

# Queen's University 34<sup>th</sup> Annual Anesthesiology Research Day

*Scientific Program Directors and Residency Research Coordinators:*

**Ian Gilron, MD, MSc, FRCPC**

**Elizabeth VanDenKerkhof, RN, MSc, DrPH**

*Scientific Adjudicators:*

**Kim Turner,**  
MD, MSc, FRCPC

**Devin T. Sydor,**  
MD, FRCPC

**Gilles Plourde,**  
MD, MSc, FRCPC (Guest)

*Department Head:*  
**Joel Parlow, MD, MSc, FRCPC**

*Residency Program Director:*  
**Michael Cummings, MD, FRCPC**

*Postgraduate Medical Secretary:*  
**Kim Asselstine**

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*Research Facilitator:*  
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*Research Coordinator:*  
**Debbie DuMerton Shore, RN, CCRP**

*Research Nurse:*  
**Sarah Walker, RN, MSc**

*Research Nurse:*  
**Jessica McCourt, RN**

*Institutional support:*

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Held at Donald Gordon Centre, Kingston, Ontario, CANADA, April 12, 2013.

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*Queen's University 34<sup>th</sup> Annual Anesthesiology Research Day*

**SCIENTIFIC PROGRAM OUTLINE**

- 0800 – 0810 Opening Remarks**  
– Dr. Joel Parlow
- 0810 – 0830 Research Day Introduction**  
– Dr. Ian Gilron
- 0830 – 0930** \*\*\* Keynote Lecture \*\*\*  
**"Why Does the Research Board Want Answers to so Many Questions?"**  
– Dr. Albert Clark
- 0930 – 1015 Oral presentations**
- 1015 – 1045 Poster presentations and nutrition break**
- 1045 – 1130 Oral presentations**
- 1130 – 1230 \* LUNCH (provided) \***
- 1230 – 1430 Oral presentations**
- 1430 – 1500 Poster presentations and nutrition break**
- 1500 – 1545 Oral presentations**

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**EACH 10-MINUTE ORAL PRESENTATION WILL BE FOLLOWED BY A 5-MINUTE QUESTION PERIOD**

**The Judges will be:**

**Dr. Gilles Plourde**, Professor, Department of Anesthesia, McGill University

**Dr. Kim Turner**, Associate Professor, Queen's Department of Anesthesiology & Perioperative Medicine

**Dr. Devin Sydor**, Assistant Professor, Queen's Department of Anesthesiology & Perioperative Medicine

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**1545** **Dr. Gilles Plourde**, Professor, Department of Anesthesia, McGill University

\*\*\* **Guest Lecture** \*\*\*

**Wine & Cheese** to follow with \* **Awards Presentation** \* (Donald Gordon Center)

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## **Oral Presentations**

*(in alphabetical order, presentation order to be announced)*

**Jessie COLLINGS, PGY4**

**“Comprehensive sonoanatomy module to improve skill in neuraxial block performance among trainees”** (update)

**Tricia DOYLE, PGY4**

**“A Survey of Health Professional Education in Patient Safety at Queen's University”** (update)

**Patrick GRENIER, PhD Candidate, Queen's University Department of Biomedical & Molecular Sciences**

**“Assessing Changes In Opioid And Noradrenergic Interactions In Nerve-Injured Rats Using The Conditioned Place Preference Paradigm”** (Data presentation)

**Darryl HOFFER, PGY2**

**“Does the use of peri-operative gabapentin and pregabalin reduce opioid-related adverse-events? A systematic review.”** (proposal)

**Karmen KROL, PGY2**

**“Measurement of cardiac output with the ultrasonic cardiac output monitor versus transthoracic echocardiography”** (proposal)

**Yuri KOUMPAN, MD Candidate, Queen's University School of Medicine**

**“Glycosylated Hemoglobin Screening For Elective Surgical Patients”** (data presentation)

**Mahmoud LABIB, PGY2**

**“Determining the minimum degree of needle angulation towards the midline in thoracic epidurals using 3D CT imaging, a pilot study”** (proposal)

**Mark LIPSETT, PGY3**

**“Elevated Intra-Cranial Pressure During Long-Duration Space Flight”** (data presentation)

**Ella MANN, PhD Candidate, Queen's University School of Nursing**

**“Medical self-management of neuropathic versus nociceptive pain: Is there a difference?”**

**Judy MAROIS, PGY3**

**“The Effect of Intraoperative Labetalol on Time to Discharge and Hemodynamic Stability in Laparoscopic Cholecystectomy”** (update)

**Alex MATTIOLI, PhD Candidate, Queen's University Department of Biomedical & Molecular Sciences**

**“Ultra-low dose opioid antagonists modulate opioid tolerance and hyperalgesia via distinct mechanisms that are Toll-like receptor 4-independent”** (data presentation)

**Nicole MCFADDEN, PGY2**

**“A survey of scope of practice in Family Medicine Anesthesia”** (proposal)

**Edmund ONG, PhD Candidate, Queen's Biomedical & Molecular Sciences**

**“Prolonged morphine treatment alters delta opioid receptor post-internalisation trafficking”** (data presentation)

**Frank SECRETAIN, PhD Candidate, Queen's Faculty of Engineering & Applied Science**

**“Detection and Breakup of Potential Cerebral Air Emboli”** (data presentation)

**Vanessa SWEET, PGY2**

**“Electronic Anesthesia Consult Record: Does it Improve Efficiency and Effectiveness of Pre-Operative Inpatient Anesthetic Consults?”** (proposal)

## **Poster Presentations**

**Alex FLOREA**, PGY3

**“Methylene Blue Aids In Management Of Central Venous Perforation”**

**Patrick GRENIER**, PhD Candidate, Queen's University Department of Biomedical & Molecular Sciences

**“Systemic Administration Of Ultra-Low Dose Alpha2-Adrenergic Antagonists Atipamezole And Efaroxan Enhance Morphine Analgesia And Reduce The Development Of Tolerance Following Nerve Injury”**

**Yasser HAYAT**, PGY4

**“The economics of drug wastage”**

**Ella MANN**, PhD Candidate, Queen's University School of Nursing

**“Sex differences in chronic pain description, self-management, and satisfaction with ability to control pain”**

**Daniel MOK**, MD Candidate, Queen's University School of Medicine

**“Prevalence and patient impact of chronic post-sternotomy pain following coronary artery bypass graft (CABG) surgery at a Canadian tertiary care centre”**

**Bonnie SHUM**, MD Candidate, Queen's University School of Medicine

**“Combination pharmacotherapy for fibromyalgia: A systematic review”**

## **Critical Appraisal Essays**

**James Cheng**, MD, PGY-1, Queen's Anesthesiology

*“Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes.”* Anesth Analg 2012;115(6):1343-50.

**Tanya Griffiths**, MD, PhD, PGY-1, Queen's Anesthesiology

*“The Risks of Aprotinin and Tranexamic Acid in Cardiac Surgery: A One-Year Follow-Up of 1188 Consecutive Patients.”* Anesthesia & Analgesia 2008;107(6):1783-1790.

**Serena Shum**, MD, PhD, PGY-1, Queen's Anesthesiology

*“High-sensitive cardiac Troponin T is superior to echocardiography in predicting 1-year mortality in patients with SIRS and shock in intensive care.”*

BMC Anesthesiology 2012 12:25.

**Julie Zalan**, MD, PGY-1, Queen's Anesthesiology

*“Predicting Prognosis in Thermal Burns with Associated Inhalational Injury: A Systematic Review of Prognostic Factors in Adult Burn Victims”* J Burn Care Res. 2010 Jul-Aug;31(4):529-39.

## ABSTRACTS

### “Comprehensive sonoanatomy module to improve skill in neuraxial block performance among trainees”

Jessie Collings, PGY4

Research supervisors: Dr Shyam, Dr Murdoch, Dr McMullen; thanks to Rachel Phelan, Val Wilson

#### **Background:**

The traditional method for neuraxial regional analgesia relies on palpation of landmarks which may not be accurate or evident. Even the most experienced anesthesiologists incorrectly estimate the interspace level by palpation 71% of the time (1). Ultrasound can increase accuracy in identifying intervertebral levels to 76% compared to 30% with palpation (2). Studies on parturients show that ultrasound also results in more successful blocks, fewer complications, and increased overall patient satisfaction. Anesthesia trainees had a higher success rate and steeper learning curve with ultrasound-guided epidurals compared to the group that was taught the traditional palpation technique for needle insertion (3). Our goal in this study is that through use with normal models, residents will become confident with using ultrasound to identify sonoanatomy and optimal needle insertion point before attempting to use it on difficult patients. We evaluated the efficacy of our educational module at increasing competence and confidence for accurate lumbar ultrasound performance in our anesthesiology residents.

#### **Methods:**

Residents had unlimited access to our online instructional module, which describes the role of ultrasound for spine demarcation before placement of a neuraxial block and familiarizes residents with ultrasound technology and techniques. They then attended weekly sessions with instructor-guided lumbar ultrasound performance on a model. Residents were then assessed for the image quality of their ultrasound scan and their ability to measure the depth of the dura/ligamentum flavum in both the transverse and paramedian views. Through a follow-up survey, we investigated whether residents have integrated ultrasound into their own neuraxial technique, and if not, the barriers to its use.

#### **Results:**

Five residents were assessed following their training and again 6 months later to evaluate retention of skill. The average number of structured training sessions attended was 2.2. The average number of lumbar ultrasounds performed prior to the module was 2.2. The average number of times trainees utilized spinal ultrasound in their clinical practice since completing the training module was 1.2. Residents acquired better quality ultrasound images and estimated the depth of the dura more accurately during their initial assessment compared to the follow up assessment six months later. On a scale of 1-7, with 1 being “strongly disagree” and 7 being “strongly agree”, prior to the ultrasound module, the average score for confidence in their ability to image the lumbar spine was 2.2. After the module, confidence rose to 5.6, and six months later the average was 3.4. Eighty percent of residents found the hands on teaching the most valuable part of the module.

#### **Conclusions:**

Our study showed that over time, residents did not retain the level of skill acquired following their training module, and we identify barriers to the use of ultrasound for neuraxial techniques during residency training.

#### References:

1. Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell, R. Ability of anesthetists to identify a marked lumbar interspace. *Anaesthesia* 2000; 55: 1122-6.
2. Watson MJ, Evans S, Thorp JM. Could ultrasonography be used by an anaesthetist to identify a specified lumbar interspace before spinal anesthesia? *Br J Anaesth* 2003; 90: 509-11.
3. Grau T, Bartussek E, Conradi R, Martin E, Motsch J. Ultrasound imaging improves learning curves in obstetric epidural anesthesia: a preliminary study. *Can J Anesth* 2003; 50: 1047.

## **Patient safety in medical education from the perspective of the trainees**

Patricia Doyle, David Goldstein, Dana Edge, Elizabeth VanDenKerkhof

### **Background**

Safety is central and critical to quality healthcare and the need for urgent patient safety (PS) reform is recognized on a global level. Effectively integrating PS content into the training programs of healthcare workers is essential for advancing this initiative. Assessment of trainees' individual perspectives on PS is a necessary component to understanding the success with which these PS concepts have been integrated and actualized within curricula. Currently, there is little evidence garnering student perspectives in this domain, particularly amongst medical trainees. The purpose of this study is to understand undergraduate and postgraduate medical trainees' perspectives on the quality, content, and culture of PS education in medical education at Queen's University in Kingston, ON, Canada.

### **Study Design and Methodology**

This study is a cross-sectional web-based survey. Undergraduate (n ~436) and postgraduate (n ~406) medical trainees were invited to complete the online Modified Health Professional Education in PS Survey (HPEPSS), a questionnaire designed to measure health professionals' self-reported confidence on six socio-cultural dimensions of PS – working in teams, communicating effectively, managing safety risks, human factors, recognizing and responding to risks and culture, as well as eleven broader PS principles. Participants scored each question on a Likert scale of 1 (strongly disagree) to 5 (strongly agree). Data collection occurred from January to March 2012. Univariate statistics were used to describe each question and each dimension. The paired samples t-test was used to compare scores on the six dimensions of PS in the classroom versus the clinical setting. The related-samples McNemar test was used to compare agreement on specific clinical safety measures between the class and clinical setting. The independent samples t-test was used to compare scores on broader principles of PS and comfort speaking up. All analyses were stratified by medical students versus residents.

### **Results**

Response rate was 63% (n=254) for medical students and 32% (n=140) for residents. Fifty-two percent of medical students and 83% of residents were female. The largest proportion of residents came from family medicine (38%), internal medicine (12%) and anesthesiology (10%). Overall, both medical students and residents were more positive than negative in their confidence in what they were learning about PS in the six PS domains. Scores for medical students ranged from 2.91 for culture of safety in the clinical setting to 3.76 for communicating effectively in the classroom setting. Medical students were more confident about what they learned in the clinical compared to the classroom setting regarding working in teams (class 3.28; clinical 3.47, p=.02) and managing safety risk (class 3.09; clinical 3.63, p<.01). However, they were more confident in what they learned in the classroom about recognizing and responding to risks of harm (class 3.15; clinical 2.91, p<.01) and culture of safety (class 3.42; clinical 3.21, p<.01). In all but one dimension, residents were significantly more confident in what they learned about PS in the clinical setting compared to the classroom setting. However, in the classroom they were more confident in what they learned about working in teams (class 3.81; clinical 3.38, p<.01). Both groups were most confident in what they learned about hand hygiene in both setting (83% - 92%). Only 54% of medical students and 68% of residents were confident in what they learned about medication safety in the classroom, however this increased in the clinical setting to 61% and 82%, respectively. Residents were more confident in what they learned about the broader principles of PS, while in some instances medical students were more confident about speaking up about PS.

### **Conclusions**

This study could enhance and develop PS curricula and serve as a baseline to track trainees' perspectives about PS over time, all of which will contribute to advancing the PS agenda.

## **Methylene Blue Aids In Management Of Central Venous Perforation: A Case Report**

Alexandra Florea, David Mark

### **Introduction**

Vessel perforation by a central venous catheter can be life-threatening. This report illustrates a case of central venous catheter perforation identified during emergency surgery, and the use of methylene blue as a decision aid in a critical situation.

### **Clinical features**

REB approval and written consent by the patient were granted for publication of this report. A 62 year old female developed a right hemothorax and uncontrolled internal bleeding one day after undergoing exploratory sternotomy. While being resuscitated she was urgently transferred to the operating room for a second exploratory sternotomy. She arrived with a right internal jugular (IJ) central line, a right brachial PICC line which was infected and not to be used, and venous pacer wires in her left IJ. The right IJ line was her sole venous access through which blood and vasopressors were infused with good response. The surgical team identified the source of bleeding as a superior vena cava perforation by an indwelling venous catheter. It was not immediately possible to know which of the three central catheters was responsible, and the team was reluctant to remove the right IJ catheter without certainty of its corruption. Methylene blue was injected through the right IJ catheter and the dye was visualized by the surgeons exiting its tip into the patient's chest. A new femoral venous central line was established and the offending catheter was removed. The patient survived this critical event and was eventually discharged from hospital.

### **Discussion**

Perforation or erosion of central venous catheters occurs in 0.4-0.5% of catheter placements.<sup>1,2</sup> Perforation can occur immediately during cannulation, but has been reported up to 60 days after placement.<sup>2</sup> Factors increasing the risk for vascular erosion are left-sided placement<sup>1</sup>, large or multiple lumen catheters (14 gauge or larger)<sup>1,3</sup>, an incidence angle of catheter tip to SVC of 40° or greater and stiff catheters or those with very mobile tips.<sup>3</sup> This case report illustrates a novel use of methylene blue as an indicator dye in the direct visualization of central catheter perforation. Methylene blue was chosen due to its relative safety, potential benefit from inducible nitric oxide synthase inhibition, and immediate availability in the operating room. Other dyes such as isosulfan or patent blue are less readily available and have a higher risk of allergy<sup>4</sup>. Propofol is also easily visualized, but was unacceptable due to the severe hemodynamic instability of the patient.

### **Conclusion**

We describe a case of a successful resuscitation and surgical treatment for central line erosion presenting with hemorrhagic shock. The use of methylene blue to identify the culprit catheter was an important tool that contributed to the efficient management of this life-threatening event.

### **References**

1. Mukau L, Talamini MA, Sitzmann JV. Risk factors for central venous catheter-related vascular erosions. *J Parenter Enteral Nutr* 1991; 15: 513–516.
2. Duntley P, Siever J, Korwes ML, Harpel K, Heffner JE. Vascular erosion by central venous catheters. Clinical features and outcome. *Chest* 1992; 101:1633-1638
3. Gravenstein N, Blackshear RH: In vitro evaluation of relative perforating potential of central venous catheters: Comparison of materials, selected models, number of lumens, and angles of incidence to simulated membrane. *J Clin Monit* 7:1-6
4. Bezu C, Coutant C, Salengro A, Darai E, Rouzier R, Uzan S. Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surgical Oncology* 2011 20(1):e55-9. Epub 2010

**SYSTEMIC ADMINISTRATION OF ULTRA-LOW DOSE ALPHA<sub>2</sub>-ADRENERGIC ANTAGONISTS  
ATIPAMEZOLE AND EFAROXAN ENHANCE MORPHINE ANALGESIA AND REDUCE THE  
DEVELOPMENT OF TOLERANCE FOLLOWING NERVE INJURY**

P Grenier (1), B Milne (2), CM Cahill (1,2,3). (1) Department of Biomedical & Molecular Sciences, (2) Department of Anesthesiology, and (3) Centre for Neuroscience Studies, Queen's University

**Introduction:** Development of analgesic tolerance to opioids and decreased efficacy are significant problems in the treatment of chronic pain states. Previous studies have shown that administration of ultra-low dose (ULD) opioid antagonists paradoxically enhances morphine efficacy and attenuates the development of analgesic tolerance. This phenomenon has also been observed when opioids are co-administered with ULD alpha-adrenergic antagonists in pain naïve animals, but this has not previously been investigated in a model of neuropathic (NP) pain.

**Objective:** To investigate the effects of chronic systemic administration of ULD  $\alpha_2$ -adrenergic antagonists atipamezole and efaroxan on: 1) the development of chronic morphine tolerance in pain naïve animals. 2) the development of thermal hyperalgesia and mechanical allodynia following nerve injury. 3) acute morphine analgesia in sham and NP animals. 4) on chronic morphine tolerance following nerve injury.

**Methods:** To determine the effects of ULD  $\alpha_2$ -adrenergic antagonists on the development of opioid tolerance in pain naïve animals, male Sprague-Dawley rats were randomly assigned to groups receiving once daily subcutaneous injections of morphine (5mg/kg), morphine (5mg/kg) plus atipamezole (5ng), atipamezole alone (5ng) or saline vehicle. Thermal tail flick latencies were assessed on day one and day seven over a two hour time course to assess the effect of atipamezole on acute morphine tolerance. Tail flick latencies were also assessed daily, thirty and sixty minutes post-injection for seven days to assess the effect of atipamezole on development of chronic morphine tolerance. This study was repeated with ULD efaroxan (5ng) in place of atipamezole.

To determine the effect of ULD  $\alpha_2$ -adrenergic antagonists on acute morphine analgesia in a model of NP pain, separate rats were randomly assigned to one of two groups: sham or NP. NP pain was induced through chronic constriction injury (CCI) of the sciatic nerve. Half the animals in each group received once daily subcutaneous injections of ULD atipamezole (5ng) or saline for eleven days. Thermal and mechanical responses were assessed on days four, seven and ten post-surgery. Once pain hypersensitivity was established, a single injection of morphine (5mg/kg) was administered to all animals, and behaviour was assessed over a two hour time course to determine changes in acute opioid analgesia. This study was repeated with ULD efaroxan (5ng).

To determine the effects of chronic systemic ULD  $\alpha_2$ -adrenergic antagonists on chronic morphine tolerance following nerve injury, NP pain was induced in male Sprague-Dawley rats through chronic constriction injury (CCI) of the sciatic nerve. Half the animals received once daily subcutaneous injections of morphine (5mg/kg), while the other half received morphine *plus* ULD atipamezole (5ng) for ten days following nerve injury. A separate group of animals was used to test ULD efaroxan (5ng). Behavioural responses were assessed at four, seven and ten days post-surgery by thermal tail flick assay and assessment of mechanical paw withdrawal thresholds by von Frey filaments.

**Results:** Opioid tolerance developed rapidly over the seven days in morphine-treated animals. In rats co-administered atipamezole, an approximate 30% attenuation of tolerance was observed compared to morphine alone. Neither atipamezole alone nor saline vehicle had any effect on tail flick latencies. Morphine co-administered with efaroxan significantly attenuated development of tolerance compared to morphine alone.

Development of mechanical allodynia was observed in CCI animals over the ten days following surgery, and was significantly attenuated by day ten in those receiving daily low-dose atipamezole compared to saline. No effect on thermal tail flick latencies was observed over the same period.

On day ten, a single acute injection of morphine restored mechanical withdrawal thresholds to pre-surgery baselines in the CCI animals. The duration of the anti-allodynic effects of morphine was significantly prolonged in the animals that had been chronically treated with atipamezole compared to saline. The same effects were observed with efaroxan. Similarly, following the acute morphine injection, the thermal anti-nociceptive effects were prolonged in the CCI animals treated with atipamezole compared to saline controls.

NP animals that had been chronically co-administered ULD atipamezole (5ng) along with morphine experienced enhanced and prolonged thermal and mechanical analgesia compared to those that had been treated chronically with morphine alone. Animals co-treated with ULD atipamezole were still experiencing significant analgesia two hours post-injection following ten days of chronic treatment while the morphine alone group were not. The same effects were observed with ULD efaroxan in the mechanical but not thermal testing.

**Conclusion:** These studies provide strong evidence that ULD  $\alpha$ -adrenergic antagonists may one day prove clinically effective in enhancing opioid analgesia and reducing development of tolerance.



## ASSESSING CHANGES IN OPIOID AND NORADRENERGIC INTERACTIONS IN NERVE-INJURED RATS USING THE CONDITIONED PLACE PREFERENCE PARADIGM

P Grenier, T Stephens, CM Cahill. Department of Biomedical & Molecular Sciences, Queen's University

**Introduction:** Neuropathic (NP) pain is not only characterized as a disruption in sensory responses, but there is a significant ongoing, negative affective or emotional component as well. Two important neurotransmitter systems involved in pain modulation include the opioid and noradrenergic systems and cross-modulation between these systems impacts sensory responses and perception of pain. Following nerve injury, opioid and noradrenergic receptor expression and activity can be significantly altered. Recent studies in our lab have shown that compared to sham animals, in NP rats systemic morphine potency to produce a conditioned place preference (CPP) is increased, whereby a CPP can be induced in NP animals but not in shams at the same dose (2mg/kg), suggesting the preference may be a result of pain relief and not reward associated with opioid administration (Cahill et al., 2013). Surprisingly, acute intrathecal administration of the alpha2-adrenergic agonist clonidine (13µg) on the post-conditioning day appears to not only abolish morphine CPP in nerve-injured rats, but is actually aversive in these animals. Why this aversion is observed is not known, nor is it known if a similar aversion is also observed following a cocaine CPP.

**Aims:** 1) to determine if this clonidine-induced aversion from the morphine-paired compartment was a result of increased pain or withdrawal. 2) To determine if the clonidine-induced aversion to the drug-paired compartment is also observed following a cocaine CPP.

**Methods:** NP pain was induced by chronic constriction injury (CCI) of the sciatic nerve of the hind paw. Sham animals received a similar surgery, but without nerve manipulation or ligation. Animals were left to recover for seven days before the start of the CPP paradigm.

Using a balanced, unbiased CPP paradigm, sham and NP animals were conditioned with morphine (2mg/kg, subcutaneous) every other day for eight days. A separate group of sham and NP animals were conditioned with cocaine (5mg/kg, i.p.) every other day for eight days. On the post-conditioning day, all animals received a single acute intrathecal injection of clonidine (13µg) and were placed in their respective boxes for thirty minutes to assess if there were any changes in compartment preference. 24 hours later, a second day of post-conditioning was performed where the morphine CPP animals were given another morphine injection, and the cocaine CPP animals were given another cocaine injection to determine if compartment preference still existed (state-dependent testing).

In *separate* groups of animals, following eight days of morphine CPP conditioning, sensory and withdrawal testing was performed. Using von Frey filaments, mechanical withdrawal thresholds were assessed following clonidine administration to determine if clonidine-induced aversion to the morphine-paired compartment was due to increased pain. To determine if clonidine was perhaps causing aversion due to some type of withdrawal state all animals were administered a subcutaneous injection of naloxone (1mg/kg) on what would be their post-conditioning day. Half of the animals then received an injection of clonidine (13µg, i.t.) or saline under isoflurane anesthesia and assessed for withdrawal behaviour, including locomotion, vocalization, piloerection, rearing, urination and defecation.

**Results:** There were no significant differences between the drug- and saline-paired compartments in NP or sham animals following either morphine or cocaine conditioning after intrathecal clonidine administration on the post-conditioning day. However, morphine *was* able to produce a state-dependent preference to the drug-paired compartment, while cocaine was not. Acute intrathecal clonidine administration following eight days of morphine conditioning was able to attenuate mechanical allodynia in the ipsilateral hindpaw of NP animals. Following intrathecal clonidine administration, however, an increase in piloerection and urination was observed, along with a decrease in locomotion and rearing responses.

**Discussion:** It appears that perhaps the cocaine dose that was used may have been too low to produce a CPP and further studies to determine an optimal dose will need to be performed in order to determine if there are differences between the morphine and cocaine CPP groups. Because mechanical allodynia was attenuated following clonidine administration, any aversion from the morphine-paired compartment could not be a result of increased pain responses. While some withdrawal behaviour appeared to be increased following clonidine administration, some appeared to be decreased. While it cannot be said that the clonidine-induced aversion to the morphine-paired compartment is a direct result of withdrawal in those animals, a closer inspection of spinal, supraspinal and brain regions associated with the observed behavioural changes could give a better understanding of how these systems are being altered. Understanding changes in opioid and noradrenergic systems following nerve injury and how these systems are able to modulate each other could one day lead to novel treatments of NP pain states.

## The Economics of Anesthesia Drug Wastage

Investigators: Dr. Y. Hayat, Dr. R. Tanzola, Dr. R. Rooney, Dr. Dale Engen

**Background:** Soaring health care costs and budgetary deficits at federal and provincial levels led to increased economic pressure on hospitals and their medical departments, including Anesthesiology, to lower their costs and justify expenditures. Anesthetic drugs are a major variable cost for the department. Last year OR anesthetic drug expenditure at KGH was approximately ½ million dollars. Recent critical shortage of intravenous anesthetic agents further necessitated the need to quantify drug wastage and develop drug conservation strategies.

Gillerman et. al., using a mathematical model, estimated the cost of anesthetic drug wastage to be 26% of an Anesthesiology department's total drug expenditure. At KGH, this wastage could be approximately \$125,000. Weinger calculated per case wastage cost of US \$ 13.51, identified potential cost saving of \$10-\$15 per case and estimated potential aggregate annual savings of US \$250-\$350 million in the USA. Wagner et al. used regularly drawn drugs (epinephrine, ephedrine, lidocaine, atropine and succinylcholine) and estimated total savings of \$ 66,000 per year in a tertiary care hospital.

However, none of these studies have directly quantified the amount of total drug wastage. Therefore, the purpose of our study was to quantify financial cost associated with anesthetic drug wastage using actual wasted quantities.

### Hypothesis:

At least twenty five percent of the anesthetic drugs are wasted on a given day

### Objective:

To quantify the magnitude of the anesthetic drugs wastage

To identify the most commonly wasted drugs

To suggest strategies to improve anesthetic drug utilization

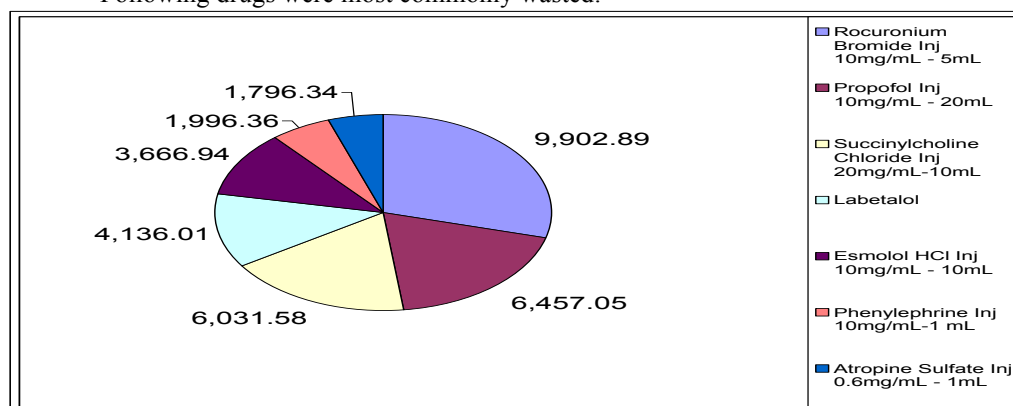
### Method:

Following institutional ethics approval, we carried out wasted anesthetic drugs collection study for a two week period starting on January 30th 2012. All opened and incompletely used syringes and vials of anesthetic drugs were collected in clearly marked containers. Investigators went through the drug collection daily to record the quantities of the wasted drugs.

### Results:

Following represent minimum anesthetic drug wastage captured for the two week period, excluding controlled drugs, volatiles, oral and infrequently used anesthetic drugs. It is minimum drug wastage that was captured as some drugs from the operating rooms were likely discarded elsewhere and were missed from the study.

- Total projected cost of wasted intravenous anesthetic drugs was \$ 45,552
- Following drugs were most commonly wasted:



### Discussion:

This study quantified the magnitude of Anesthetic drug wastage. The three most commonly wasted medications were Rocuronium, Propofol, and Succinylcholine. The following strategies may help optimize drug utilization

- Have labeled syringes ready to draw drugs such as Atropine and Succinylcholine as oppose to routinely drawing them
- Draw smaller quantities and save remaining vials for later use if full quantity is not needed for a patient
- Carry stock of pre-mixed syringes of Ephedrine and Phenylephrine prepared by OR pharmacy
- Consider purchasing secure anesthetic drug dispensing & management system with option for the safe storage of pre-drawn unused syringes for later use and to ensure patient safety

### References:

1. Gillerman R G, Browning R A: Drug Use Inefficiency: A Hidden Source of Wasted Health Care Dollars, *Anesthesia & Analgesia* 2000; 91:921-4
2. Weinger M B: Drug Wastage Contributes Significantly to the Cost of Routine Anesthesia Care, *Journal of Clinical Anesthesia* 13:491-497, 2001
3. Driver R P, et. al., Sterility of anesthetic and resuscitation drug syringes used in the obstetric operating room. *Anesth Analg* 1998; 86: 994-997
4. Wagner D S, et. al., Potency and sterility of anesthetic drugs in obstetric anesthesia. *International Journal of Obstetric Anesthesia* (2002) 11, 252-254

**Does the use of peri-operative gabapentin and pregabalin reduce opioid-related adverse-events?  
A systematic review.**

Darryl Hoffer, Ian Gilron, Elizabeth VanDenKerkhof

While we have come a long way in post-operative pain management, current treatments, namely opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and regional techniques, have limitations. Thus there is a need to identify, develop and evaluate new analgesic treatments for post-operative pain. Over the past 10-15 years, gabapentin and pregabalin have emerged as novel candidate drugs which could be useful in the treatment of post-operative pain.

Systematic reviews have demonstrated efficacy of gabapentin and pregabalin in reduction of standardized pain scores and opioid requirements when used peri-operatively. A key concept to consider is whether a decrease in opioid consumption correlates with a decrease in opioid-related adverse effects. In a meta-analysis, Marret et al 2005 found that a 30% opioid sparing from peri-operative NSAID administration resulted in a 30% reduction in post-operative nausea, vomiting and sedation. No such review has been done for gabapentin or pregabalin in post-operative pain.

We propose to conduct a systematic review to evaluate the effect of peri-operative gabapentin and pregabalin administration on opioid adverse events in patients treated with post-operative opioids. Articles to be included will be double-blinded randomized controlled trials, comparing gabapentin or pregabalin to placebo. Studies must be of major surgery that necessitated post-operative opioid administration. We will exclude studies that included children, regional techniques, need for mechanical ventilation during first 24 hours postoperatively, and studies with less than 24 hours of follow up. We will search articles in MEDLINE, Cochrane, EMBASE.

Our primary outcomes will be the incidence of opioid-related adverse events, and opioid consumption at various timepoints post-operatively. Secondary endpoints will be pain scores and other adverse events related to gabapentin and pregabalin. Our primary analysis will be a linear regression of the incidence of opioid adverse events versus opioid consumption. Subgroup analyses will be done according to surgical procedure, presence or absence of intraoperative opioid administration, presence or absence of intraoperative reversal of muscle relaxant, and by known risk factors for post-operative nausea and vomiting.

**Measurement of cardiac output with the ultrasonic cardiac output monitor  
versus transthoracic echocardiography**

Karmen KROL, MD, PhD; Supervisors: Drs. John Murdoch and Mike McMullen

Reliable perioperative measurements of cardiac output (CO) have been achievable mainly with invasive modalities like pulmonary artery catheters, and transesophageal echocardiographic methods. Non-invasive and non-continuous modalities such as transthoracic echocardiography (TTE) are impractical intraoperatively, given surgical needs for patient positioning, and limited precordial exposure or access. Given the invasive nature of gold standard methods of measuring CO, their regular use in the operating room is correctly reserved for clear indications in order to defend the risk-benefit profile for the patients. However, CO monitoring has a great deal of utility in the perioperative hemodynamic management of any patient with a tenuous cardiovascular status. The Ultrasonic Cardiac Output Monitor (USCOM) is a completely non-invasive, handheld device designed to provide beat-to-beat measures cardiac output and related parameters. It has been clinically validated perioperatively in the hemodynamic management of adults and children. We here propose a pilot study to investigate the fidelity of USCOM for measuring cardiac output in patients undergoing elective lower extremity orthopedic procedures under spinal anesthesia. USCOM data will be compared with TTE data (obtained by experienced cardiac anesthesiologists, blinded to USCOM findings) for patients prior to and following the induction of spinal anesthesia for their procedure. CO will again be measured at clinically important intraoperative periods (eg, reaming; pressurizing cement) and in the recovery room. It is anticipated that USCOM will provide measures of cardiac function that are congruent with TTE; findings from this study are expected to inform further trials using USCOM to help guide perioperative goal-directed therapy.

## Glycosylated Hemoglobin screening for elective surgical patients

Yuri Koumpan, Janet van Vlymen, Elizabeth VanDenKerkhof

**Introduction:** Uncontrolled blood glucose levels in the perioperative period are associated with a higher incidence of surgical site infections, greater utilization of resources, and increased mortality. These outcomes are modifiable with improved blood glucose control. However, preoperative screening for diabetes in elective surgical patients is not routinely done. The objective of this study was to determine 1) the incidence of elevated glycosylated hemoglobin (HbA1c) in patients with no previous history of diabetes; 2) the adequacy of recent glycemic control among diabetic patients; and 3) the validity of random blood sugar (RBS) and fasting blood sugar (FBS) (using HbA1c as the gold standard) to identify patients with sub-optimal glycemic control.

**Methods:** Following local ethics committee approval, 406 patients were enrolled in the study. All patients  $\geq 18$  presenting to the pre-surgical screening clinic in preparation for elective surgery were eligible. All participants completed a questionnaire to identify risk factors for diabetes and patients with a history of diabetes completed an additional questionnaire assessing their perceived level of glycemic control. HbA1c and RBS testing were completed in the clinic and FBS was done on the day of surgery. Frequencies and valid percentages were calculated.

**Results:** Of the 406 patients screened, 82% (n=334) had no history of diabetes and 18% (n=72) had a previous diagnosis of diabetes. Among patients with no previous diagnosis of diabetes, 23.1% (n=77) were considered to be at very high risk for diabetes (HbA1c= 6.0-6.4%) and 3.9% (n=13) had a provisional diagnosis of diabetes (HbA1c  $\geq 6.5\%$ ). The majority of diabetic patients, 60% (42/70), had sub-optimal glycemic control (HbA1c  $\geq 7.0$ ), 52% (n=22/42) of whom believed that their blood sugars were reasonably or very well controlled. For patients with a provisional diagnosis of diabetes (HbA1c  $\geq 6.5\%$ ), only 15% (n=2/13) had an elevated RBS ( $\geq 11.1$ ) while 67% (n=8/12) had an elevated FBS ( $\geq 7.0$ ) on the day of surgery. For the sub-optimally controlled diabetics (HbA1c  $\geq 7.0\%$ ), 42% (n=16/38) had an elevated RBS ( $\geq 11.1$ ) while 85% (n=33/39) had an elevated FBS ( $\geq 7.0$ ).

**Discussion:** There is a significant number of elective surgical patients not previously recognized to be at very high risk of diabetes. These patients are at considerable risk for unrecognized postoperative hyperglycemia and associated adverse outcomes. Among patients with a history of diabetes, the majority have sub-optimal glycemic control. Relative to HbA1c, RBS testing has limited value in identifying patients with poor glycemic control in pre-surgical screening. These results suggest that HbA1c may be a more appropriate test for the preoperative assessment of diabetic patients. Future study is needed to determine if HbA1c testing is a cost-effective screening tool for patients with no previous history of diabetes.

## **Determining the minimum angle of needle angulation towards the midline while placing thoracic epidurals using the classic paramedian approach, a pilot study**

Mahmoud Labib PGY2

Supervisor: Dr. Ronald Seegobin

### **Background**

Thoracic epidurals offer an effective post operative analgesia in major abdominal and thoracic surgeries. Success rates are variable as is the time taken for catheter placement. Any aids to maximizing success rate and minimizing insertion time would be useful. Reaching the epidural space is technically more challenging for thoracic epidurals than for lumbar epidurals. The acute caudal angulation of the spinous process, especially at the high-thoracic spine, makes the midline approach more difficult. The classic paramedian approach is favored by many clinicians for thoracic epidurals.

Determining the minimum angle of needle angulation to midline could be challenging and is vital for reaching the interlaminar space. The angle quoted in the literature is 10-24 degrees. However, to our knowledge, no one has used spine imaging of any modality to measure this angle. Visualisation of a digital model immediately prior to or during needle /catheter placement and a review of the optimal angle of needle approach may be of value.

### **Objective**

1. Generate digital 3D models of the spine developed from an age related archive of CT scans at the KGH.
2. Determine the minimum degrees of needle angulation towards the midline to reach the interlaminar space in the classic paramedian thoracic epidurals.

### **Methods**

For our pilot study, we plan to use forty subjects. Twenty males and twenty females, both with ages 18-30 years old. We will examine six vertebrae for each subject, T4-T9, a total of 240 vertebrae. The CT would have been done originally for abdominal/pelvis pathology rather than spine pathology. This will help us exclude obvious or subtle spine pathology that may effects our results. Subjects with obvious spine abnormality will be excluded and replaced to adhere to our sample size. The CT images of the abdomen/pelvis will be extracted and formatted into the spine protocol then volume-rendered. After determining the orientation of the 3D spine in space which allows sufficient visualization of the interlaminar space, the angle in question will be measured:

A horizontal line (A) will be drawn from the mid tip of the spinous process and to the right parallel to the coronal plane. This will be the presumed insertion site used by most clinicians. A second line (B) will be drawn from the end of line A and into the transverse plane (posterior to anterior) reaching the most superior aspect of the lamina. Line B, can be thought of as the virtual Touhy, will then be incrementally angulated towards the sagittal plane till the obstructing bony structures to the right are cleared, and a clear path is established between the insertion point and the interlaminar space. The minimum angle to achieve an unobstructed path to the interlaminar space will be recorded.

## Elevated Intra-Cranial Pressure During Long-Duration Space Flight

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### Introduction

The majority of astronauts experience changes in cerebral fluid dynamics exemplified via facial plethora, vestibular disorientation (space adaptation syndrome) and ocular permutations. Recently it has been suggested that microgravity exposure may also induce elevations in intra-cranial pressure. Preliminary studies have indicated that a surrogate for intra-cranial pressure (intraocular pressure) is positively correlated with duration of microgravity exposure. As future human space exploration shifts from short-term flights to long duration missions, mitigating the risk of elevated intra-cranial pressure becomes paramount.

Terrestrially, elevated intra-cranial pressure is associated with headache, vertigo, nausea, decreased mental capacity, respiratory depression and death. Currently, the mechanisms of microgravity-associated intra-cranial pressure elevation are poorly understood. The goal of the present study was to review the literature regarding microgravity associated changes in intra-cranial pressure, develop non-invasive means of evaluating intra-cranial pressure and devise future studies to elucidate the specific molecular pathways of altered cerebral fluid dynamics in space-fairing individuals.

### Findings

A retrospective analysis of diopter change in astronauts suggested that ~30% of individuals on short-duration missions (4-15 days) and ~60% on long-duration missions experienced noticeable changes in vision. Following numerous investigations of non-invasive measurements of altered intra-cranial fluid dynamics, an intra-orbit ultrasound globe analysis along with terrestrial lumbar opening pressure and MRI scans were performed. A group of 7 long-duration astronauts aboard the International Space Station were found to have evidence of increased intra-cranial pressure using both intra-orbit ultrasound analysis and terrestrial investigations. These findings included orbital disc edema, tortuosity of ophthalmic nerve, flattening of globe and papilledema. Opening pressures in 4 of these astronauts illustrated increased intra-cranial pressures (>20 cm H<sub>2</sub>O) for a duration of up to 18 months post-flight. Further more, preliminary trials of a cardiac-gated MRI scan protocol were performed to measure intra-cranial compliance and determine intra-cranial pressure. These initial studies indicated great promise in providing a non-invasive means of determining pre- and post-flight intra-cranial pressure.

### Conclusion

Space-fairing individuals have a dramatically increased risk of altered homeostatic regulation of intra-cranial pressure. We have been able to develop numerous terrestrial and orbital means of non-invasively determining intra-cranial pressure. Future studies evaluating the potential mechanisms of altered cerebral fluid dynamics including fluid shifts related to weightlessness, elevated partial pressure of carbon dioxide and high-energy radiation are required to further elucidate this homeostatic dysregulation.

**Sex differences in chronic pain description, self-management, and satisfaction with ability to control pain.**

E.G. Mann RN MSc, E.G. VanDenKerkhof RN DrPH, M.B. Harrison RN PhD,  
& S. LeFort RN PhD

Problem: Little is known about men's experience of living with chronic pain. This study compared men and women on pain characteristics, medical and emotional self-management, and satisfaction with ability to control pain.

Methods: This study is a secondary analysis of a recent cross-sectional survey on chronic pain in the general population of Canada. Respondents were screened for chronic pain with two questions: "are you currently troubled by pain or discomfort, either all of the time or on and off?" and "have you had this pain or discomfort for more than 3 months?" Respondents completed the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale, Level of Expressed Need scale, Brief COPE, body diagram, and rated satisfaction with ability to control pain.

Results: Of the 740 participants reporting chronic pain, 375 were male (51%) and 365 were female (49%). Men and women described their pain in a similar way, however men were twice as likely to report no treatments/prescriptions for pain (relative risk [RR]= 2.10, 95% confidence interval [CI] 1.40-3.16) and 34% less likely to report complete satisfaction with their ability to control pain (RR=0.66, CI 0.48-0.89). There was no difference between men and women in use of acceptance (RR=0.94, CI=0.88-1.01) or denial (RR=0.74, CI=0.49-1.12) to manage the stress of living with pain.

Conclusions: Although pain characteristics are similar, men and women report different pain self-management experiences. Clinicians should consider these sex differences when discussing and recommending pain management options. Further research is needed to explore the interaction between sex and satisfaction with pain control.



## **Medical Self-Management of Neuropathic Versus Nociceptive Pain: Is There a Difference?**

E.G. Mann RN MSc, E.G. VanDenKerkhof RN DrPH, M.B. Harrison RN PhD,  
& S. LeFort RN PhD

**Problem:** Individuals with neuropathic and nociceptive pain report unique pain experiences. This study explored the medical management strategies used by individuals with chronic pain with and without neuropathic characteristics (NC).

**Methods:** This analysis was based on a subset of participants in a recently completed cross-sectional survey on chronic pain in the general population of Canada. Respondents were identified as having (1) chronic pain if they reported pain for more than three months, and (2) NC if they scored 12 or greater on the Self-Report Leeds Assessment of Neuropathic Signs and Symptoms Pain Scale. Data collection included the Health Care Utilization & Medication Use Questionnaire, and Level of Expressed Need Scale.

**Results:** One hundred and eighty-eight participants screened positive NC (26.5%) and 522 respondents screened negative (73.5%). Individuals in both groups identified family doctors as their most helpful pain management clinician, however individuals with NC were more likely to report five or more visits in the past 12 months (Relative risk [RR] 1.7, 95% confidence interval [CI] 1.3-2.3). Individuals with NC were less likely to both manage their pain solely with non-pharmaceutical interventions (RR 0.4, CI 0.2-0.8), and to report complete satisfaction with ability to control pain (RR 0.5, CI 0.3-0.9).

**Conclusions:** Differences exist in the medical self-management of chronic pain with and without NC. Further research is necessary to identify and test pharmacological and non-pharmacological approaches specific to the management of NC.

**Update:** The Effect of Intraoperative Labetalol on Time to Discharge and Hemodynamic Stability in Laparoscopic Cholecystectomy

**Investigators:** Judith Marois, Rob Tanzola, Dale Engen, Elizabeth VanDenKerkhof

**Background:** Surgical stimuli such as incisional pain or pneumoperitoneum from abdominal insufflation, can provoke increases in intraoperative heart rate (HR) and blood pressure (BP). These increases in HR and BP are thought to be indicative of pain and are often treated with opioids such as fentanyl. Pneumoperitoneum alters hemodynamic stability by rapidly increasing HR, BP, as well as systemic and central venous pressure. These changes are partially due to acute autonomic/sympathoadrenal responses. It has been shown that pneumoperitoneum (and the applied CO<sub>2</sub> in particular) evoked sympathoadrenal responses only in patients who received intraoperative opioids but not esmolol. These data suggest that intraoperative beta-blockade may be superior for the management of hemodynamic changes associated with abdominal insufflation as required for laparoscopic cholecystectomy. Several studies indicate that intraoperative esmolol administration may also be associated with reduced opioid consumption, improved analgesia, reduced PONV, expedited patient recovery and a reduced time to discharge following laparoscopic cholecystectomy. Labetalol has a mode of action similar to esmolol but is cheaper, easier to administer, and clinical experience would suggest that labetalol may be more effective than esmolol for hemodynamic control.

**Purpose/Hypothesis:** The purpose of the current investigation is to assess whether labetalol and esmolol compared to fentanyl provide sufficient hemodynamic control during laparoscopic cholecystectomy; whether they have opioid-sparing effects; and whether they result in decreased side effects and reduced time to discharge from PACU. The current investigation examines the efficacy of labetalol which clinical experience may suggest is superior to esmolol for hemodynamic control. We hypothesize that labetalol will be *at least* as effective as esmolol for hemodynamic control; will reduce the length of stay in PACU and will reduce time to discharge.

**Outcomes:** The primary outcome will be the time from arrival in PACU until readiness to discharge from PACU. Secondary outcomes will include intraoperative hemodynamics measured by HR, mean arterial pressure (MAP), systolic BP and diastolic BP, incidence and required treatment of PONV in PACU, pain scores in PACU as measured by the VAS (0-10), fentanyl used in PACU, fentanyl, labetalol, and esmolol administered intraoperatively. Participants will receive a 24 hour follow-up phone call inquiring as to pain scores, analgesics used, satisfaction with postoperative care, and adverse events.

**Study Design:** Following signed informed consent, patients presenting for ambulatory laparoscopic gallbladder surgery will be randomly assigned to one of 3 groups: 1) will receive intravenous (iv) fentanyl bolus 50 mcg q5minutes; 2) will receive iv labetalol (bolus 5mg q5minutes) and 3) will receive iv esmolol (bolus 0.25mg/kg then titrated infusion 5-15mcg/kg/min) for intraoperative hemodynamic control if necessary. Participants will be monitored until discharge for the outcome measures.

**Update:** This prospective, randomized, double-blinded clinical trial has been approved by the Queen's University and Affiliated Teaching Hospitals' Research Ethics Board. It is currently underway with 17 patients recruited so far. We anticipate completion of data collection within 2.5 years.

**Ultra-low dose opioid antagonists modulate opioid tolerance and hyperalgesia via distinct mechanisms that are Toll-like receptor 4-independent.**

**Authors:** T.A. Mattioli, G. Skelhorne-Gross, C.J.B. Nicol, B. Milne, C.M. Cahill

Ultra-low doses (ULD) of the opioid receptor antagonists, naloxone and naltrexone, augment the analgesic actions of morphine, block the induction of tolerance, and reverse established tolerance by an unknown mechanism. Preclinical studies demonstrate that chronic morphine administration induces spinal gliosis and that inhibition of gliosis prevents the development of analgesic tolerance to opioids. Activation of glial Toll-like receptor-4 (TLR4) induces gliosis and may contribute to analgesic tolerance and/or opioid-induced hyperalgesia. Antagonism of TLR4 by the opioid receptor-inactive (+) stereoisomer of naloxone was identified as a potential mechanism by which ULD antagonists modulate opioid analgesia. Thus, naloxone enantiomers were used to determine if ULD naloxone stereoselectively attenuates tolerance to chronic morphine and opioid-induced hyperalgesia via an opioid receptor-mediated mechanism. The involvement of TLR4 in acute morphine analgesia, tolerance to chronic morphine, and opioid-induced hyperalgesia, was also evaluated using genetically mutated mice (C3H/HeJ) in which TLR4 is non-functional.

Acute morphine-induced analgesia was not augmented in the TLR4-mutant mice compared to wild type (C3H/HeOuJ) controls. Chronic morphine treatment (10mg/kg i.p., once daily) resulted in significant loss of analgesia after 5 days of treatment in both genotypes, indicating functional TLR4 was not required for the development of tolerance. Similarly, opioid-induced hyperalgesia was evident in both mouse genotypes following chronic administration of escalating doses (10-40mg/kg, i.p. BID) of morphine. The development of analgesic tolerance to chronic morphine was blocked by ULD (-)naloxone (1ng/kg, i.p.), but not (+)naloxone; however, both isomers blocked the up-regulation of CD11b and glial fibrillary acid protein (GFAP) mRNA expression in the dorsal lumbar spinal cord. Interestingly, ULD naloxone non-stereoselectively blocked opioid-induced hyperalgesia induction in both TLR4-mutant and wild type mice.

Collectively, these studies demonstrate analgesic tolerance and opioid-induced hyperalgesia occur through distinct mechanisms. ULD naloxone attenuates analgesic tolerance likely via an opioid receptor-mediated mechanism that is TLR4-independent. ULD antagonists do not attenuate tolerance via inhibition of spinal gliosis as hypothesized. In contrast, ULD antagonists prevent opioid-induced hyperalgesia by inhibiting opioid-induced gliosis in an opioid receptor- and TLR4-independent manner.

## **A Survey of Scope of Practice in Family Medicine Anesthesia** **Dr. Nicole McFadden, Dr. Cummings, Dr. Mahoney.**

*Thanks to Dr. Chris Richardson*

### **Background**

Current trends in healthcare provision involve specialized training and resources only available in tertiary centers. It is not practical, however, for all surgical, anesthesia, and obstetric services to be provided by specialists in referral centers. Many of these services can safely be provided in smaller hospitals, keeping wait lists more manageable and allowing local access to healthcare for more Canadians<sup>1</sup>. For many years these services have been provided by family physicians with additional training in anesthesia. Currently, however, there are few national regulations for family practice anesthesia. There is no standardized national curriculum and no end-of-training examination. There is no assessment of competence process for physicians trained outside of Canada. There are no requirements for continuing medical education and a lack of relevant CME opportunities. It is well recognized that FPAs help maintain a higher standard of healthcare in many underserved areas by providing emergency, surgical, and obstetric services as well as special skills in airway management and resuscitation<sup>3</sup>. Without further advancements in their training, regulation, and support in practice, however, the sustainability of family practice anesthesia and the care they provide for thousands of Canadians is at risk.

### **Study Design**

We propose to survey current Family Practice Anesthetists (FPAs) about their scope of practice to provide valuable data on which to base further curriculum development, evaluation and assessment, and continuing education.

We will develop a survey to assess FPA scope of practice including questions on demographic information, site characteristics of the facilities they work in, scope of case work, airway management, technical skills, and CME. The survey will be evaluated by a research specialist in survey design to ensure it is well constructed. We will then create an online version for distribution electronically. We hope to obtain a comprehensive list of practicing FPAs and distribute the survey via email. Responses will be kept anonymous and electronically coded to ensure no duplication. After the deadline for survey completion, data will be analyzed to establish the scope of practice and range of variation across Canada.

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## **Prevalence And Patient Impact Of Chronic Post-Sternotomy Pain Following Coronary Artery Bypass Graft Surgery At A Canadian Tertiary Care Centre**

Daniel Mok, MD Candidate, Queen's University School of Medicine

**Introduction and Hypothesis:** Coronary artery bypass graft (CABG) surgery is a common surgical procedure with over 260,000 cases performed in the United States and Canada in 2005-2006. Chronic post-sternotomy pain is a common complication of CABG. This pain syndrome is often overlooked as a significant medical problem by many physicians and the literature remains controversial in terms of underlying causes and effective treatments. The present study aimed to estimate the prevalence of chronic post-sternotomy pain at a Canadian tertiary care centre, describe its distinctive pain characteristics, and highlight its impact on patients' lives after CABG surgery. We hypothesized that chronic post-sternotomy pain would affect at least 20% of patients and be associated with considerable interference with daily activities.

**Methods:** Following institutional ethics approval, patients who underwent CABG at a Canadian tertiary care centre in 2011 were contacted by telephone 6-18 months after their operation and asked to participate in a telephone-administered questionnaire. The questionnaire was composed of questions to identify chronic post-sternotomy pain, the Short-Form McGill Pain Questionnaire (SF-MPQ), Brief Pain Inventory – Interference (BPI-I) subscale, and questions on healthcare usage. For the purposes of this investigation, chronic post-sternotomy pain was defined as chest pain arising post-operatively at the surgical site which persists for at least 6 months and is different from pre-operative pain. Pain scores were reported on a numeric rating scale (0-10) and scores > 4 were considered to be in the moderate to severe range.

**Results:** Of the 100 patients who responded, 30% reported chronic post-sternotomy pain. Amongst those with chronic pain, 37% (11/30) reported their Worst Pain in the Last 24 Hours as being moderate to severe, while 50% (15/30) described their Pain When Moving to be moderate to severe. The majority of pain descriptors reported were in the Sensory category of the SF-MPQ. Over 30% of those with chronic pain reported moderate to severe interference with General Activity (9/30), Sleep (11/30), and Normal Work (12/30) yet 63% (19/30) did not seek medical attention from their primary care physician for pain. Additionally, 12% of all patients (12/100) described persistent post-saphenectomy pain, five of whom also reported concurrent chronic post-sternotomy pain.

**Conclusions:** Our findings indicate a high prevalence (30%) of chronic post-sternotomy pain after CABG at our tertiary care centre. Despite the considerable impact of pain on daily activities (as indicated by the BPI-I subscale), patients surprisingly tended not to seek medical attention to manage pain. Efforts to increase awareness of chronic post-sternotomy pain amongst patients undergoing CABG are needed and should include discussion of this complication during patient consent for the procedure. Future research should aim to address the gaps in knowledge regarding etiology, prevention, and treatment of chronic post-sternotomy pain.

## **Prolonged morphine treatment alters delta opioid receptor post-internalisation trafficking**

Edmund ONG, PhD Candidate, Queen's Biomedical & Molecular Sciences

The delta opioid receptor (DOR) undergoes internalisation both constitutively and in response to agonists. Previous work has shown DOR to traffic from intracellular compartments to neuronal cell membranes following prolonged morphine treatment. Here, we examined the effects of prolonged morphine treatment on the post-internalisation trafficking of DOR. Using primary cultures of dorsal root ganglia (DRG) neurons, we measured the co-localisation of endogenous DOR with post-endocytic compartments following both prolonged and acute agonist treatments. We first show a departure from the constitutive trafficking pathway following acute DOR agonist-induced internalisation by Deltorphan II. That is, DOR undergoes agonist-directed post-endocytic sorting. Second, we demonstrate an augmentation of constitutive DOR trafficking following prolonged morphine treatment. Third, we show an unmasking of DOR agonist-directed post-endocytic sorting by SNC80 following prolonged morphine treatment. Finally, we show that the mu opioid receptor agonist DAMGO induces DOR internalisation and trafficking following prolonged morphine. The results support the hypothesis that prolonged morphine treatment induces the formation of MOR-DOR interactions and subsequent augmentation of cell surface available DOR, at least some of which are in the form of a M/DOR species. Such a species appears to have pharmacology and trafficking unique from those of its individual constituents.

## Detection and Breakup of Potential Cerebral Air Emboli

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### Abstract

Neurological dysfunction ranging from stroke or coma to cognitive deficits that arise from open heart surgery is still among the most common negative outcomes after a successful operation [2]. Presently, there is no standardized method of detecting, quantifying or eliminating potential cerebral emboli. Annual studies have shown neurological dysfunction in 30-45% of all patients that undergo open heart surgery and a fatality rate up to 4% post cardiac surgery associated with cerebral emboli [1].

### DETECTS™

A prototype software has been designed that can identify and measure potential emboli. This patient pending software, appropriately named DETECTSTM (Detection of Emboli using Transesophageal Echocardiography for Counting, Total volume, and Size estimation) uses existing TEE technology to quantify the amount of potential emboli and displays this to the surgeon. A reliable software program that could quantify the potential air emboli could standardize deaeration techniques for all open heart cardiac surgeries.

### Bubble Breakup

The focus of this work is on the relationship between large band acoustic signals, surface oscillation and instabilities of collapsing bubbles (figure 1). We hypothesize that we will be able to collapse larger potential air emboli within the arterial system using acoustic methods to smaller (micro) potential emboli. These microbubbles should then theoretically travel harmlessly through the body until being absorbed into the blood. The non-intrusive breakup of air emboli would completely change the deaeration procedures set in place today.

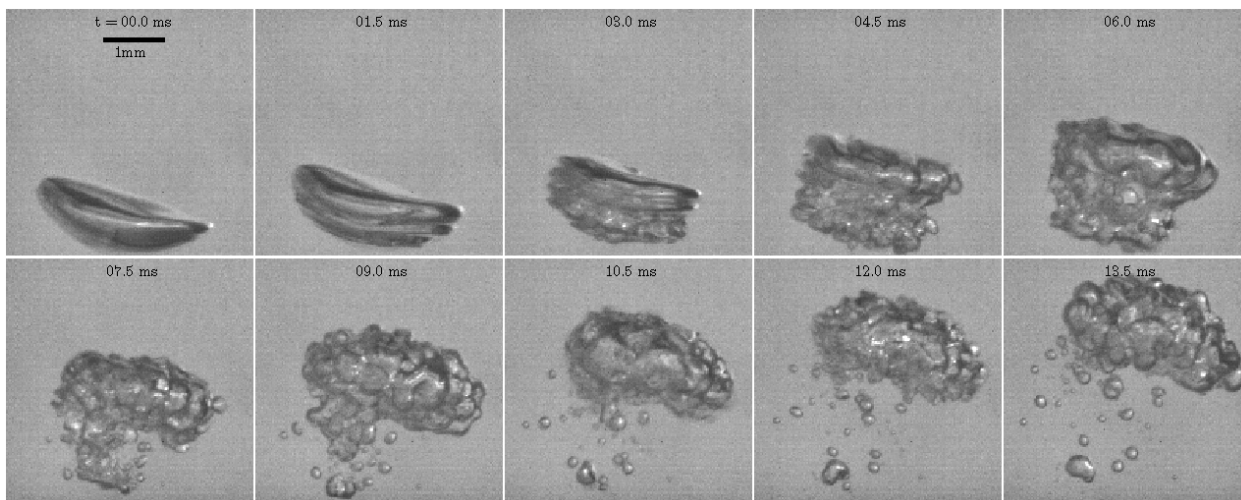


Figure 1: Bubble break-up evolution sequence with a 1.5 kHz acoustic signal captured at 10000 frames per second (fps) using a high speed camera; images displayed at 667 fps.

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## **Combination pharmacotherapy for the treatment of fibromyalgia**

Bonnie Shum, BSc, MD Candidate, Ian Gilron, MD, MSc, FRCPC,  
R. Andrew Moore, DPhil, Phil Wiffen, MSc, MRPharmS

### **Objectives:**

Fibromyalgia trial results suggest incomplete relief with single-agent pharmacotherapy due to limited efficacy and dose-limiting side effects. Evidence suggests that combination pharmacotherapy is a common clinical practice. Thus, the purpose of this review is to assess the efficacy, tolerability, and safety of the combination of two or more drugs for the treatment of fibromyalgia pain.

### **Methods:**

Double-blind, randomized controlled fibromyalgia trials evaluating combinations of two or more drugs compared to at least one other comparator were identified from CENTRAL, MEDLINE and EMBASE databases, and handsearches of other reviews. Primary outcomes include the proportion of patients reporting  $\geq 30\%$  pain reduction or  $\geq$  moderate relief. Secondary outcomes include adverse effects and trial drop-outs. The Cochrane risk of bias tool was applied to all included trials.

### **Preliminary results:**

We screened 193 records; nine studies met review criteria and 6 demonstrated superiority of the combination although results were not consistent for all reported outcomes. Eight studies demonstrated important sources of bias. Only one combination (alprazolam and ibuprofen) was evaluated by  $>1$  trial.

### **Conclusion:**

Evidence supporting polypharmacy in fibromyalgia is currently limited. This review serves to identify future research needs to better evaluate this important treatment strategy for patients suffering from fibromyalgia.



## **Electronic Records: Do they Improve Efficiency and Effectiveness of Outpatient Pre-Anesthesia Clinic Assessments?**

Vanessa Sweet, PGY2

Supervisor: Dr. David Goldstein

### **Background**

Demand for health care services is growing in a resource-limited environment. Measures are sought after which foster system efficiency and fiscal responsibility. Unanticipated delays or cancellations for surgical procedures are very costly to the health care system. Therefore, pre-operative optimization is an integral part of the surgical process. Within a pre-operative/pre-anesthetic clinic, we endeavor to determine if patients are fit for surgery, and to arrange for investigations or interventions required to optimize patients, ultimately allowing for optimal use of OR time and resources.

Key to this effort is the collection and dissemination of patient information. Our current information management system at Hotel Dieu Hospital (HDH) has evolved into a paper-digital compilation of patient information. There are redundancies in record keeping, and given that records are primarily paper-based, the anesthesiologist providing care on the day of surgery can often be faced with a record that has incomplete, inaccurate, or outdated information such as lab results, as well as illegibility of the anesthetic record. These issues do not enable efficiency, accuracy, accessibility, and value to the end user.

### **Purpose**

Electronic record keeping is evolving within health care. We believe that the use of an electronic pre-anesthetic record (eRecord) will optimize the flow of information from the clinic to the day-of surgery anesthesiologist. The purpose of this study is to determine whether the implementation of such a record will improve clinic efficiency, accuracy and accessibility of the information, and value of the consultation to the anesthesiologist on the day of surgery.

### **Hypotheses**

1. The implementation of an eRecord will improve the accuracy, accessibility, and value of information collected in pre-anesthesia clinic
2. The eRecord will decrease the amount of time patients spend at the pre-anesthesia clinic
3. The eRecord will improve clinic physician satisfaction

### **Methods**

In the current study, we propose the implementation of an eRecord at pre-anesthesia clinic at HDH. This will contain all information gathered at the clinic, and will automatically populate with the most current investigations available within the hospital's electronic records.

The study will be completed in two phases. Phase I will be an audit of the current paper-based information management system. During this phase, a survey will be placed in all anesthetic records completed at HDH PAC, to be completed by the anesthesiologist providing care on the day of surgery. The survey will assess the accuracy, accessibility, and value of information within the record on the day of surgery.

Phase II will involve the implementation of the eRecord at the HDH PAC for 50% of the clinics. The same survey from Phase I will accompany all of the eRecords, again to be completed by the anesthesiologist providing care on the day of surgery. We will assess for any differences in the accuracy, accessibility, and value of information between the paper record (Phase I) and eRecord (Phase II). The efficiency of the new system will be assessed during this phase by comparing eRecord clinics to paper-based clinics, looking specifically at 1) total patient time in clinic and 2) clinic physician satisfaction with the record keeping systems.

## Critical Appraisal

By: **James Cheng**, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine

Publication title: "*Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes.*"

Authors: *Doherty A, Ohashi Y, Downey K, Carvalho JC.*

**Anesth Analg. 2012 Dec;115(6):1343-50.**

### General:

1. Title: it does seem like an important question. The problem they are trying to solve may potentially change our practice. Since it is unclear which practice (bolus or infusion) is superior, answering this question may give us evidence to choose one practice over another.
2. The authors are Doherty et al. They are from the department of anesthesia from Mount Sinai Hospital, University of Toronto.

### Introduction:

1. The problem being addressed is whether phenylephrine is better given as repeated boluses or as a continuous infusion in patients undergoing elective C-Section under spinal anesthetics.
2. According to this article, both practices are clinically accepted. Currently, there's no evidence that one method is superior to the other.
3. The author's hypothesis is that the phenylephrine infusion will cause less of a deviation in the patient's cardiac output from her baseline than repeated boluses. The author does not give any reasons for this hypothesis.
4. This hypothesis does help to solve the problem. Obviously if the authors is proven correct, it may show evidence to support the use of an infusion versus giving repeated boluses.

### Methodology:

1. The study design is a prospective, experimental, randomized and double blinded study
2.
  - a. The population studied is human.
  - b. Obviously, this is the most appropriate population to study to look at the effects of different phenylephrine regimens in the patient undergoing elective C-Section under spinal anesthetic.

Phenylephrine has been in use for a long time and there's no control of drug safety in human populations

- c. There is no control group in this study as there is no group which receives placebo. Historically, we do know that spinal anesthetic can be associated with significant hemodynamic changes and phenylephrine is commonly used to mitigate these effects.
- d. Their sample size of a minimum 30 patients per study group who be sufficient for a 80% power to detect an absolute difference in cardiac output change of 1.2L/min
- e. The population studied is definitely similar to what I have seen in my practice so far.

3. This study is ethically sounds. It has been approved by the author's institutional ethics board. The experimental protocol has steps in place to prevent excessive drops in blood pressure to ensure patient safety.

4. The exclusion criteria for patients includes patient refusal, inability to communicate in English, allergy or hypersensitivity to phenylephrine, hypertension, cardiovascular or cerebrovascular disease, fetal abnormalities, diabetes (excluding gestational diabetes), or contraindication to spinal anesthesia. Most of these exclusion criteria are there because patients with these factors may have adversely affected during the study. The inclusion of inability to communicate in English is likely because it will make it difficult to assess for nausea.

5.
  - a. Yes the experimental protocol is designed to test the hypothesis.
  - b. The protocol is documented in detail and I believe is enough so that the experiment will be reproducible.
  - c. There was no mention of validation of the methodology in the paper.
  - d. The drugs and equipment used were detailed. They document the dosages and the concentrations of the medications used. They also describe the pumps, the syringes used and the how each was labeled.

- e. Randomization was performed using a randomized computer generated number table.
6. The primary endpoints are the patients change in their intraoperative cardiac output compared to their pre-operative baseline. Their cardiac output is measured non-invasively using BioReactance technology.
7. The protocol is clinically relevant. It mimics what clinicians would be during in the OR.
8. All patients on arrival to the OR had a baseline systolic blood pressure. Patient's CO and SV is measure by BioReactance continuous until 10 minutes after delivery. BP, HR, and pulse oximetry was measured every 1min. Patients were also told to let the anesthesiologist know when they feel nauseous during the surgery. With the continuous data for SV and CO, means and standard deviations were use to summarize the data.
9. Statistical analysis: the Student's t-tests were used for the analysis of the continuous factors. Fisher's exact tests were used for the categorical factors. I believe these are appropriate methods analyze for significant data.

## Results:

1. Both groups were comparable in terms of their baseline hemodynamic measurements, age, height, weight, nulliparas, and gestational age.
2. From the bolus group, 5 were excluded (2 requiring extra analgesia, 2 due to pump error, and 1 could not be calibrated properly). From the infusion group 4 were excluded (3 due to pump error, and 1 could not be calibrated properly).
3. Yes there are adequate details provided. There were tables and graphs in the article which details the result findings.

## Discussion:

1. The main conclusion from this study is that there is no statistically significant different in terms of CO control between the bolus and the infusion group, and that the hemodynamic effects of both regimens were similar.
2. The result of the study do support conclusion. There were no significant differences between changes in CO as well as other clinical endpoints between the 2 study groups.
3. The results do address the stated purpose.
4. Oddly enough, the authors do not really explain why there were similar results between the two groups. The authors simply said that their findings corresponded

to an earlier study by Ferguson. Ferguson's study found that comparable regimens for phenylephrine bolus or infusion could cause similar drops in HR. The other finding the authors noticed was that the systolic BP was better controlled in the first 6 minutes with bolus regimen compared with infusion. The reason that the author proposed is that with the bolus dose will deliver an effective dose quicker. As a result, there will be less fluctuation in the patients blood pressure.

5. I don't think there are any other alternative interpretations for the data.

6. As the author states, the results found are clinically significant. Between both study groups, the incidences of nausea or vomiting were the same. As well, the neonatal data collected seems to suggest that there is no difference in terms of fetal outcomes.

7. As previously mentioned, this study corresponds to an earlier study from Ferguson.

8. This result seems to suggest that in terms of clinical outcomes, both bolus vs infusion regimens can yield similar results. However, it is noted that the bolus regimen required less total phenylephrine to be administered. As well, they noted better control of systolic BP immediately after initiation of spinal anesthetic. As such, it would suggest that perhaps overall, the bolus method should be preferred.

9. One of the main limitations in this study is that the bioreactance technology has not been validated in pregnancy. The other limitation the study talks about is that the dosages used for phenylephrine is higher than other previous studies. As such, the results of this study may only be applicable to using phenylephrine at these dosages.

10. As the study alluded to, using different dosages for the boluses and infusions may yield different results. It would be interesting to see if higher infusion doses will make a difference in SBP control initially after spinal anesthetic as it will be delivering an effective dose quicker.

## Applicability of the paper:

1. I learnt about the physiology of behind spinal anesthetic and the effects of phenylephrine. I also learnt a little about bioreactance. I had never heard of this technology before. Finally, the paper's results showed that perhaps phenylephrine bolus should be the preferred method for BP control in patients with spinal anesthetics for elective C-section

2. I would not alter my practice. From what I've seen so far, most staff I have worked with use the bolus method to control BP. Even though this paper showed no clinical differences between the infusion method and the bolus method, I would still use the bolus method because it used less phenylephrine in total and seemed to have better SBP control initially after a spinal.

## Critical Appraisal

By: **Tanya Griffiths, MD, PhD, PGY-1, Queen's Anesthesiology & Perioperative Medicine**

**Publication title: "The Risks of Aprotinin and Tranexamic Acid in Cardiac Surgery: A One-Year Follow-Up of 1188 Consecutive Patients."**

**Authors: Klaus Martin, Gunther Wiesner, Tamas Breuer, Rudiger Lange, Peter Tassani.**

**Anesthesia & Analgesia. 2008; 107(6). 1783-1790.**

### Background

The risk of blood loss during cardiac surgery is high due to the use of anti-coagulants and platelet inhibitors as well as reoperation and post-operative bleeding. In addition, the exposure of the patient's blood to cardiopulmonary bypass causes a host of changes including increased capillary permeability and an upregulated inflammatory state with effects on the coagulation and fibrinolytic systems [1]. Antifibrinolytics such as aprotinin and tranexamic acid are administered by anesthesiologists during cardiac surgery to try and minimize blood loss and reduce the need for blood transfusions [2]. Over the past several years, debate has existed regarding the safety profile of aprotinin, as compared to tranexamic acid, when used in cardiac surgery. A well-known and much discussed multicenter blinded randomized trial, the Blood Conservation Using Antifibrinolytics in a Randomized Trial or BART study [3], compared high risk cardiac surgical patients who received aprotinin, tranexamic acid, or aminocaproic acid. The primary outcome in their study was massive postoperative bleeding and a secondary outcome included death from any cause at 30-days. The BART study was terminated early due to the higher rate of death in patients receiving aprotinin. The authors concluded that even though there was a "modest reduction in the risk of massive bleeding" with the use of aprotinin, "the strong and consistent negative mortality trend" should prevent its use in high-risk cardiac surgery [3]. The use of aprotinin was temporarily suspended in Canada in November 2007 based on the results of the BART study. However, after a review of the evidence, Health Canada advised that the benefits of aprotinin outweighed the risks when used for basic CABG surgery and the manufacturer, Bayer Inc., was permitted to resume production of aprotinin in September 2011. Aprotinin is not advised for use in complex, higher risk surgeries such as valve replacement/repair [4] and it is still largely withdrawn from the worldwide market (Canada excluded) due to evidence showing an increased risk of renal failure, cardiovascular events, and mortality [5].

Aprotinin and tranexamic acid are both involved in inhibition of fibrinolysis, although they work by different mechanisms. Aprotinin is a serine protease inhibitor that inhibits the coagulation, fibrinolytic, and inflammatory pathways by interfering with mediators such as thrombin, plasmin, and kallikrein [5]. Tranexamic acid, on the other hand, is a lysine analog that binds to plasminogen and blocks its ability to bind to lysine residues on fibrin, thus inhibiting fibrinolysis [2].

With the existing controversy and conflicting evidence about the safety and efficacy of different antifibrinolytics in different types of cardiac surgery, the authors of the current study aimed to "investigate postoperative complications and mortality after administration of aprotinin compared to tranexamic acid in an unselected, consecutive cohort." [6]

### Study Design

This single-centre, prospective consecutive cohort study observed adult patients undergoing cardiac/cardiovascular surgery at the German Heart Centre in Munich, Germany between September 2005 and June 2006. The study was approved by the Ethical Committee of the Technical University Munich. This institution was in a unique position to do a prospective consecutive cohort study: up until February 2006, aprotinin was used almost exclusively during cardiac surgery; after this time, in light of the safety concerns that were being raised about aprotinin, its use was completely stopped and tranexamic acid was instead exclusively used. The perioperative data of all patients undergoing cardiac/cardiovascular surgery with cardiopulmonary bypass in the specified time frame was analyzed (n=1239) and 27 cases were excluded due to no, multiple, or inadequate dose of antifibrinolytic used. Additionally, if a patient underwent reoperation for nonbleeding reasons during the same admission, only data from the first operation were included in the analysis; this resulted in another 24 cases being excluded leaving a study cohort of 1188 patients. The first study group consisted of all patients (n=596) in a five month period undergoing cardiac/cardiovascular surgery with cardiopulmonary bypass who were administered

aprotinin as the antifibrinolytic. The second study group consisted of all patients (n=592) in the following five month period undergoing cardiac/cardiovascular surgery with cardiopulmonary bypass who were administered tranexamic acid as the antifibrinolytic. The authors state that all aspects of surgical and anesthetic management were unchanged from previous once tranexamic acid was used exclusively in the place of aprotinin. Standard cardiopulmonary bypass settings were used. Inotrope and vasopressor therapy parameters were also specified by the authors.

Outcomes were based on blood loss, cardiac, renal, and neurological complications (Table 1), as well as 30-day and 1-year mortality. At 3- days and 1-year post surgery, all-cause mortality was assessed. There was primary and secondary loss, the former comprised of foreign patients who were primarily excluded from follow-up and the latter comprised of non-responders. The follow-up for mortality data was 96.5%.

**Table 1. Postoperative morbidity measurements (outcomes).**

Parameter measured	Method of measurement
Postoperative blood loss	Chest tube output at 6, 12, and 24 h after surgery
Requirement for transfusion	Amount of transfused allogenic blood products <sup>a</sup>
Reoperation for bleeding	Clinical diagnosis
Postoperative renal dysfunction	Serum creatinine level > 1.3 mg/dL with an increase over baseline of at least 0.5 mg/dL
Postoperative renal failure	Dysfunction requiring dialysis
New persistent atrial fibrillation	Clinical diagnosis
Acute myocardial infarction	New Q waves, persistent ST-segment or T-wave changes and CK-MB higher than three times the upper limit of normal
Heart failure	Need for inotropic support and intraaortic balloon pump
New seizure or stroke/transitory ischemic attack	Clinical diagnosis, stroke was confirmed by CT scan

<sup>a</sup>in this study, patients required a transfusion if the hematocrit dropped to less than 18% while on cardiopulmonary bypass and/or less than 24% during the postoperative course or if the patient had clinical signs of hypoxemia

In addition to the numerous outcome and mortality endpoints, the cohorts were analyzed together (ALL) as well as stratified for a post hoc analysis based on what type of cardiac/cardiovascular surgery they were having. The subgroups were: (i) primary CABG (CABG), (ii) primary valve surgery (i.e. mitral and/or aortic) (VALVE), and (iii) high risk surgery (e.g. combined and redo operations, aortic surgery, transplantation) (HIGH RISK). The study was appropriately powered (80%) in all the subgroups.

Numerous statistical analyses were performed including the Mann-Whitney U-test for continuous variables, the

$\chi^2$  test for categorical variables, and Kaplan-Meier analysis and Mantel-Cox log-rank test for mortality differences. Significance was considered as a P value <0.05.

The experimental protocol, drugs, and equipment descriptions are certainly detailed enough to be reproducible and the methodology is valid, but there was no hypothesis proposed in their study objective. The authors appear to be surveying a large number of outcomes (based on previous literature) and mortality with the hopes of attributing observed differences to treatment with aprotinin or tranexamic acid.

## Results

As described in the study design, analyses were performed on patients undergoing all types of cardiac/cardiovascular surgery (ALL) and on the subgroups CABG, VALVE and HIGH RISK. The number of patients undergoing each type of surgery was

comparable between the tranexamic acid and aprotinin groups (Table 2), although no statistical analysis was performed on this data, only the raw numbers were presented.

**Table 2. Subgroups of cardiac/cardiovascular surgery in the study cohort.**

Operation type	Tranexamic acid (n=592)	Aprotinin (n=596)
CABG	250	258
VALVE	165	172
HIGH RISK	177	166

Preoperative and operative data. Of the preoperative (i.e. demographics, medical history, risk profile, preoperative medication, preoperative laboratory values) and operative data collected, the only significant difference within the entire cohort was that more patients were taking clopidogrel in the group who received aprotinin (tranexamic acid: 15.2% of patients, aprotinin: 19.6% of patients,  $P=0.044$ ). Some statistically significant differences were found in the post hoc subgroup analysis for preoperative and operative data, but will not be presented here.

The postoperative morbidity data (Table 1) was analyzed for the entire cohort (ALL) as well as for the CABG, VALVE, and HIGH RISK subgroups.

Blood loss. In ALL patients as well as the three subgroups, blood loss was significantly less in the group who received aprotinin and the requirement for

postoperative RBC and FFP transfusions was significantly decreased in ALL patients as well as the VALVE subgroup who received aprotinin. Therefore, aprotinin appeared to have a significant effect on reduction of postoperative bleeding and the requirement for blood products.

Renal, cardiac, and neurologic outcomes. An analysis of ALL patients as well as analysis of the subgroups demonstrated that renal dysfunction/failure, persistent new atrial fibrillation, acute myocardial infarction, and seizures were the comorbidities that were found to be significantly different depending on whether the patients received aprotinin or tranexamic acid (Table 3). Aprotinin was associated with a significantly higher incidence of renal dysfunction and acute myocardial infarctions while tranexamic acid was associated with a significantly higher incidence of renal failure, persistent new atrial fibrillation, and seizure.

**Table 3. Outcome data with significant findings, presented as incidence and ( $P$  value).**

Outcome	Tranexamic acid				Aprotinin			
	ALL	CABG	VALVE	HIGH RISK	ALL	CABG	VALVE	HIGH RISK
Renal dysfunction	NS <sup>a</sup>	15.2%	NS	NS	NS	22.5% (0.036)	NS	NS
Renal failure	NS	NS	9.7% (0.002)	NS	NS	NS	1.7%	NS
Persistent new atrial fibrillation	5.7% (0.022)	NS	7.9% (0.020)	NS	3.0%	NS	2.3%	NS
Acute myocardial infarction	2.2%	2.0%	NS	NS	4.4% (0.036)	5.8% (0.027)	NS	NS
Seizure	4.6% ( $<0.001$ )	NS	7.9% (0.003)	7.3% (0.035)	1.2%	NS	1.2%	2.4%

<sup>a</sup>NS=no significant difference in incidence between the two groups

Mortality. There was no significant difference in mortality in ALL patients and across the subgroups at 30-days and 1-year post surgery with the exception of the HIGH RISK group who received aprotinin. In this

subgroup, here was a significant increase in mortality at 1-year (tranexamic acid: 9.8% of patients; aprotinin: 17.7% of patients;  $P=0.034$ ).

## Discussion

The authors had two main conclusions in this study. First, they concluded that use of aprotinin as the antifibrinolytic drug during cardiac/cardiovascular surgery significantly decreased postoperative blood loss when compared to the use of tranexamic acid, but there was no difference in the amount of transfused blood products in two of the subgroups (CABG and HIGH RISK). This highlights an important question of whether the decreased blood loss with aprotinin use is truly clinically significant. Second, the statistically significant increase in adverse events following tranexamic acid use in VALVE surgery had not previously been reported in

the literature and the authors feel this is an important avenue for future research.

Evidence suggests that aprotinin use has demonstrated an increased risk of renal dysfunction [5]. In the current study, there was no difference in the incidence of renal dysfunction or failure requiring dialysis in ALL patients receiving either aprotinin or tranexamic acid. However, in patients undergoing CABG, significantly more patients developed renal dysfunction with aprotinin use. In the VALVE subgroup, significantly more patients developed renal failure with tranexamic acid use.

Increased mortality due to aprotinin use generates a considerable amount of discussion. In fact, associations of higher mortality with aprotinin use in cardiac surgery are what caused the drug to be suspended in Canada several years ago [4]. The current study demonstrates a significant increase in mortality at 1-year post surgery in HIGH RISK patients who received aprotinin. The authors also note that there is a trend towards increased short-term mortality in CABG and HIGH RISK patients receiving aprotinin and that the limited number of patients and fatal events may have prevented these from reaching statistical significance.

Seizures following tranexamic acid use (Table 3) was an important finding in the current study as significantly more seizures occurred during VALVE and HIGH RISK surgeries in patients receiving tranexamic acid compared to aprotinin. The authors state that the mechanism for this phenomenon is unknown, although a few possible explanations were put forth.

Overall, the authors conclude that aprotinin should be avoided in CABG and HIGH RISK patients and tranexamic acid should not be used in open heart procedures until more research into its safety profile is completed. The avoidance of aprotinin in CABG surgery is in direct conflict with the Health Canada decision where aprotinin is only indicated for basic CABG surgery [4].

Limitations of the study. Although this was an observational study and a hypothesis is not strictly necessary, it was not made clear what the authors

hypothesized would occur with aprotinin versus tranexamic acid use in their patient population. It was also difficult to interpret exactly what the authors' main conclusion from all their data was. In addition, large data sets were presented, but many of the findings (e.g. a higher incidence of renal failure in the VALVE subgroup treated with tranexamic acid) were simply not addressed. There was also no explanation of exactly how a seizure was clinically diagnosed. In light of the significant increase in seizures observed in patients receiving tranexamic acid in this non-blinded study, a more strict set of criteria for seizure diagnosis should be described in their work. Also, the severity of the seizures, how they were treated, and if any residual neurological deficits were present would also be important to report. A randomized, controlled, multi-centre, double blind clinical trial is the gold standard in clinical research and a single-centre consecutive cohort study of this nature can introduce bias due to the non-blinded investigators, the possibility of a small change in surgical or anesthetic procedures over the 5 month period, and institution-specific practices and procedures that may affect outcomes.

Overall, this study raised many more questions and presented conflicting data to our current Health Canada guidelines. Current clinical practice should be based on federal regulations and institution specific findings and outcomes. A consideration for future work that arose from this study is the prevention of seizures with tranexamic acid use in patients undergoing cardiac surgery.

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## Critical Appraisal

By: **Serena Shum, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine**

**Publication title: "High-sensitive cardiac Troponin T is superior to echocardiography in predicting 1-year mortality in patients with SIRS and shock in intensive care."**

**Authors: Bergenzaun L, Ohlin H, Gudmundsson P, During J, Willenheimer R, Chew MS.**

**BMC Anesthesiology 2012 12;25.**

### Introduction

Cardiac troponin I and T (cTn) are regulatory proteins that control the calcium-mediated interaction between actin and myosin. Injury disrupts cardiac myocyte membrane integrity and releases intracellular constituents into the extracellular space. As such, detection of cTn in peripheral blood indicates cardiac injury, irrespective of cause. Cardiac troponin is considered to be superior to other biomarkers of cardiac injury, including CK-MB and myoglobin, due to its high myocardial specificity and sensitivity (1,2). A major limitation to traditional cTn assays is the few hours' delay in detecting increased circulating levels. High-sensitivity troponin T (hsTnT) assays not only allow earlier diagnosis of cardiac injury (3), but have also demonstrated increased accuracy (4) and prognostication (3,5) in patients with pre-existing cardiac disease and the general population (6).

In the critically ill, cTn elevations are commonly thought to reflect demand ischemia (7,8). cTn elevations are associated with a worse prognosis (9,10). Rosjo et al. (11) showed that elevated hsTnT is associated with disease severity, but does not predict in-hospital

mortality in patients with severe sepsis and septic shock. Brain natriuretic peptide (BNP) is a hormone released primarily from the ventricles in response to high ventricular filling pressures, such as is often seen in heart failure (12). BNP concentrations are frequently elevated among critically ill patients (13) and its prognostic importance is not well-established (14). Echocardiographic changes of left ventricular (LV) function are frequently described in the critically ill (15); however, there are conflicting data regarding the prognostic value of LV systolic and diastolic function in patients in the intensive care unit (ICU) (16,17).

Little research has been done on the prognostic value of hsTnT in critically ill patients. In addition, while elevated BNP levels and impaired LV function as measured by echocardiography have been well-documented in the critically ill, their utility as prognostic markers have not been solidified. In the current study, the authors evaluate the prognostic value of each of these parameters on 1-year mortality in ICU patients with Systemic Inflammatory Response Syndrome (SIRS) and shock.

### Methodology

#### Summary

The authors employed a prospective observational cohort study design. Fifty-five consecutive patients with SIRS and shock, defined as failure to maintain mean arterial pressure  $\geq 70$  mmHg despite adequate fluid resuscitation, were included. Exclusion criteria were pregnancy, pre-existing abnormalities of coagulation, fibrinolytic therapy, compromised immunity, or a "Do Not Attempt Resuscitation" order.

Blood samples were taken from arterial lines within 12 hours of inclusion. HsTnT was measured using immunoassay and in accordance with previously validated methods (Giannitsis et al. 2010). Plasma BNP levels were analyzed using the UniCel Dxl 800 Beckman Access Immunoassay system. Biochemical samples were

coded before analysis and laboratory personnel were blinded to clinical and echocardiographic data.

TTE examinations were performed within 12 hours of inclusion by either of four experienced echocardiographers. Two dimensional imaging examinations were performed in the standard apical four- and two- chamber views. Parameters of LV systolic function included LV ejection fraction (LVEF), mean atrioventricular plane displacement (AVPDM), peak systolic tissue Doppler velocity imaging (TDIs) and velocity time integral in the LV outflow tract (LVOT VTI). Analyses of the measures were made  $>16$  weeks after data acquisition.

*Critical Appraisal*



As it is both impossible and unethical to randomize patients to different prognostic factors, the ideal study design to identify the presence of and determine the increased risk associated with a prognostic factor is a cohort study (18), which was indeed executed by the authors. However, I feel there are two weaknesses in methodology which may threaten the validity of the results. Firstly, I do not believe that the sample of patients were representative and well-defined. Furthermore, it is difficult to ascertain whether the patients were at a similar point in their course of disease.

The authors attempt to identify objective criteria for defining the health condition of interest by using criteria outlined by Dellinger et al. (19). Dellinger et al. describe severe septic shock and sepsis as failure to maintain mean arterial pressure  $\geq 70$  mmHg, despite adequate fluid resuscitation. However, one could argue this criteria is far less comprehensive than the criteria for diagnosing SIRS and septic shock provided by Annane et al. (20), which is more widely adopted. Moreover, there appears to be a lack of compliance to these guidelines. Two-thirds of the sample was comprised of individuals suffering from septic shock while the remaining third suffered from shock due to a variety of different causes. This included pancreatitis, post-major non-cardiac surgery, intoxication and multi-organ failure, gastrointestinal bleeding and portal hypertension, and unknown cause. An individual with a MAP of  $< 70$  stemming from septic shock likely has a different prognosis than another patient who is suffering from shock post-operatively. Furthermore, some subtypes of shock are more amenable to treatment than others. For example, therapy for pancreatitis is usually supportive while implementation of early-directed therapy for septic shock has significant impact on outcomes. Thus, the

## Statistical Methods

Data are presented as median (inter-quartile range [IQR]), percentages, or absolute values. Medians and quartiles are appropriate given the study's small sample size. Variables that are not normally distributed were analyzed using non-parametric tests. Spearman's rank correlation was used to establish correlation between two variables while Mann-Whitney's U test was used to detect differences between two groups. Categorical data were analyzed with Fisher's exact test. HsTNT and BNP were log transformed due to its skewed distribution. Receiver operating characteristics (ROC) were used to define optimal cut-off values using the maximal area under the curve (AUC).

## Results

### Summary

The study initially enrolled 55 consecutive patients. A total of 6 patients were excluded; two lacked written  
*April 12, 2013*

heterogeneity of the sample of patients compromises the validity of the results.

In addition to the heterogeneity of the sample population, another flaw is that it is difficult to discern whether the patients were all at a similar point in their disease process. We are told that blood samples and TTE examinations were performed within 12 hours of inclusion, which is somewhat of a large time frame and in no way accounts for the patient's stage of disease at ICU admission. For example, some of these patients be transfers from the ward after a prolonged admission with little physiological reserve or just admitted from the emergency department following an acute onset of illness - even then, patients come to medical attention at different stages of their disease. One potential solution would be to tighten the inclusion criteria. This would involve, for example, restricting enrollment to patients meeting the criteria for septic shock as defined by Annane et al. as opposed to solely meeting a MAP criteria. Other prognostic factors, such as site of infection, type of infection, antimicrobial therapy, and initiation of early goal-directed therapy were not accounted for in the analysis. It is unclear also if institutional guidelines on the management of septic shock were present, and if so, whether they evolved over the study period as the time frame for the study was not noted.

On the other hand, the authors do provide a detailed exclusion criteria. However, reasons for exclusion are unclear in some cases. For example, the exclusion of individuals who are immunocompromised is questionable as these individuals are most susceptible to septic shock.

The primary outcome of this study was the odds ratio between several predictor variables and 1-year mortality following SIRS and septic shock. This was accomplished via a logistic regression model, which is appropriate for dichotomous variables such as mortality. Due to the study's small sample size, the authors rightfully perform univariate analysis first (Table 2) to determine which factors differ between the non-survivors and survivors. Subsequently, they put these into the logistic regression model. The authors perform a multivariate logistic regression analysis based on 4 variables (hsTNT, APACHE II, E/e and age), which is again, appropriate for the sample size of their study (21).

consent, one expired before echocardiographic examination, one was too obese to allow TTE, one was incorrectly registered in the echocardiography database

and one was lost to follow-up after moving abroad. A total of 49 patients included for analysis.

Thirty-three patients suffered from septic shock while the remaining suffered from shock due to a variety of causes that were described previously. Pre-existing cardiac disease was present in 24% of patients, which was defined as severe arrhythmia, heart failure, or ischemic heart disease. Forty-nine percent of patients had "pre-existing treatment" with beta-blockers, ACE-inhibitors, calcium channel blockers, and/or nitrates. Vasopressors and inotropes used included norepinephrine, dobutamine (n=12), epinephrine (n=1) and levosimendan (n=10).

HsTNT was detectable in all 49 patients, with a range of <5 to 2,592 ng/l (median 80 ng/l [IQR 24.0-193.5]). HsTNT was elevated (>14 ng/l) in 45 patients (92%). With regards to 1-year mortality, AUC for hsTNT was 0.76 (95% CI 0.612-0.907, p=0.004), with 72% sensitivity and 82% specificity for the cut-off value of 117.5 ng/l. HsTNT was significantly higher in non-survivors (median 168 [IQR 89.8-358] ng/l) than in survivors (median 60 [IQR 17-99.5] ng/l), p=0.003. Multivariate analysis identified hsTNT as the only independent predictor of 1-year mortality (p=0.010) with an adjusted odds ratio of 2.0 (95% CI 1.2-3.5). Logistic regression showed increasing odds ratios for mortality for increasing hsTNT quartiles. Furthermore, hsTNT correlated with critical illness scores APACHE II (r=0.335, p=0.019) and SOFA (r=0.301, p=0.036).

BNP ranged from 29 to 2031 pmol/l (median 189 pmol/l [IQR 107-375]) and was elevated (>30 pmol/l) in 48 (98%) patients. AUC for BNP was 0.603 (95% CI 0.415 to 0.791, p=0.26). Univariate analysis reveals insignificant differences in BNP levels between non-survivors and survivors (p=0.26). As such, BNP was not included in multivariate analysis.

Other variables that were identified as being significantly different between non-survivors and survivors by univariate analysis included APACHE II, SOFA, age and LV diastolic function parameters E/e and La volume. However, multivariate analysis did not identify these variables as independent predictors. Moreover, creatinine and pre-existing cardiac disease made no significant contributions to the model when they were included in the model as independent variables.

A total of 46 echocardiographic examinations were available for analysis, since 3 examinations were lost. Intra- and inter-observer variability for echocardiographic parameters of LV systolic and diastolic function ranged from 3.1% to 9.9% and 3.2% to 9.6%, respectively. There were no significant difference between survivors and non-survivors in any of the measured LV systolic function parameters (LVEF p=0.87, AVPM p=0.087, TDIs p=0.93, LVOT VTI

p=0.18). As for diastolic function parameters, E/e and La volume, which serve as surrogates of LV filing pressure, differed significantly between survivors and non-survivors. E/e median was 9.9 in survivors versus 11.7 in non-survivors (p=0.023), and La volume median was 24 ml/m<sup>2</sup> in survivors vs 31 ml/m<sup>2</sup> in non-survivors (p=0.024). Of note, La volume was only feasible in 38 patients.

### Critical Appraisal

The authors excluded 6 patients from analyses, leading to an attrition rate of 12.2%. Patients were excluded for a variety of reasons, most of which are unrelated to the outcome. Specifically, patients were excluded due to lack of written consent (n=2), death before echocardiographic examination (n=1), obesity precluding TTE examination (n=1), incorrect registration into the echocardiography database (n=1) and relocation disallowing longer follow-up (n=1). An attrition rate of 20% is commonly considered acceptable (Stinner & Tennent, 1996); however, an attrition rate of 12.2% is relatively large when the event rate is 36.7% and may jeopardize the study's validity. Moreover, it would be reassuring had the authors provided pertinent demographic and clinical data on the patients who were unavailable for follow-up to ensure that they were similar to those for whom follow-up was possible. The study lost an additional 3 echocardiographic examinations during the installation of a new storage system, leading to a barely acceptable attrition rate of 19.6% for echocardiographic studies. Besides from quantifying loss to follow up, the authors shed little light on their methods of obtaining follow up (i.e. by telephone, in person, etc) and provide no information on cause of mortality.

One may argue that this study fails to quantify pre-existing cardiac disease, which may confound the results but presents an insurmountable test of foresight. Despite the impracticalities of obtaining baseline measurements of the variables of interest, the authors do attempt to account for differences between survivors and non-survivors by including pre-existing cardiac disease and creatinine in their univariate and, if applicable, multivariate model. Obtaining baseline measures may not only be impractical, but irrelevant, given that there was no significant impact made by the inclusion of creatinine and pre-existing cardiac disease as independent variables in the model. However, I argue that the authors could have characterized and quantified pre-existing cardiac disease with more diligence and I suspect creatinine levels were drawn simultaneously with other biochemical markers (i.e. after ICU admission) and do not reflect pre-morbid renal function. Pre-existing heart disease encompassed severe arrhythmia - which included atrial fibrillation, but it is ambiguous whether there were other types of arrhythmias - heart failure, and ischemic heart disease. It is unclear whether these were

pre-defined conditions that the authors looked for in their patients, or whether the authors were comprehensive and attempted to characterize all known cardiac disease in their sample. Furthermore, in Table 1, the proportion of patients with "cardiac disease" is noted to be 24% while 49% is noted to be on "pre-existing therapy." Since the authors define "pre-existing therapy" as treatment with beta-blockers, ACE-inhibitors, Ca-channel blockers, and/or nitrates, all of which are drugs used in the treatment of cardiac disease, one would expect these proportions to be consistent.

The primary outcome for this study - 1 year mortality - is easily measured without significant judgment, although it is unclear how this information was obtained. Biochemical samples were coded before analysis and laboratory personnel were blinded to clinical and echocardiographic data. Large ranges in values were obtained for both hsTNT and BNP measurements. This attests to the limitation of a small sample size. In their interpretation of ROC curves, Fan et al. (2006) describe ROC curves with an AUC  $\leq$  0.75 as not clinically useful, thus implying that the cut-off value identified in this study for hsTNT being prognostic has little clinical utility.

Multivariate logistic regression identified hsTNT as the only independent predictor of 1-year mortality with an adjusted odds ratio of 2.0 and 95% CI of 1.2-3.5. I consider this an imprecise estimate of likelihood as the true odds of suffering 1-year mortality based on an elevated hsTNT lies somewhere between approximating no effect to 3.5 times more likely. Thus, the estimates of likelihood are, at best, of fair precision, and is likely a complication of the study's small sample size. The predictive relationship between elevated hsTNT and 1-year mortality is strengthened by logistic regression analysis revealing increased odds ratio for mortality with

### Follow-Up

Existing literature suggests that most deaths resulting from SIRS, sepsis, severe sepsis, and septic shock occur within the first six months of insult (Perl et al., 1995; Sasse et al. 1995). Therefore, follow-up at 1 year is more than likely adequate. Previously quoted rates at 1 month, 6 months and 1 year after admission date were 40.5%, 64.7%, and 71.9%, respectively (Sasse et al. 1995). The reviewed article does not specifically measure event rate at 6 months, which is when one would expect it to be

### Generalizability

Overall, I think the study patients were similar to those I would encounter in my practice based on the authors' description that the study took place in a "mixed-bed"

increasing quartiles of hsTNT. However, the wide CIs again indicate the need for larger studies.

TTE examinations were performed by 4 different individuals, who appear to be the authors, and the intra- and inter-observer variability for these parameters seems to be clinically significant. The authors decide to analyze echocardiographic measures > 16 weeks after data acquisition when it is believed the reader would be "less aware of the diagnosis." Again, this suggests that the authors were not blinded to the prognostic factors of interest and have the potential to bias the outcome. Fortunately, given that test-retest in psychometric literature usually has a washout period of 10-14 days, 16 weeks should be adequate for reducing potential carryover effects due to memory.

While unethical to control for, a possible confounding factor is inotropic agent/pressor use. In my opinion, the authors did not strive to quantify the exact proportion of patients receiving inotropic support, duration of therapy, and which patients necessitated inotropic/pressor support. It is clear that a significant proportion of patients received inotropes and pressors. Conceivably, a subgroup of sicker patients, say, those with pre-existing cardiac disease, received inotropic and pressor support. Presumably, inotropic agents would positively affect echocardiographic measures of LV systolic, thus attenuating differences between survivors and non-survivors. Concurrently, most pressors and inotropic agents would negatively affect LV diastolic function (Overgaard & Dzavik, 2008) and compound the difference in non-survivors and survivors. It is quite possible that the current study may have identified a subgroup of critically ill patients with cardiac disease. Furthermore, depending on the duration of agent use, inotropes and pressors may induce myocyte injury (Overgaard & Dzavik, 2008) and exaggerate the elevated hsTNT levels between non-survivors and survivors.

highest, and does not evaluate the prognostic use of hsTNT at this point, which may be useful. Furthermore, although the current study reports event rates over time for the sample as a whole, a more practical approach would be to compare mortality rates through the year between patients with elevated hsTNT and those without. In addition, the manner in which mortality over time is reported is ambiguous as the rates are not cumulative or proportional.

ICU at a university hospital and contained "the sickest of ICU patients." In terms of medical history, I do not feel the authors provided sufficient information to allow

comparison to the readers' own patients. The list of conditions identified is far from comprehensive, definitions are lacking, and rather broad categories are used to cover rather heterogeneous conditions. For example, "diabetes mellitus" presumably captures both type I and type II and "cardiac disease" covers various conditions. The authors also do not quantify the pre-morbid disease status. Table 1 shows a median age of 65 years, which I suspect is consistent with the patient population at KGH. However, there is certainly an under-representation of female patients, who only comprised 29% of the study sample. The proportion of patients with co-morbidities such as diabetes mellitus and hypertension appears to be compatible. Because of the ambiguity surrounding the true proportion of patients with pre-existing cardiac disease, I cannot say for certain whether our patients are similar in this regard.

### Implications for Management

I do not believe the results of this study will affect the management of ICU patients with severe sepsis and septic shock. An elevated troponin level may be prognostic of 1-year mortality, but it is unlikely that this will change the acute management of a critically ill patient admitted to the ICU. The results may be useful for counseling patients, but is of limited utility beyond providing the odds ratio for 1-year mortality for a patient

### Conclusion

This study offers a good starting point for additional studies on the prognostic use of hsTNT on 1-year mortality in ICU patients with septic shock. Major limitations of the current study include 1) heterogeneity of the study sample; 2) small sample size; and 3) possible confounding relationship between hsTNT and

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Conversely, I feel the authors do provide sufficient measures of disease severity once in the ICU through the use of SOFA and APACHE II scores as well as the proportion of mechanically ventilated patients. These parameters are probably more relevant when making comparisons to one's own ICU population. As KGH does not utilize either SOFA or APACHE II scores, I could only compare the populations based on the proportion of mechanically ventilated patients, which was 90% in the study and 71% at KGH. This suggests that the study sample may have been sicker than the general ICU population at KGH. One potential bias of the study is the "referral filter bias," that may limit generalizability of the results to settings such as community ICUs. Specifically, more severe and unusual cases are usually referred from primary to tertiary centers such as university hospitals. This may also increase the likelihood of adverse outcomes and introduces a bias toward the alternate hypothesis.

with elevated hsTNT. The current study does not provide insight as to whether these odds vary with time, the nature of morbidities affecting non-survivors, or the causes of mortality. While this current study and several others in the past have shown that troponin elevation is associated with a worse prognosis, it is unclear whether any intervention would improve outcome.

pre-existing cardiac disease or renal insufficiency. More importantly, as it has been well-established in the existing literature that troponin elevations in patients with critical illness are associated with a worse prognosis, I contend that the bigger question that needs answering is what implications this has for management.

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## Critical Appraisal

By: **Julie Zalan, MD, PGY-1, Queen's Anesthesiology & Perioperative Medicine**

Publication title: "***Predicting Prognosis in Thermal Burns with Associated Inhalational Injury: A Systematic Review of Prognostic Factors in Adult Burn Victims.***"

Author: ***Colohan SM.***

**J Burn Care Res. 2010 Jul-Aug;31(4):529-39.**

### Introduction

Burn injuries can cause significant airway and respiratory tract compromise, leading to a respiratory emergency. While studying pediatric medicine at Kingston General Hospital, I was involved in the management of two cases which peaked my interest in burn management.

The first case was a 6-year old girl who suffered from smoke inhalation following a house fire. The second case was a 13-year old boy who inhaled ethanol and bromide following the explosion of a homemade volcano concoction. Both histories were particular for direct airway injury upon presentation, as well as delayed symptomatology. In both cases I asked the question: "to intubate or not to intubate?" I have learned in the past about criteria that help decide the answer to this question, but when I started to review the literature, I could not find a great deal of evidence to support them. There are many retrospective studies, but few randomized controlled trials or large meta-analysis. A combination of sparse data, retrospective studies and dated research make it difficult to develop best practice

guidelines. It is difficult to randomize patients to different prognostic factors and this is likely the reason that there are so few studies.

With that introduction, I would like to present a systematic review on Predicting Prognosis in Thermal Burns With Associated Inhalational Injury, published in the Journal of Burn Care Resuscitation, 2010. Dr. Shannon M. Colohan, from the Department of Surgery, Dalhousie University in Halifax was the lead researcher. Thinking back to my case, I wanted to know the possible outcomes of a burn injury and the frequency with which these outcomes can be expected to occur (e.g. airway edema in a patient with burn injury, mortality rates).

Burn injuries are a significant problem with >500 000 people requiring medical treatment, 40 000 hospitalizations, and 4 000 deaths per year in the U.S.<sup>1</sup> Prognostic risk stratification is important because it can assist clinical decision making, help guide patient counseling, define risk groups, and allow outcomes to be compared between patients and treatment centres.<sup>1</sup>

### Methodology

This overview addressed one focused clinical question: which prognostic variables are predictive of in-hospital mortality in adult thermal burn patients? (I was not able to find a study specific for pediatric populations.)

It used non-quantitative methods to summarize the results. The methodology was explicitly reported to enable reproducibility and help support validity. Individuals must have sustained a thermal burn injury requiring hospitalization to meet inclusion criteria. Identified studies must have produced an estimate of prognosis by identifying possible prognostic factors, including inhalational injury. Pre-existing risk factors and exposures involved in the burn injury were considered as predictor variables. Only multivariate studies were included.

A table outlining a summary of the studies included in the systematic review, reveals a similar study design - all observational cohort studies. Any variables identified

after the acute care period were excluded. Studies that included multiple burn etiologies were excluded if the proportion of thermal burns was <50%. Extremes of age were excluded to better evaluate studies with comparable populations. There were a total of 13 studies with 16, 812 patients. Of the reviewed studies, only two demonstrated reproducibility using prospective cohorts, while the rest used retrospective cohorts. Age range varied between studies and some included extremes of age, while others did not. As well, the specific exposures and burn etiology were not specified. The applicability of these results may thus not be universal. Another pitfall is the lack of a consensus on definition of inhalational trauma (IHT). It was an important prognostic variable, yet not every study delineated how it was defined, or by what it means. Tedget et al used bronchoscopy, Brusselaers et al only classified as having IHT if ventilated, while some did not specify

whatsoever, or based the diagnosis of IHT on symptomatology alone.

Authors conducted a thorough search for studies that met their inclusion criteria using OVID Medline and OVID EMBASE. Authors only noted scanning the title and abstracts, narrowing their search and then assessed each for inclusion/exclusion criteria and general relevance to their research question. Searches were also carried out using the Web of Science database and the Cochrane Collection, as well as a general Google Search. A total of 19 articles were reviewed and the reference lists of these articles were also examined. There is no mention of contacting experts in the area. Authors may have missed published studies (including studies that are in press or not yet indexed or referenced) and unpublished studies may not have been identified. The omission of unpublished studies increases the chances of publication bias – a higher likelihood for studies with positive results to be published, while not including negative results, or results not supporting the hypothesis. Non-English-language publications and unpublished data were not included.

The original prognostic studies included within the review had to be individually critically appraised to

## Results

The heterogeneity of the studies, as well as their failure to report odds ratios, makes it impossible to summarize the increased risk that inhalational trauma adds to burn prognosis. However, the overall mortality rate among the studied burn patients was 13.9% (range 4-28.3%); while mortality with inhalational injury was 27.6% (range 7.8-53.5%). Multivariate analysis revealed that % Total Body Surface Area and inhalational injury (12 studies) and age (11 studies) are the strongest predictors for mortality in burn patients. It did not specify the extent of inhalational injury, or its definition. It also did not specify on how age contributes to in-hospital mortality.

Generalizability is a problem in prognostic studies

## Discussion

I continue to question whether these results will help me in caring for my patients. To be quite honest, I am not certain. Age, % total body surface area and inhalational injury are all prognostic variables identified as primary determinants of mortality common to most of the studies reviewed. However, this information is vague. The degree to which the mortality is increased is uncertain, since there is no consensus on a proper prognostic model, and there is a paucity of information regarding “risk” and “odds” with respect to these prognostic factors.

The results offer counselling to patients regarding expected outcomes, without considering medical

assess their respective validity. There is no mention of long-term follow-up, which is a key part of a prognostic study. The end point was in-hospital mortality, but it would have been helpful to include data on long-term morbidity. Also, there was not a well-defined sample of patients at a similar point in the course of disease, in any of these articles. Each patient population is different, the exposures unique, making them heterogeneous samples to compare.

This overview is based on a small number of small studies with weakly positive effects, making it susceptible to publication bias. The validity of the included studies was appraised with the National Institute for Clinical Health and Excellence. This examined the internal and external validity/generalizability of studies. The authors also cited referencing criteria for “prognostic studies” outlined in the Journal of the American Medical Association series on evidence-based medicine. Only one author is cited as extracting the data from each study and summarizing the information in tabular form. Having two or more people participate in this process guards against errors.

because they are often limited to a single historical period, geographic location, methodological approach, disease spectrum or follow-up period. This study was heterogeneous with respect to time, place and patient characteristics. The general care provided to burn patients has also changed a great deal over the time span covered by these studies.

The current studies are possible victims of overfitting: when too many independent variables are fitted into an analysis that has too few outcome events, leading to reduced accuracy. The regression analyses performed in these studies also failed to assess interaction between the variables it was testing.

interventions. The patient population and geographical area is quite broad and limitations in applicability may exist as outlined above. Because there is no ability to standardize every individual's clinical situation, the prognostic evaluation serves only as an estimate. Various clinical and patient factors can influence this prognosis that is not included in the model. Informing any patient about his/her prognosis might help him/her plan better, but can also cause anxiety, confusion or increase the disease burden. The benefits must be weighed against the potential harms and costs, even for a prognostic study.

Future research is required in this area examining a

specific exposure and outcome while adjusting for multiple possible prognostic factors. The sample size needs to be large enough, completed in multiple similar

populations, yet in different geographical locations to demonstrate generalizability. A definition and method of diagnosis of inhalational injury should be included.

## Conclusion

Reflecting back on the original two cases, the additional information that I was able to provide the family based on this review was minimal. The applicability to the pediatric population was limited and the etiology of the second case was not a thermal injury. Management was

expectant for both and neither received more invasive treatment. Each had inhalational injury diagnosed on history and clinical exam alone. I believe that more research in this area is required before clinical practice guidelines and best practices can be established.

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**Queen's University Department of Anesthesiology Publication List – 2011-2013** [page 1/6]

(in alphabetical order of 1st author, Department members/cross-appointees highlighted in bold)

**Arellano R**, Nurmohamed A, Rumman A, **Milne B**, **Tanzola R**. Point of care transthoracic echocardiography as an alternative to transesophageal echocardiography to confirm internal jugular guidewire position, *Can J Anesth.* 2012; 59(1):103–104.

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**Queen's University Department of Anesthesiology Publication List – 2011-2013** [page 2/6]

(in alphabetical order of 1st author, Department members/cross-appointees highlighted in bold)

**Gilron I.** Clinical Pharmacology of Antidepressants and Anticonvulsants for the Management of Pain, Pain 2012 - An Updated Review, Refresher Course Book., Vol. 2012; (14):3-19.

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