitals). Patients with pain for at least 12 weeks were randomly assigned to usual care or integrated care (participatory ergonomics and a graded activity program based on cognitive behavioral principles). Although patients in the integrated group return to work faster, there was no difference between groups in terms of pain.

	Integrated Care (n = 66)	Usual Care (n = 68)
Baseline characteristics		
Age, mean yr ± SD	45.5 ± 8.9	46.8 ± 9.2
Physical demands of work, %	64	62
Mental demands of work, %	36	38
Full absence from work, %	49	47
Mean pain intensity (0–10 score) ± SD	5.7 ± 2.2	6.3 ± 2.1
Duration of first continuous sick leave, median days (range)*	88 (52–164)	208 (99–366)
Days of sick leave over 12 months, median days (range)†	82 (51–164)	175 (91–365)
Functional status improvement at 3, 6, and 12‡ months, mean	3.76, 4.81, 7.16	3.82, 4.97, 4.43
Pain improvement at 3, 6, and 12 months, mean	1.11, 1.26, 1.64	1.59, 2.26, 1.85

* $P = 0.004$; † $P = 0.003$; ‡ $P = 0.01$.

Interpretation

In this integrated multidisciplinary approach for managing low back pain, patients returned to work earlier and had improved functional status. Surprisingly, there was no improvement in pain. These data further reinforce that chronic low back pain is a psychosocial and work-related phenomenon. Studies suggest positive improvement in the adverse effects of low back pain with an integrated care approach.

Efficacy and safety of a single intrathecal methylprednisolone bolus in chronic complex regional pain syndrome. Eur J Pain 2010; 14: 523–8

Merits of publishing a negative and prematurely ended study on intrathecal methylprednisolone for severe and longstanding complex regional pain syndrome (CRPS-I). Eur J Pain 2010; 14: 453–5

Little is known about the mechanisms underlying central sensitization in complex regional pain syndromes type I (CRPS). Methylprednisolone demonstrated reductions in spinal cord microglia activation and prevention of nerve injury pain in rats and had a pain-reducing result in patients with postherpetic neuralgia.

Because central inflammatory responses accompany many chronic pain conditions in experimental animals, a double-blind randomized placebo-controlled parallel-group trial was initiated to investigate the efficacy and safety of a single intrathecal administration of 60 mg methylprednisolone (ITM) in patients with chronic CRPS. Patients had a median of 4.5 yr of severe pain, movement disorders, and other CRPS symptoms at baseline.

At the interim analysis, 21 patients were enrolled (10 had received ITM) and the trial was stopped prematurely for failure to reach its primary outcome of change in pain after 6 weeks or any other outcome measure. In some cases there was a worsening of myoclonus. Treatment-emergent adverse events were not different between the ITM and placebo groups.

Interpretation

No beneficial effect of ITM was observed in patients with CRPS, and there were no apparent adverse events. The accompanying editorial applauds the attempt, comments on the importance of halting the trial early after interim analysis, and emphasizes the importance of publishing the negative data from the ITM injection trial.

Substitution of (*R*,*S*)-methadone by (*R*)-methadone: Impact on QTc interval. Arch Intern Med 2010; 170:529–36

Administration of the synthetic μ-opioid receptor antagonist methadone has been shown to reduce illicit drug consu-

mption, decrease risk for human immunodeficiency virus infection and mortality, and increase socioprofessional rehabilitation for opioid-dependent patients. However, methadone is administered as a chiral mixture of (*R*,*S*)-methadone; although the (*R*)-methadone is attributed with the opioid efficacy, the (*S*)-methadone has been associated with adverse reactions, such as drug-induced long QT syndrome, leading to potentially lethal ventricular tachyarrhythmias.

This prospective study of 39 opioid-dependent patients receiving methadone maintenance treatment was conducted to investigate whether (*R*)-methadone alone could reduce the corrected QT (QTc) interval. Patients received (*R*)-methadone (half-dose) for 14 days. Some patients had the option to remain on (*R*)-methadone alone based on changes in QTc interval values.

No differences in the mean daily dose of (*R*)-methadone were apparent before trial entry compared with on study (53.8 mg before study entry *vs.* 54.0 week 2). Opioid adverse effects and withdrawal symptoms were either absent or of low intensity and remained unchanged during the study. (*S*)-methadone was detected but at low levels in 4 of 34 patients at day 14. The QTc interval decreased when (*R*,*S*)-methadone was replaced by a half-dose of (*R*)-methadone (median values were 423 ms at day 0 *vs.* 412 ms at day 14; $P = 0.06$). The QTc value decreased by a mean of −3.9 ms per week ($P = 0.04$). In a subset of patients (n = 29), when (*R*,*S*)-methadone was reintroduced for 14 days, the QTc value increased ($P = 0.01$) by a mean of 4.7 ms per week ($P = 0.006$).

Interpretation

Methadone is a mainstay of treating opioid-dependent patients. Patients in this study experienced deceased QT intervals with the *R*-enantiomer compared with the racemic mixture in the absence of changes in opioid withdrawal symptoms. However, further research is needed to determine whether the *R*-enantiomer leads to decreased risk of cardiovascular complications (such as tachyarrhythmias) and death in patients taking methadone.

Suggested by: Joseph Antognini, M.D.