

# Queen's University 25<sup>th</sup> Annual Anesthesiology Research Day

*Scientific Program Coordinators:*

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

**Elizabeth Vandenberg, RN, MSc, DrPH**

*Scientific Adjudicators:*

**Catherine Cahill, PhD**

**Homer Yang, MD, CCFP, FRCPC (Guest)**

*Queen's Anesthesiology Residency Program Director:*

**Melanie Jaeger, MD, FRCPC**

*Queen's Anesthesiology Department Head:*

**John Cain, MD, FRCPC**

*Postgraduate/Undergraduate Medical Secretary:*

**Mrs. Kim Asselstine**

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# Queen's University

## 25<sup>th</sup> Annual Anesthesiology Research Day

### SCIENTIFIC PROGRAMME

- 0900 – 0915      **Opening Remarks – Dr. John Cain**
- 0915 – 0930      **Introduction – Dr. Ian Gilron**
- 0930 – 0945      **Dr. Nancy Ghazar, PGY-4**  
**"The impact of workforce changes on the supply of Canadian anesthesia providers: results of a 2002 national survey"**  
(Resident data presentation)
- 0945 – 1000      **Mr. Benjamin McNaull, BSc, MSc candidate, (Pharmacology & Toxicology)**  
**"The effects of ultra- low doses of opioid receptor antagonists on acute spinal morphine tolerance"** (Student data presentation)
- 1000 – 1015      **Dr. Jack McGugan, PGY-3**  
**"Can diagnostic quality TEE images be streamed over a LAN?"**  
(Resident research proposal)
- 1015 – 1045      **Poster presentations** and coffee break
- 1045 – 1100      **Ms. Maya Rubenstein, BA, MA candidate, (Psychology)**  
**"Psychosocial predictors of postoperative pain: An examination of the effect that presurgical pain, mood, and pain catastrophizing have on postoperative pain"** (Student data presentation)
- 1100 – 1115      **Dr. Tarit Saha, Clinical Fellow**  
**"An unusual case: What's the diagnosis?"** (Fellow's case presentation)
- 1115 – 1130      **Dr. Angela Northey, PGY-2**  
**"ASA physical status classification: interpretation and utility"**  
(Resident research proposal)
- 1130 – 1145      **Mr. Sean Hall, PhD candidate, (Pharmacology & Toxicology)**  
**"Cardiac ryanodine (RyR2) phosphorylation status, troponin I degradation and left ventricular dysfunction following acute intracranial hypertension in rats"** (Student data presentation)
- 1145 – 1200      **Dr. Lisa Silcox, PGY-4**  
**"Perceptions about research during anesthesiology residency"**  
(Resident data presentation)
- 1200 – 1300      Lunch (provided)

- 1300 – 1315 **Dr. Bethann Meunier, PGY-4**  
**“Personal protective system (PPS) and endotracheal intubation: “It’s about time””** (Resident research proposal)
- 1315 – 1330 **Dr. Kyle Doerksen, PGY-2**  
**"Post-operative analgesia for radical retropubic prostatectomy"**  
(Resident research proposal)
- 1330 – 1345 **Dr. Rob Anderson, PGY-4**  
**"Postoperative analgesia and inflammatory bowel disease"**  
(Resident research proposal)
- 1345 – 1400 **Mr. Tuan Trang, BSc, PhD candidate, (Pharmacology & Toxicology)**  
**"Evidence for activity of spinal cannabinoid (CB1) receptors in induction of opioid physical dependence"**  
(Student data presentation)
- 1400 – 1430 **Poster presentations** and coffee break
- 1430 – 1445 **Dr. Gillian Ramsey, PGY-3**  
**"The effects of intraperitoneal ketorolac on postoperative pain following laparoscopic cholecystectomy"** (Resident research proposal)
- 1445 – 1500 **Dr. Sumit Sharan, PGY-2**  
**"Cervical spine movement during laryngoscopy: objective assessment and comparisons of indirect fiberoptic and prismatic laryngoscopes"**  
(Resident research proposal)
- 1500 – 1515 **Mr. Clive Hansen, BSc, MSc candidate, (Pharmacology & Toxicology)**  
**"Effects of intrathecal gabapentin on spinal morphine tolerance in the rat tail-flick and paw pressure tests"**  
(Student data presentation)
- 1515 – 1530 **Mr. Richard Ahn, MD candidate, (Queen’s Medicine)**  
**"The effects of obesity and COPD on extubation times after cardiac surgery"** (Student data presentation)

(Each 10-minute presentation will be followed by a 5-minute question period)

1530 **Guest Lecturer: Dr. Homer Yang**  
**“Patient Safety: what are the issues?”**

1830 **Holiday Inn, Bellevue Ballroom, 5<sup>th</sup> floor - Cocktails and Dinner**

**\* \* \* Presentation of awards following dinner \* \* \***

**Poster Presentations**

**Dr. Trevor Bardell**, MD, PGY-1, (Surgery)

**"Anastomotic quality in CABG: when life depends on millimetres"**

**Mr. Maneesh Deshpande**, MSc, MD candidate, (Queen's Medicine)

**"Quantifying the impact of pain reduction on quality of life and mood during neuropathic pain treatment: Implications for analgesic clinical trials"**

**Ms. Sarah Holdridge**, BSc, MSc candidate, (Pharmacology & Toxicology)

**"Anti-hyperalgesic effects of delta opioid receptor agonists in a model of neuropathic pain"**

**Ms. Noufissa Kabli**, BSc, MSc candidate, (Pharmacology & Toxicology)

**"Enhanced axonal transport of mu and delta opioid receptors in a model of neuropathic pain."**

**Ms. Alison Kelly**, BA Honours candidate, (Psychology)

**"The role of interpersonal sensitivity in depression, perceived social support, and chronic pain"**

**Ms. Margo McAlister**, BSc Honours candidate, (Psychology)

**"Presentation of preliminary data from an epidemiological survey of chronic pain in Southeastern Ontario: disability, depression, medication and health care usage"**

**Ms. Kim Oxbro**, BSc, MSc candidate, (Pharmacology & Toxicology)

**"The effects of spinal ultra-low doses of an opioid receptor antagonist on systemic morphine dependence"**

**\* \* \* The Judges will be: \* \* \***

**Dr. Homer Yang**, Professor and Chairman, Department of Anesthesia, University of Ottawa

**Dr. Catherine Cahill**, Assistant Professor, Departments of Pharmacology & Toxicology and Anesthesiology, Queen's University

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**Critical Appraisal Essays**

**Dr. Jason Erb**, MD, PGY-1

Title of Appraised Publication: **"Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly, high risk patients"**

**Dr. Dave Robertson**, MD, PGY-1

Title of Appraised Publication: **"Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial"**

## **The effects of ultra- low doses of opioid receptor antagonists on acute spinal morphine tolerance**

**Benjamin McNaull, BSc & Khem Jhamandas, PhD**  
**Department of Pharmacology & Toxicology, Queen's University**

**Background:** Sustained exposure to opioid analgesic drugs can lead to the development of acute or chronic tolerance, which manifests as loss of drug potency. Recently, we showed that intrathecal administration of ultra low doses of naltrexone (NTX), a non-selective opioid receptor antagonist, paradoxically augments the analgesic effects of morphine and effectively blocks or reverses the loss of potency resulting from chronic spinal administration of the agonist.

**Methods:** Since administration of morphine over a short period can induce acute tolerance that mechanistically resembles chronic tolerance, we examined whether ultra low doses of NTX, can influence this type of tolerance. Additionally, the effects of a mu antagonist CTAP, delta antagonist naltrindole (NTI), and kappa antagonist norbinaltorphamine (nBNI) were also examined. Acute tolerance was induced in male Sprague Dawley rats by administering three successive injections of intrathecal morphine (15ug) at 90-minute intervals. Antinociception was assessed using the tail-flick and paw-pressure tests. Quantitative estimates of drug potency, reflected by the ED<sub>50</sub> value, were obtained from the cumulative morphine dose-response curves derived 24 hours post treatment.

**Results:** Repeated intrathecal morphine administration produced a rapid decline of the antinociceptive response in both tests and yielded an approximate 6-fold increase in morphine ED<sub>50</sub>, reflecting a marked loss of potency. Co-injection of morphine with ultra low doses of NTX (0.005ng, 0.05ng), or CTAP (0.00114ng) or NTI (0.006ng) or nBNI (0.1ng) prevented both the decline in analgesic response and the increase in morphine ED<sub>50</sub> value. Additionally, intrathecal 8-phenyltheophylline (3ug) and adenosine receptor antagonist attenuated the ability of NTX to facilitate morphine action.

**Discussion:** The results suggest that ultra low doses of opioid receptor antagonists can effectively inhibit the induction of acute morphine tolerance and that its facilitatory action is likely expressed via spinal adenosine.

## Can diagnostic quality TEE images be streamed over a LAN?

**McGugan, J., MD, Ali, M., MD, FRCPC, Babcock, J.**  
**Department of Anesthesiology, Queen's University**

**Background:** TEE is finding its niche as a minimally invasive intraoperative monitor that provides detailed hemodynamic information. Those with TEE training are increasingly relied upon to provide intraoperative TEE imaging and interpretation and are being asked to provide assistance to those early in their TEE training. Better intraoperative TEE training and service may be provided if we can make the TEE video available outside of the OR to those that can provide expert opinion. The relatively low cost of robust computer technology and video encoding software along with our existing, under-utilized wireless network makes this kind of option extremely simple to explore. Review of the literature does indeed indicate that some work has been put into digitizing ultrasound video for storage or transmission. Gold standard for storage of video information in echocardiography remains sVHS. While digital video technology has its own limitations, it has the advantage of being available over a computer network. MJPEG, MPEG-1 and MPEG-2 have been investigated for archiving and real-time transmission of ultrasound video. Each codec was designed for optimal video quality at certain bitrates. None of the aforementioned codecs were intended specifically for network streaming of video signals. MPEG-4 is a codec intended to perform well at the lower bitrates required for streaming over a limited bandwidth network and MPEG-4 use for storage or transmission of ultrasound images has not been reported in the literature. While MPEG-4 encoding at bitrates over 1000 kbs gives less return in quality for increases in bitrate, they are of a quality competitive with MPEG-2, a codec intended for bitrates from 2250 to 5000 kbs. Since the network we will be working with is, at the moment, limited to 11 000 kbs, we need to be thinking of bitrates that will not tax the capacity of the network. The practical throughput of our 11 megabit network will be somewhere between 2500 and 3000 kbs.

**Materials & Methods:** We intend to integrate a late model Pentium 4 PC with a video capture card and wireless network capability with the TEE machine. It will be "headless"; that is, with no monitor and will be controlled over the network using a remote computer. Data collection will consist of recording intraoperative TEE studies on the sVHS recorder on the echo machine and capturing the streamed video signal on the remote computer. In the manner of Soble et al (1), each matched sVHS and MPEG-4 video pair will be evaluated by two readers. Their findings will be recorded using a reporting tool and discrepancies subsequently evaluated. Again, in the manner of Soble et al, intrareader and interreader discrepancies will be evaluated and categorized as either major or minor. Intrareader discrepancies will be evaluated by a consensus panel to determine concordance with either sVHS or MPEG-4. We expect that diagnostic quality video can be encoded at 800 to 1200 kbs and streamed across the lan that will at least rival the gold standard sVHS.

**Timeline & Cost:** Purchase and setup of hardware and software could take as little as a month. Following the example of Soble et al leads us to a starting point of 58 TEE studies. This may take up to a year to obtain. Evaluation of the results should take place concurrently and should wrap up weeks after the last study is obtained. Hardware costs along with labour costs for hardware, software, and network setup needs to be accounted for. Of course, reader time will be a component of the study cost. In all, this should be completed within a year and a half.

1. Comparison of MPEG digital video with super VHS tape for diagnostic echocardiographic readings. Soble JS, Yurow G, Brar R, Stamos T, Neumann A, Garcia M, Stoddard MF, Cherian PK, Bhamb B, Thomas JD. J Am Soc Echocardiogr. 1998 Aug;11(8):819-25.

## **Psychosocial predictors of postoperative pain: An examination of the effect that presurgical pain, mood, and pain catastrophizing have on postoperative pain**

**Rubenstein, M.L., B.A. Hon.<sup>1</sup>, Tripp, D.A., Ph.D.<sup>1</sup>, Harrison, M., M.D.<sup>2</sup>,  
Goldstein, D., M.D.<sup>3</sup>, Gagliese, L., Ph.D.<sup>4</sup>**

<sup>1</sup>Department of Psychology, Queen's University, Kingston, ON.

<sup>2</sup>Department of Orthopedic Surgery, Kingston General Hospital, Kingston ON

<sup>3</sup>Department of Anesthesiology, Kingston General Hospital, Kingston, ON

<sup>4</sup>School of Kinesiology and Health Science, York University, Toronto, ON

**Background:** Total knee arthroplasty is used to treat knee osteoarthritis, which is a degenerative joint disease. The prevalence of this surgery is increasing and no data exists on, nor how to accurately predict, acute postoperative outcome.

**Objective:** This study examines acute postoperative outcome and its psychosocial predictors in order to better understand the pain management needs of this patient population.

**Methods:** 64 (34 males and 30 females; mean age 68.18, standard deviation 9.881) surgical patients were recruited and assessed on the day of their surgery and on 3 consecutive days postoperatively during their hospitalization. Participants preoperatively and postoperatively completed the Short Form McGill Pain Questionnaire (SFMPQ), in order to measure pain quantitatively and qualitatively, the Pain Catastrophizing Scale (PCS), in order to measure pain catastrophizing, and the Shortened Version of Profile of Mood States (SPOMS), in order to measure mood. Demographic information, such as age and sex, was also collected.

**Results:** Descriptive analyses indicate that the mean pain, pain catastrophizing, and mood scores appear to follow a decreasing trend in their magnitude from highest at the preoperative assessment to lower mean scores through each consecutive postoperative day. Follow-up one-way ANOVA demonstrates that this decreasing trend is only significant for mood, where mean preoperative scores are higher than the mean score on each postoperative day. Correlation analyses indicate a significant positive relationship between pain and pain catastrophizing, pain and mood, and pain catastrophizing and mood on the preoperative, postoperative day 1, and postoperative day 2 assessments. A significant positive relationship is found between pain and mood on postoperative day 3. Standard regression analyses were conducted in order to examine predictors of pain. Pain catastrophizing appears to be the best predictor of pain on the preoperative, postoperative day 1, and postoperative day 2 assessments, however, it does not significantly predict pain on postoperative day 3. Mood is also predictive of pain on postoperative day 2, is the only significant predictor on postoperative day 3, however, does not significantly predict pain preoperatively and on postoperative day 1. Age and sex also significantly predict pain on the preoperative assessment. Presurgical pain, pain catastrophizing, and mood do not significantly predict pain on any of the postoperative days.

**Conclusions:** Psychosocial variables, such as pain catastrophizing and mood, appear to play an important role in the relationship that they have with pain and the manner in which they predict pain both preoperatively and postoperatively. Attention and awareness of patients' pain catastrophizing and mood before and after their knee surgery might lead to more effective pain management for this cohort. Continued research in this area is warranted in order to further flush out the impact of these psychosocial variables, as well as to guide pain management.

**An unusual case – What is the diagnosis?**

**Tarit K Saha, MB,BS (Cardiac and TEE Fellow),  
Mohamed Ali, MD, FRCPC, Glorianne Ropchan, MD, FRCSC  
Departments of Anesthesiology and Surgery, Queen's University**

A 47-year-old male was admitted to the Kingston General Hospital with an acute inferolateral myocardial infarction. He was treated with thrombolytic drugs, scheduled for further investigations and then scheduled for surgical coronary revascularization.

His previous history was significant for smoking, diabetes, inflammatory bowel disease, endarterectomy and gastroesophageal reflux disease. During his admission he had a transthoracic echocardiogram, which showed dilation of the right coronary sinus, consistent with a 1.5 cm sinus of Valsalva aneurysm.

The patient was scheduled for a CABG and repair of the sinus of Valsalva aneurysm. In the operating room, while the patient was under general anesthesia, an intraoperative TEE was done which was not conclusive of a sinus of Valsalva aneurysm. The TEE pointed towards a different diagnosis and finally the surgical decision had to be changed.

What is the diagnosis?



## **ASA physical status classification: interpretation and utility**

**Angela Northey, MD & Joel Parlow, MD, MSc, FRCPC**  
**Department of Anesthesiology, Queen's University**

**Background:** The modern ASA (American Society of Anesthesiologists) physical status classification has been in use since 1961. Originally proposed for statistical analysis, it has since been used for such diverse purposes from evaluation of peri-operative risk to remuneration.

**Proposed Methods:** The plan is to survey anesthesiologists in Kingston and eventually other sites. They will determine the ASA class for 10-15 cases. These patients will have characteristics that are potentially contentious with respect to their ASA class.

**Discussion:** The purpose of this study would be to show that there is inter-rater variability between Canadian anesthesiologists when assigning patients' ASA classification. Another aim would be to qualify the patient and anesthesiologist variables that might lead to these discrepancies.

## Cardiac ryanodine (RyR2) phosphorylation status, troponin I Degradation and left ventricular dysfunction following acute intracranial hypertension in rats

Sean Hall, PhD candidate, Louie Wang MD, MSc, FRCPC,  
Brian Milne MD, MSc, FRCPC, Murray Hong PhD,

Departments of Anesthesiology and Pharmacology & Toxicology, Queen's University

**Background:** Traumatic brain injury with intracranial hypertension (ICH) is complicated by myocardial dysfunction that is catecholamine mediated. Stress-induced activation of the sympathetic nervous system results in hyperphosphorylation of the sarcoplasmic reticulum calcium ( $\text{Ca}^{2+}$ ) release channel/cardiac ryanodine receptor (RyR2) causing leaky RyR2 channels leading to  $\text{Ca}^{2+}$  overload and systolic dysfunction. We tested the hypothesis that hemodynamic instability following ICH is associated with RyR2 hyperphosphorylation.

**Methods:** Halothane-anesthetized male Sprague-Dawley rats were divided into 3 treatment groups: control (saline only), vehicle (35 $\mu\text{l}$  of DMSO and 465 $\mu\text{l}$  of saline) and calpeptin (35 $\mu\text{l}$  of a 100  $\mu\text{g}/\mu\text{l}$  stock solution dissolved in DMSO vehicle and 465 $\mu\text{l}$  of saline). Drugs were infused via the jugular vein over 5 minutes. After pretreatment, an intracranial subdural 3F Fogarty catheter was inflated over the left frontoparietal cortex for 60 seconds to induce ICH. Intracranial, arterial and LV pressures were recorded and the electrocardiogram was monitored. Hearts were excised and Western blotting was used to examine the phosphorylation status of RyR2 and cardiac troponin I (TnI).

**Results:** Elevating intracranial pressure resulted in a significant increase in plasma catecholamines, increased myocardial activity and the appearance of cardiac dysrhythmias in control and DMSO treated rats. Within minutes, left ventricular function deteriorated in a progressive manner (Table 1). There was evidence of hyperphosphorylation of RyR2 and TnI degradation (27kDa immunoreactive band versus 31kDa band). Although inhibiting endogenous calpain with calpeptin (3500 $\mu\text{g}$ ) preserved left ventricular function, this had no effect on the phosphorylation status of RyR2 or TnI degradation levels.

**Conclusion:** The impairment in myocardial function after ICH is associated with posttranslational changes in RyR2. Further studies are required to determine if the impairment in LV performance is the result of defective RyR2 channel function due to maladaptive hyperphosphorylation. Secondly, impairment in LV performance was associated with TnI degradation; however, their causal relationship in our model of intracranial hypertension is unknown

**Table 1. Hemodynamic response 30 minutes after induction of acute ICH.**

Group	MAP (mmHg)	HR (bpm)	LVDP (mmHg)	dP/dt <sub>max</sub> (mmHg.sec)	dP/dt <sub>min</sub> (mmHg.sec)	RPP (mmHg.bpm x 10 <sup>3</sup> )
Control	41±6*	316±37	66±4*	2917±421*	2273±386*	21±2*
DMSO	34±8*	303±13	59±9*	2604±452*	1757±548*	18±3*
Calpeptin	65±20	355±61	95±24	4140±1437	3847±1600	35±15
Sham	85±8	385±47	106±8	5033±1002	4892±941	41±8

Results reported as mean ± S.D.

\*  $P < 0.05$  within group compared to preinflation levels.

## Perceptions about research during anesthesiology resident training in Canada

Lisa C Silcox MD, Ted L Ashbury MD, Elizabeth G VanDenKerkhof DrPH, Brian Milne MD  
Queen's University, Department of Anesthesiology, Kingston General Hospital

**Introduction:** Controversy continues regarding the role of research activity during residency training.<sup>1,3</sup> This study was undertaken to assess perceptions and attitudes towards research experience in Canadian anesthesiology residency training programs.

**Methods:** With institutional approval, a national mail survey was distributed in November 2003 to all 476 Canadian anesthesiology residents and 16 program directors (PD). A follow-up e-mail reminder was sent in January 2004. In March 2004 a second and final mailing of questionnaires succeeded this.

**Results:** Descriptive analysis of 193 (40%) resident and 13 (80%) PD questionnaires were completed, to date. Approximately 60% of residents are involved in a research project, which include case reports, poster presentations, or abstract submission. Despite the finding that 85% of residency programs have mandatory research requirements, 60% of residents feel research should not be a mandatory component of residency training. Program directors indicate a lack of resident and faculty interest in research as the two main impediments to resident participation. However, residents indicate that continuing a project during non-anesthesia rotations is one of the most common institutional barriers (35%). Rationale for lack of research participation provided by the residents includes: lack of interest; the need to learn 'clinical' anesthesia; and the time commitment required. The majority of resident (90%) and program director (85%) respondents see the importance of acquiring protected time to undertake a research project and ranked this as a somewhat to very influential requisite. Interestingly, 75% of residents, when asked, suggest alternatives to undertaking a research project. Transesophageal echocardiography (TEE) training skills (56/145), teaching courses, and administration programs, were cited most often. One third of residents indicate an interest in an academic career, involving research.

**Discussion:** Many residents feel that it is important to add to the body of anesthesiology knowledge (60%), and suggest that research training should at least be offered during residency. Although most programs require residents to undergo an intellectual inquiry of some form, 75% of residents would prefer spending their time in an alternate learning endeavor, if given the option. Currently, anesthesiology residents feel the most substantial barrier to undertaking research is the perceived lack of time. This has been shown in other Canadian studies.<sup>1,2,3</sup> Protected time for research inquiry is of paramount importance.

### References:

1. Ann. RCPSC, 26(5): 283-288
2. Acad. Med, 76(5): 477
3. Ann, RCPSC, 31 (5): 233-235

## **Personal protective system (PPS) and endotracheal intubation: “It’s about time”**

**B.D. Meunier, MD, J. Murdoch, MD, L. Patterson, MD, J.E. Zamora, MD, FRCPC**  
**Department of Anesthesiology, Queen’s University**

**Background:** The global outbreak of severe acute respiratory syndrome (SARS) in 2003 has resulted in more stringent infection precautions for health care workers (HCW)- the “New Normal”. The SARS associated coronavirus (SARS-CoV) has been found to spread via droplet and direct contact, infecting hosts primarily via respiratory and ocular mucosa. The virus may remain infectious outside of the body for up to 48-72 hours.<sup>1</sup> The “New Normal” for intubating a low-risk patient includes eye protection, gloves, and N95 mask (gown if anticipate exposure to body fluids). Intubation of patients diagnosed with severe respiratory illness (SRI), has been identified as a high-risk intervention requiring additional precautions. A full personal protective system (PPS) consisting of a N95 mask, eye protection, gloves, complete coverage suit and respirator, is required during intubation of these patients.<sup>2,3</sup> A subjective note of lengthy time to don full PPS, subsequent difficulty with movement, visualization and communication were noted by staff involved with the Toronto outbreak of SARS<sup>1</sup> as well as during training sessions held at the Kingston General Hospital. To date there are no published studies evaluating intubating conditions/abilities while wearing full PPS.

**Methods:** Ten volunteers from the department anesthesiology (staff and residents with prior PPS training) will intubate a Laerdal intubating mannequin twice: once while wearing the low-risk (“New Normal”) precautions and once wearing full PPS as for a SRI patient. Volunteers will be randomly assigned as to which intubation they will complete first. Data collected will include total time to intubation (from donning respective protective equipment); timing of intubation process only (i.e. exclusive of time for donning protective equipment); number of intubation attempts and incidence of endobronchial intubations. Subjective documentation of Laryngeal grading, ease of intubation, fit of protective equipment as well as perceived effects on ease of intubation will also be collected. Direct comparison of intubation times will be compared for the two types of simulated patients. Subjective data will be analysed for correlation with objective findings (timings and successful intubation).

**Status:** The volunteer consent form has been approved by Research Ethics. The Department of Respiratory Therapy has allocated personnel to participate as assistants in the simulation and has provided all required personal protective equipment. Completion of study is expected within one month.

### **References:**

1. Peng PWH, Wong DT, Bevan D Gardam M: Infection control and anesthesia: lessons learned from the Toronto SARS outbreak. CJA 2003; 50(10):989-97.
2. Ontario Ministry of Health and Long-Term Care. Directive HR03-12: Directive to All Ontario Acute Care Facilities for High-Risk Respiratory Procedures. 22 October 2003. Available at [http://www.health.gov.on.ca/english/providers/program/pubhealth/sars/docs/docs2/dir\\_2102203\\_high\\_risk\\_respiratory.pdf](http://www.health.gov.on.ca/english/providers/program/pubhealth/sars/docs/docs2/dir_2102203_high_risk_respiratory.pdf)

## **Post-operative analgesia for radical retropubic prostatectomy: Study proposal**

**Kyle Doerksen, MD & Alison Froese, MD, FRCPC**  
**Department of Anesthesiology, Queen's University**

**Introduction:** Radical Retropubic Prostatectomy (rRPP) is a commonly used curative treatment for clinically localized prostate cancer. Multiple analgesic strategies have been employed following this procedure including spinal or epidural opiates, continuous epidural block, IV ketorolac and intravenous Patient-Controlled Analgesia (PCA-IV). Prior to the year 2000 continuous epidural block was commonly used in our institution. Interestingly, studies on determinants of post-operative stay after rRPP revealed that the use of epidural analgesia may contribute to delay of discharge. This has led to a move away from epidural analgesia towards PCA-IV in this population. Some anesthesiologists in our hospital have employed Paravertebral Blocks (PVBs) as a means to improve on the analgesia provided by PCA-IV alone. The relative effectiveness of these three techniques (continuous epidural, PCA-IV, or PCA-IV with PVB) after rRPP is not known.

**Purpose:** To determine the effectiveness, side-effect profile, and safety of the analgesic regimes used for radical Retropubic Prostatectomy in our institution.

**Methods:** A descriptive, institution-based, retrospective review will be carried out on patients undergoing rRPP from the year 2000 to 2003. This time frame will encompass the transition from epidural analgesia to PCA-IV analgesia with or without PVB. Primary outcome measures will include maximum VAS scores, narcotic use, and time to discharge. Other outcomes to be assessed will include analgesic side-effects including PONV, sedation, pruritis, and length of intestinal ileus.

**Comment:** It is known that narcotic use increases the incidence of N/V, sedation, pruritis, and prolonged ileus in a dose-dependant manner. Our preliminary data suggest that PVBs used in conjunction with PCA-IV substantially decrease parenteral narcotic requirements for up to 24 hours post-operatively. This suggests that PVBs may both decrease hospital stay, as well as increase patient satisfaction as compared to PCA-IV alone after rRPP. A prospective randomized trial would confirm this.

**Inflammatory bowel disease and postoperative analgesia:  
Is it as bad as we think?**

**Robert Anderson, MD, David Bond, MD, MSc, FRCPC, and Paul Belliveau, MD, FRCSC  
Department of Anesthesiology & Surgery, Queen's University**

**Background:** Epidural and patient controlled analgesic options have revolutionized perioperative pain management. Decreasing the dose of narcotic and local anesthetic using synergistic medications and appropriately placed epidurals has improved analgesia and decreased side effects. Many anesthesiologists treat patients with inflammatory bowel disease differently than the general population based on the perception that these patients have higher postoperative requirements. Virtually all large randomized controlled trials specifically exclude this group of “difficult” patients. The perioperative analgesic requirement of the IBD patient has not been described previously.

**Purpose:** To describe the perioperative analgesic requirements of IBD patients undergoing laparotomy compared to non-IBD patients. Further, if these patients describe more pain, this endeavor will help generate hypotheses for future randomized controlled trials examining analgesic strategies and mechanisms of increased pain expression.

**Hypothesis:** Patients with IBD have higher VAS scores at rest and with movement than non-IBD patients after laparotomy.

**Design:** Retrospective case control design reviewing the last 3 years experience of the acute pain service at this institution. Data will be collected from all patients who underwent elective laparotomy without dissection of the perineum by one of two surgeons including diagnosis, type of surgery, analgesic modality, analgesic consumption, VAS, side effect profile, number of APS visits, duration of monitored bed use and time to discharge. In addition to direct comparison between IBD and Non-IBD patients, Crohn's Disease and Ulcerative Colitis will analyzed separately as well as laparotomy with or without pelvic dissection.

**Outline and Status:** This project has been approved by the Research Ethics Board and a list of patient numbers has been generated. 20 charts will be reviewed and then analyzed for data extraction quality and whether other variables should be recorded. The rest of the charts will then be reviewed.

## Evidence for activity of spinal cannabinoid (CB1) receptors in induction of opioid physical dependence

Tuan Trang<sup>1</sup>, Jean-Guy Chabot<sup>2</sup>, Remi Quirion<sup>2</sup>, Khem Jhamandas<sup>1\*</sup>.

<sup>1</sup>Dept. Pharmacology & Toxicology, Queen's University, Kingston, ON; <sup>2</sup>Douglas Hospital Research Centre and Department of Psychiatry, McGill University, Montreal, QC

**Background:** Evidence from pharmacological and neurochemical studies suggest that increased activity of calcitonin gene-related peptide (CGRP), at the spinal level, is involved in the development of opioid tolerance and physical dependence. The sensory neurons that release CGRP co-localize opioid and cannabinoid receptors. Like opioid receptors, activation of cannabinoid receptors inhibits CGRP release. In light of considerable evidence suggesting interaction between the opioid and cannabinoid systems, we examined whether endocannabinoids modulate changes in spinal CGRP that occur in the development of opioid physical dependence.

**Methods:** Physical dependence was established using escalating systemic doses of morphine (5-50 mg/kg) over a 5-day period. In chronically morphine treated animals, CGRP-like immunoreactivity was markedly increased in the spinal dorsal horn, and capsaicin evoked a greater *in vitro* peptide release from the spinal cord.

**Results:** Administration of naloxone (2 mg/kg; i.p.), an opioid receptor antagonist, depleted CGRP-like immunoreactivity, increased Fos (a marker of neuronal activation) expression in the dorsal horn, and precipitated an intense withdrawal syndrome. Intrathecal co-administration of AM-281, a selective CB1-receptor antagonist, with daily morphine prevented depletion of CGRP-like immunoreactivity, suppressed Fos-induction, attenuated the behavioural manifestations of withdrawal, and reduced capsaicin-evoked CGRP release.

**Discussion:** The results of this study suggest that modulation of spinal CGRP activity by CB1-receptors contribute to induction of opioid physical dependence. [Supported by Canadian Institutes of Health Research]

## The effects of intraperitoneal ketorolac on postoperative pain following laparoscopic cholecystectomy

G. Ramsey, MD, J. Murdoch, MD, Y. Borshch, MD, T. Saha, MD, D. Tod, RN  
Department of Anesthesiology, Queen's University

**Background:** Delay in discharge from day surgery is frequently secondary to postoperative pain.<sup>1</sup> Some of the pain following laparoscopic procedures has been attributed to the rapid distension of the peritoneum causing traction and tearing of blood vessels and nerves, and release of inflammatory mediators. The amount of pain after laparoscopy may be related to the concentration of these locally induced mediators, including prostaglandins. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit inflammatory mediator release through the inhibition of cyclooxygenase synthetase. NSAIDs, administered by various routes, have been shown to be more effective in reducing postoperative pain in laparoscopic surgery when compared to placebo or acetaminophen. Prior work has suggested that intraperitoneal installation of the NSAID tenoxicam, combined with lidocaine, significantly reduces postoperative pain following laparoscopic cholecystectomy relative to placebo.<sup>2</sup>

**Aim:** The aim of this study is to determine the analgesic effectiveness of intraperitoneal ketorolac for postoperative analgesia following laparoscopic cholecystectomy and to compare this route with intravenous administration. Secondary analysis will include incidence of nausea and vomiting and overall patient satisfaction.

**Methods:** Seventy five (75) patients ASA I-III, aged 18-65 years old undergoing elective day case laparoscopic cholecystectomy will be recruited following Ethics Board approval and informed consent, and they will be randomized to 3 treatment groups. Group 1 will receive intravenous (IV) saline 1ml, intraperitoneal (IP) saline 250ml. Group 2 will receive IV ketorolac 30mg, IP saline 250ml. Group 3 will receive IV saline 1ml, IP ketorolac 30mg in 250ml saline. All investigators and the subjects will be blinded to the contents of the solutions administered. All patients will receive 975mg PO acetaminophen 1 hour prior to surgery and all incision sites will be infiltrated with 0.25% bupivacaine. A standard anesthetic protocol will be followed for all subjects. Visual Analog Pain (VAS) scores at rest and with movement will be recorded in the recovery by a blinded observer at 30min, 1 hour, and 2 hours post injection and prior to discharge. Follow up will be made at 24 hours post surgery with a telephone questionnaire. Further follow up will be done 30 days post-operatively. Time to first request for analgesia, total analgesic requirement, incidence of shoulder tip pain, side effects, incidence of nausea and vomiting, and patient satisfaction will also be recorded.

**Progress:** The research proposal was submitted to the Research Ethics Board (REB) in January, 2004. Minor modifications to the protocol and consent form were requested and were subsequently altered. Final approval of the study by REB is pending.

### References:

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2. Elhakim M, Amine H, Kamel S, Saad F: Effects of intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2000; 44: 929-33.



## **Cervical spine movement during laryngoscopy: Objective assessment and comparisons of indirect fiberoptic and prismatic laryngoscopes**

**Investigators: Dr. S. Sharan, Dr. J. E. Zamora, Dr. K. Sutherland**  
**Departments of Anesthesiology & Radiology, Queen's University**

**Background:** Direct laryngoscopy requires cervical spine movement. The GlideScope is a video laryngoscope that is inserted conventionally. The physician can monitor the passage of the laryngoscope tip down to the epiglottis area. The Viewmax laryngoscope blade is a prismatic modification of the Macintosh laryngoscope blade that allows the user a more anterior view of the larynx. In a suspected cervical spine injury, the goal of the anesthesiologist is to secure the airway without worsening the patient's neurological condition. Routine intubation requires direct laryngoscopy that involves extension of the head at the occipito-atlanto-axial complex and flexion of the lower cervical vertebrae. In cervical spine trauma patients, there is a conflict between minimizing this movement and allowing sufficient laryngeal exposure to allow tracheal intubation. The Bullard laryngoscope is an indirect fiberoptic laryngoscope. Several studies have shown that it decreases cervical spine movement during intubation when compared to more conventional laryngoscopes such as the Macintosh and Miller blades. One of the claimed advantages of the GlideScope is less neck movement resulting in less trauma to the patient. Currently there is a single correspondence that shows an improvement in laryngeal view when comparing the GlideScope with the Macintosh laryngoscope. At the present time, no publications exist mentioning the Viewmax laryngoscope. The aim of this study is to compare cervical spine movement in cadavers (measured radiologically) and laryngeal view obtained with the GlideScope, Viewmax, Bullard, and Macintosh laryngoscopes.

**Research Question:** Do the GlideScope and Viewmax reduce cervical spine movement, improve laryngeal view and reduce the number of attempts during intubation when compared with other laryngoscopes?

**Study Design:** The study is a randomized, controlled, crossover trial.

**Methods:** 20 fresh cadavers will be used as subjects. Each cadaver will act as its own control. Cadavers with oropharyngeal or cervical spine pathology, decreased range of head or neck movement, and those less than 18 years of age will be excluded from the study. Each cadaver will undergo intubation by the same anesthesiologist in a standardized fashion using manual in-line stabilization. During the course of intubation lateral x-rays will be taken in the neutral position and at the time of intubation. Each cadaver will undergo intubation using each of the laryngoscopes.

**Analysis:** Changes in angle between each cervical vertebra will be determined and the mean will be calculated for each laryngoscope. If the data is normally distributed, repeated measures ANOVA will be used for comparative analysis. If data is not normally distributed, Friedman analysis will be performed. Cormack and Lehane grade and number of attempts will be analyzed using the Chi-square test using frequencies or percentages. Time to intubation will be measured in seconds and the mean time will be analyzed using repeated measures ANOVA.

**Project Timeline:** Recruiting 20 fresh cadavers will require approximately 2 years.

## Effects of intrathecal gabapentin on spinal morphine tolerance in the rat tail-flick and paw pressure tests

<sup>1</sup>Clive Hansen, <sup>1,2</sup>Ian Gilron and <sup>1,2</sup>Murray Hong

<sup>1</sup>Department of Pharmacology & Toxicology, <sup>2</sup>Department of Anesthesiology Queen's University

**Background:** Analgesic tolerance to opioids has been described in both experimental and clinical conditions and may limit the clinical utility of these agents. We have previously shown that systemic gabapentin (GBP), a non-opioid drug, prevents and reverses tolerance to systemic morphine in the rat. The aim of this study was to investigate the effect of intrathecal GBP on spinal morphine tolerance.

**Methods:** Studied rats were given 7 days of intrathecal injections with saline (10µl), GBP (300µg), morphine (15µg), or a GBP/morphine combination and analgesic testing using tail flick and paw pressure tests was conducted prior to and 30 minutes post-drug injection. On day 8, an antinociceptive dose response curve was constructed and ED50 values for morphine (given alone) were calculated for each study group.

**Results:** Co-injection of GBP with morphine blocked the development of tolerance as shown by the preservation of morphine analgesia over 7 days as well as a concomitant decrease in ED50 values on day 8 as compared to the morphine alone group. Although additive analgesia over days 1-7 cannot be ruled out, ED50 reductions in the GBP/morphine combination group indeed suggest some suppression of tolerance.

**Discussion:** These data support previous evidence that GBP prevents opioid tolerance and more specifically indicate that intrathecal GBP prevents the development of spinal opioid tolerance. Future studies are needed to examine the respective roles of supraspinal and peripheral sites of GBP/morphine interaction and to investigate the mechanisms underlying the action of GBP on opioid tolerance.

## The Effects of Obesity and COPD on Fast Track Extubation in Coronary Vessel Surgery

Richard Ahn, Queen's Medicine 2004, Dr. Joel Parlow, Dr. Brian Milne,  
Department of Anesthesiology, Queen's University

**Introduction:** Fast track extubation (FTE) following cardiac surgery is a relatively recent technique that involves extubating a patient as early as possible--usually within 6 hours--following general anesthesia. FTE was originally developed as a method to help decrease hospital costs by reducing ICU stay and its use has been shown to reduce health care costs by almost 50% one year after cardiac surgery with reduction in visits to rehabilitation facilities and length of hospital stay on readmission. Studies show that early extubation in coronary artery bypass graft (CABG) patients does not increase perioperative morbidity. Chronic obstructive pulmonary disease (COPD) and obesity are conditions not uncommon in patients undergoing cardiac surgery. COPD was found to be a risk factor for extubation failure and postoperative cerebral neurological complications following cardiac surgery. Obesity, in the setting of cardiac surgery, is correlated with an increase in sternal wound infections, sternal dehiscence, arrhythmias, and myocardial infarctions. This study aims to determine whether these conditions affect the length of time to extubation following FTE CABG surgery.

**Methods:** With ethics approval, we conducted a retrospective study of patient records involving those who were admitted for CABG operations at Kingston General Hospital, a 452-bed tertiary care teaching hospital, from January 2000 to December 2001. Patients were divided into three groups: concomitant COPD; concomitant obesity, and a control group without these conditions.

**Results:** Extubation times were: control=113 minutes, COPD=147 minutes ( $p=0.199$ ), obese=143 minutes ( $p=0.038$ ). Obese females had a mean duration of intubation of 209 minutes ( $p=0.000$ ) and were more likely to have diabetes ( $p=0.028$ ). Males did not have significantly different extubation times ( $p=0.885$ ). COPD patients were oldest ( $p=0.029$ ) and had significantly more peripheral vascular disease (PVD) ( $p=0.042$ ). PVD was associated with an increased mean extubation time of 39 minutes ( $p=0.033$ ). Extubation time increased by 23 minutes per surgical priority level ( $p=0.47$ ).

**Conclusion:** The increased extubation time for obese patients was statistically significant when compared to the control population. This difference was mainly caused by female obese patients. PVD and higher surgical priority also lengthened extubation time. The validity of the increased COPD extubation time is questionable due to the low sample size for this population. However, both COPD and obesity did not prolong intubation to a clinically relevant extent (beyond 360 minutes), nor did they increase the incidence of extubation failure or hospital length of stay. It appears that in most cases a FTE protocol is appropriate in patients with COPD and obesity following cardiac surgery.

## **Anastomotic quality in CABG: when life depends on millimetres**

**Trevor Bardell G. Andrew Y. Hamilton Douglas H. Bergstrom Mohamed J. Ali Departments of Anesthesiology and Surgery Queen's University Kingston, Ont.**

A 63-year-old man with a longstanding history of nephrotic syndrome due to membranous glomerulonephropathy, an 85% stenosis of his right carotid artery and class IV angina was referred for urgent cardiac surgery. He had a previous positive treadmill test, and a coronary angiogram revealed triple-vessel disease, including an 80% stenosis at the ostium of the left anterior descending (LAD) artery (Fig.1) with disease of its diagonal branch, 70% stenosis of the circumflex artery with occlusion of its obtuse marginal branch, and an occluded right coronary artery that filled via collaterals from the circumflex system. Coronary artery bypass grafting (CABG) was performed and included a saphenous vein graft to the diagonal and obtuse marginal arteries as well as anastomosis of the left internal thoracic artery (LITA) to the LAD artery. One challenge of CABG is that good methods of assessing graft patency have not been established. With "off-pump" CABG, or "beating heart surgery," the aorta is not cannulated or clamped as in conventional CABG, and thus the risk of stroke and other complications is theoretically reduced. Delicate arterial anastomoses are performed on a beating heart, and in order to assess the patency of these anastomoses many surgeons rely solely on the absence of myocardial ischemia when the patient is taken off bypass. Two widely used but unproven methods of assessing anastomoses rely on non-imaging, pulsed-wave Doppler ultrasonography or transit time flow measurement. For our patient, a conventional CABG technique was used. The same type of ultrasound probe that was used to detect a fragile atheromatous plaque in the patient's aorta (which can be avoided during cross-clamping and cannulation of the aorta, thus reducing the risk of intraoperative cerebral ischemia) was applied to the LITA-LAD anastomosis after the heart was restarted. Fig.2 shows this anastomosis: the blue section represents laminar flow in the LITA and in the LAD distal to the anastomosis, and the red section represents the turbulent flow in the diseased and stenosed segment of the LAD proximal to the anastomosis. The continuity of laminar flow from the LITA to the LAD suggests that the graft has bypassed the diseased LAD and is functioning as a single conduit. The image gives a glimpse of the frailty of human life—occlusion of this 2mm-wide channel is enough to make the difference between life and death. Fig.3, obtained using the same ultrasound probe, shows a pattern of blood flow at the site of anastomosis that is also consistent with a patent graft. The Doppler spectrum shows that flow increases in systole (a downward Doppler shift) and continues to increase, with longer duration, during diastole (the red baseline indicates zero flow). An occluded vessel may show only a systolic Doppler signal. The patient recovered from the CABG procedure without complications. His exercise tolerance improved, and at the time of writing he was free from angina. As the efficacy of this technology is reinforced in future clinical trials, intraoperative ultrasonography may become standard practice for many indications in cardiothoracic operating rooms.

## Quantifying the impact of pain reduction on quality of life and mood during neuropathic pain treatment: Implications for analgesic clinical trials

<sup>1</sup>Maneesh A. Deshpande, MSc, <sup>2</sup>Ronald R. Holden, PhD, <sup>1,3</sup>Ian Gilron, MD, MSc, FRCPC

<sup>1</sup>Department of Anesthesiology, <sup>2</sup>Department of Psychology, <sup>3</sup>Department of Pharmacology & Toxicology, Queen's University

**Background:** Quality of life (QOL) and mood outcomes vary widely in neuropathic pain trials. This may be explained by diversity of measurement tools but also by variable pain reduction and treatment-related adverse effects. While pain is commonly a primary trial outcome, the value of pain reduction is reinforced by corresponding improvements in QOL and mood. This pilot study evaluated the impact of pain reduction on QOL and mood in neuropathic pain.

**Methods:** Pain, QOL and mood measures from a placebo-controlled trial of non-depressed neuropathic pain patients were examined.

**Results:** Baseline data revealed impaired QOL according to SF-36 scores but mood levels, according to BDI and POMS scores, were comparable to those of a non-depressed population. Treatment-induced reductions in pain were positively correlated with improvements in QOL (SF-36) and mood (POMS). Pain reduction was positively correlated with improvements in role physical, bodily pain, vitality, social functioning and mental health domains of the SF-36 and depression-dejection, anger-hostility and confusion-bewilderment scales of the POMS. Based on a subsequent regression analysis, pain reduction from baseline of approximately 70% was estimated to improve overall QOL to a normative level.

**Discussion:** These data suggest a positive correlation between neuropathic pain reduction and improvements in QOL and mood in a clinical trial setting. We interpret that pain reduction need not be complete to restore a normal QOL and, furthermore, that reducing pain may elevate mood in the absence of clinical depression. Future studies should also evaluate the impact of treatment-related adverse effects on QOL and mood in analgesic trials.

## Anti-Hyperalgesic effects of delta opioid receptor agonists in a model of neuropathic pain

Sarah Holdridge, BSc & Catherine Cahill, PhD  
Department of Pharmacology & Toxicology, Queen's University

**Background:** Pharmacological evidence supports the involvement of the Delta opioid receptor (dOR) in antinociception; however its potential role in the treatment of neuropathic (NP) pain remains largely unknown. In the present study, we examined the effectiveness of dOR ligands following peripheral nerve injury (PNI) by means of chronic constriction of the sciatic nerve.

**Methods:** Mechanical allodynia and cold hyperalgesia were assessed in the rat at various time points following PNI.

**Results:** Neuropathic, but not sham, animals developed cold hyperalgesia as early as two days following nerve constriction, whereas the onset of mechanical allodynia occurred at later time points. Intrathecal administration of the selective dOR agonist, [D-Ala<sup>2</sup>]-Deltorphan II (30mg), produced a significant increase in the latency to respond to the noxious cold compared to pre-drug values in both NP and Sham animals. Similarly, [D-Ala<sup>2</sup>]-Deltorphan II partially reversed the tactile allodynia in Neuropathic rats, although did not alter mechanical thresholds in Sham animals. Western blotting experiments on tissue membranes prepared from lumbar dorsal spinal cords of NP rats revealed increased total dOR protein levels ipsilateral to nerve injury compared to the contralateral side and to control animals. In summary, spinal administration of a selective dOR agonist alleviated nociceptive behaviours indicative of allodynia and hyperalgesia in an animal model of NP pain. In addition, dOR protein in the spinal cord was up-regulated in NP animals, indicating that PNI produced increased synthesis of the receptor ipsilateral to the PNI.

**Discussion:** These data suggest a compensatory role of the delta opioid receptor following nerve injury and therapeutic potential for delta opioid receptor agonists in the treatment of neuropathic pain.

## **Enhanced axonal transport of mu and delta opioid receptors in a model of neuropathic pain**

**Noufissa Kabli, BSc & Catherine Cahill, PhD**  
**Department of Pharmacology & Toxicology, Queen's University**

**Background:** Ligation of the sciatic nerve has been shown to increase human beta-endorphin binding sites both proximal and distal to the site of nerve injury, which indicates bidirectional axonal transport of opioid receptors. More recently, an increase in mu-opioid receptor (MOR) protein levels distal to the site of nerve constriction in a model of neuropathic pain has been reported (Ann Neurol. 53:366, 2003). In the current study, we investigate axonal transport of mu- and delta-opioid receptors (DOR) in the sciatic nerve in a model of neuropathic pain.

**Methods:** Immunohistochemical and immunoblotting techniques were utilized to localize opioid receptors to specific cell populations of the dorsal root ganglia (DRG), and to quantify total opioid receptor protein levels in the DRG and sciatic nerve (SN).

**Results:** MOR protein levels were significantly elevated in DRG and SN ipsilateral to the site of nerve injury. Similarly, a significant increase in DOR protein levels was observed in the SN ipsilateral to the injury. Our results suggest increased protein synthesis and enhanced axonal transport of MORs and DORs ipsilateral to the site of nerve injury in a neuropathic pain model.

**Discussion:** Taken together, these findings indicate that peripherally-acting opioid analgesics may have therapeutic potential in the treatment of neuropathic pain.

## **The Role of Interpersonal Sensitivity in Depression, Perceived Social Support, and Chronic Pain**

**Tripp, D.A., Ph.D.<sup>1</sup>, B.A. Hon.<sup>1</sup>, Kelly, A.C., B.A.H. Candidate, Borshch, Y.D., M.D.<sup>2</sup>**

<sup>1</sup> **Department of Psychology, Queen's University, Kingston, ON.**

<sup>2</sup> **Department of Anesthesiology, Kingston General Hospital, Kingston, ON**

**Background:** Interpersonal factors have significant impact on the mood and pain experience of chronic pain patients. However, research has yet to elucidate the nature and roles of a multitude of interpersonal variables in the chronic pain experience.

**Objectives:** (1) Examine the relationships between interpersonal sensitivity (IS), depression, pain, perceived social support, negative responses from a significant other, and pain catastrophizing. (2) Identify the specific psychosocial predictors of pain. (3) Identify the specific psychosocial predictors of depression.

**Methods:** Fifty patients on a chronic pain physician's waiting list completed a mail-out survey that assessed IS, depression, pain, perceived social support, negative responses from a significant other, and pain catastrophizing.

**Results:** IS was positively associated with depression, pain catastrophizing, and the affective dimension of pain. Interpersonal self-esteem (IS subscale) was positively associated with perceived social support and inversely associated with negative responses from a significant other and catastrophizing. Catastrophizing ( $r = .45$ ) acted as the lone predictor of pain experience. IS ( $r = .26$ ) and negative responses ( $r = .33$ ) significantly predicted depression.

**Conclusions:** Results suggest that IS and negative interactions play important roles in the mood of chronic pain patients, and that pain catastrophizing plays a significant role in pain experience. The differential impact of IS in pain and depression highlights the need to further examine interpersonal factors in the chronic pain experience. Findings suggest that IS is worthy of further investigation in chronic pain. Continued research might help inform more effective and better tailored interventions for chronic pain sufferers.



## **Epidemiological Survey of Chronic Pain in South-Eastern Ontario: Disability, Depression, Medication Use, and Health Care Visits**

**McAlister, M.C., B.Sc. Hon.<sup>1</sup>, Tripp, D.A., Ph.D.<sup>1</sup>,  
Van Den Kerkhof, E.G., R.N., M.Sc., Dr.P.H.<sup>2,3</sup>**

<sup>1</sup> Department of Psychology, Queen's University, Kingston, ON.

<sup>2</sup> Department of Anaesthesiology, Kingston General Hospital, Kingston, ON

<sup>3</sup> Department of Community Health and Epidemiology, Queen's University, Kingston, ON

**Introduction:** Chronic pain is a significant health problem in Canada, affecting between 15 and 66% of the population. The current research aims to determine the estimated prevalence of chronic pain and depressive symptoms in South-Eastern Ontario in order to establish the need for a multidisciplinary pain centre in the region.

**Methods:** A telephone survey was conducted and the questionnaire included the Graded Chronic Pain Scale (GCPS) (von Korff et al., 1992), and questions related to depression, medication use and healthcare utilization. A random sample of households in the KGH catchment area were contacted and a response rate of 49% provided 1,067 completed questionnaires. Participants were classified into 5 different incremental grades of intensity and interference (Grade 0 = no pain; Grade 4 = high interference and disability). Analysis included frequencies, percents, measures of central tendency, chi square, t-test, ANOVA, and logistic regression.

**Results:** Point prevalence of chronic pain was 34% (Grade I), 26% (Grade II), 9% (Grade III), and 8% (Grade IV). Healthcare visits increased as pain grade became more severe ( $\chi^2(6, N = 805) = 142.84, p < .05$ ), as did medication use ( $\chi^2(9, N = 788) = 115.48, p < .05$ ). In multivariate analysis, health care visits, drug use, health rating and depression were associated with increasing levels of pain. Income, area of residence, drug use, health rating and GCPS were associated with depressive symptoms.

**Conclusions:** Data indicate that a significant proportion of the South-Eastern Ontario community experience all levels of pain and accompanying depressive symptoms. Seventeen percent experience high levels of pain and interference. These findings have important clinical implications as well as broader implications for healthcare planning and allocation.

## **The effects of spinal ultra-low doses of opioid receptor antagonists on systemic morphine dependence**

**K. Oxbro, T. Trang, M. Sutak, K. Jhamandas\*, Dept. of Pharmacology and Toxicology, Queen's University, Kingston, ON, Canada, K7L 3N6**

**Background:** The stimulatory actions of opioid agonists, sensitive to ultra-low doses of opioid antagonists, have been implicated in the genesis of opioid tolerance and physical dependence. Intrathecally administered ultra-low doses of naltrexone (NTX), an opioid antagonist, can block or reverse tolerance to the spinal analgesic action of morphine. Thus, low dose NTX may also influence the development of opioid physical dependence via its spinal action. To investigate this, we examined the effect of intrathecal NTX on behavioural and neurochemical manifestations of precipitated morphine withdrawal, an indicator of physical dependence.

**Methods:** Male Sprague Dawley rats, with indwelling spinal catheters, were given systemic ascending doses of morphine (5 to 50 mg/kg, i.p.) concomitantly with intrathecal injections of saline (control group) or NTX (0.05 ng) for 5 days. The resulting analgesic response was assessed in the tail-flick and paw pressure test.

**Results:** Opioid withdrawal was precipitated by a single NTX challenge (2 mg/kg, i.p) at the end of the treatment period. Morphine injections produced dose-related antinociceptive responses that were not significantly affected by intrathecal NTX. Administration of the antagonist challenge evoked a robust withdrawal response involving autonomic and somatic hyperactivity, depletion of calcitonin gene related peptide (CGRP)-immunoreactivity, and expression of Fos protein in the dorsal horn. Intrathecal NTX treatment attenuated the behavioural signs of withdrawal, reduced CGRP depletion and the Fos response.

**Discussion:** The results suggest that ultra-low dose NTX can attenuate the neural and behavioural responses associated with withdrawal without reducing analgesia. Thus, low dose receptor antagonist treatment could be useful in influencing both opioid tolerance and physical dependence [Supported by Canadian Institutes of Health Research]

## CRITICAL APPRAISAL ESSAY

By: Jason Erb, MD, PGY-1

Title of Publication: **“Effects of Propofol, Desflurane, and Sevoflurane on Recovery of Myocardial Function after Coronary Surgery in Elderly, High risk Patients.”**

Authors: **Stefan G. De Hert, M.D., Ph.D., Stefanie Cromheecke, M.D., Pieter W. ten Broecke, M.D., Els Mertens, M.D., Ivo G. De Blier, M.D., Bernard A. Stockman, M.D., Inez E. Rodrigus, M.D., Ph. D., Philippe J. Vander Linden, M.D., Ph.D.,**

**Anesthesiology 2003;99:314-23.**

### INTRODUCTION

The goal of a critical appraisal is to determine the validity and usefulness of a research article to one's own practice. Value can be measured in how the research adds to the knowledge base of the topic, proves an idea, answers a question, or disproves a notion. Research is done for a variety of reasons with a variety of goals. Unfortunately though there are dozens of journals published every month and each is full of research. Some of it has little clinical usefulness or at worst is misguided or contains false information. Rather than a proving ground for ideas it becomes a way to prove a point be it correct or incorrect. In the past this presented itself as biased trials or poor research methodology. It has been felt that for the current generation of clinicians it is important to have good tools of critical appraisal. In other words, to be able to look at a study and decide if it is well done or perhaps is flawed in some way.

As part of the PGY1 year in Anesthesia the appraisal of a research paper of the residents choice has been added to the curriculum. For this paper I will look at the study entitled “Effects of Propofol, Desflurane, and Sevoflurane on Recovery of Myocardial Function after Coronary Surgery in Elderly High risk Patients.” Although I have witnessed little Cardiac anesthesia, the study was interesting in that it was randomized, controlled, and seemed to ask an important question. Propofol is used in many institutions as the anesthetic of choice in cardiac anesthesia, other modalities that have been used have been an opioid/benzodiazepine combination and isoflurane. I have not seen sevoflurane or desflurane used in cardiac anesthesia but these are modalities available as they are used in this study. There is a belief that the inhaled agents have a cardioprotective effect on the myocardium, which is not present in the intravenous anesthetics. It is unclear what the exact mechanism is, although it is believed to be related to the Potassium atp pump on the mitochondria, as opposed to the sarcolemma. It is believed that these agents exert a preconditioning against ischemia, which improves protection against myocardial infarction 1.

The authors of the study are mainly from the University hospital in Antwerp with the exception of Phillippe J. Van der Linden, M.D., Ph.D. who hails from Hospitalier Universitaire, charleroi, Belgium. The publication was submitted from the University Hospital Antwerp, in Edegem in Belgium. The sponsor of the study was Fonds voor Wetenschappelijk Onderzoek in Brussels Belgium. There was no further information on this sponsor.

The answer to this question in the authors' opinion is important as it may provide an additional tool in the treatment

or prevention of peri-operative and post-operative cardiac dysfunction.

### METHODOLOGY

The study was a prospective study with patients being entered through informed consent. The patients were randomized to one of three arms of the study. The clinicians (anesthesiologists) were not blinded as to the arm as this would have been impossible. The study population was human. The patients were selected to be high risk in view of the study designers. High risk patients were defined as patients over 70, with a preoperative ejection fraction of less than 50%, and with three vessel disease. Patients were excluded if they were undergoing repeat coronary surgery, concurrent valve repair, or aneurysm resection, which appear to be reasonable exclusion criteria. As well, patients with unstable angina or with valve insufficiency were excluded. Those patients taking oral diabetic agents or theophylline were also excluded. The reason for this was that the authors were concerned about the potential for these agents to interact with the cardioprotective effects of the agents being tested. Later in the paper the authors also mention another inclusion criteria. The patients must develop impairment of myocardial dysfunction with leg raising as manifested by changes in DP/dtmax . It is unclear when this was determined or how, ie. preoperatively or on the table under anesthetic. This is unclear, as it would seem the only method of determining this is when the patient is ready to go on pump.

The ethics group that approved the study was an in house group called the Institutional Ethical Committee(University Hospital Antwerp, Edegem, Belgium). There are no details into the proceedings. From a personal standpoint these are all current methods of anesthetic delivery in practice making it difficult to criticize the study as being ethically unsound.

Patients were assigned to groups randomly via opening an envelope, which assigned them to the propofol arm, the sevoflurane arm, or the desflurane arm. In all, 15 patients were initially assigned to each arm of the study. The protocol is quite detailed and strict. There is no room for crossover between groups. The number of patients required to show a statistical difference was calculated based on cardiac troponin I level and the DP/dtmax post CPB as the primary outcome variables. The authors felt that a minimum detected difference of 2 ng/ml between treatment groups was clinically significant. To attain this for a power of 0.8 and a of 0.5 they calculated 10 patients were required to show this. As far as DP/dtmax the

team doing the study felt that 100 mmHg/s was a clinically significant difference, from this they garnered that the number of patients required to show this with a power of 0.8 and a of 0.5 was 14 per group.

Patient characteristics were compared with the Fisher exact test and a one way ANOVA where appropriate. The Kruskal-Wallis one way ANOVA test on ranks was used to compare medians. Data collected from before CPB and after CPB were tested with ANOVA as well. The Bonferroni-Dunn test was performed for post-test analysis.

Hemodynamic parameters were analyzed using linear regression analysis.

All patients received radial artery catheters, 5 lead ECG, pulmonary artery catheters, pulse oximetry, capnography, urine and blood temperature monitoring. The groups were named Group A, Group B, and Group C. Pancuronium was used across the groups as a muscle relaxant at 0.1mg/kg. In all groups, anesthesia was induced with a continuous infusion of remifentanyl at 0.4mg kg<sup>-1</sup> min<sup>-1</sup> and remifentanyl was run in steady state at 0.3-0.6mg kg<sup>-1</sup> min<sup>-1</sup> depending on the patients requirements. The remifentanyl was in addition to the anesthetic agent, which is described below.

Group A was induced using a target controlled infusion of propofol attempting to achieve roughly 2mg/ml. Anesthesia was continued in steady state with propofol infusion set to a concentration of 2-4mg/ml. Group B induction was done with diazepam 0.1 mg/kg. Once induced, the Desflurane was run at 1-4%. Diazepam was not continued beyond induction. In group C, induction was performed with Sevoflurane at 8%, which was then dropped to 0.5-2% for maintenance.

Little detail about the surgical procedure is given, whether there were variations in technique or not. Activated coagulation time was kept above 450 s throughout the procedure. Pressure manometers were used to take the pressure reading in the atria and ventricles. These measurements were made pre coronary pulmonary bypass (CPD) and post. Measurements were made by inserting 4 pre-zeroed manometers, 1 in each atria and ventricle. Measurements were taken at steady state, and with 45 degree leg elevation. Pacing was used to maintain heart rate at 90 beats per minute. Measurements were taken at end expiration with respiration stopped. A second set of measurements, were taken at 15 minutes post separation in the same manner.

Anesthesia during CPD was unchanged in each group. Post CPB, the anesthetic regime was again unchanged. Post CPD, patients were transferred to ICU and sedation was maintained on remifentanyl at 0.4mg kg<sup>-1</sup> min<sup>-1</sup> as well as propofol (all groups) at 2mg/ml.

The primary endpoints of the study are the measurement of troponin I levels post CPB at 3,12, 24, and 36 hours and were measured in the intensive care unit. The other outcome measure was DP/dtmax post CPB with and without leg elevation.

The methodology of the study appeared sound. It would also seem that the study design was well controlled. There was no crossover reported and appears to be little room for this to occur.

## RESULTS

Initial comparison of groups showed no significant differences. Male to Female ratios were the same, ages were comparable. Length, weight, body surface area were all comparable. The sevoflurane group had a somewhat lower

average ejection fraction pre-op at 39%, compared to 43 % in the propofol group and 42% in the Desflurane group. Preoperative medications appear analagous. Most importantly, the number of grafts and bypasses performed were equivalent as well. Cross clamp time and CPB time were also comparable.

One patient, in group A, was lost due to development of a myocardial infarction and died 24 hours later. One patient, in group B, developed Ventricular fibrillation after weaning from CPB, this patient was converted, and survived, but was excluded from the study and not included in the analysis. Another patient, in group B, developed atrial fibrillation but recovered spontaneously, and was included in the analysis.

One of the primary endpoints of the study was the measurement of DP/dtmax, pre and post CPB. The authors felt this was a good measure of the overall functioning of the heart and this measurement was set as one of the cornerstones of this study. The DP/dtmax was measured without loading and then increased preload via leg elevation, thereby increasing the load on the heart. Without leg elevation DP/dtmax was equivalent in all groups pre CPB at 799 mmHg, 816 mmHg and 821 mmHg in groups A, B, and C respectively. With leg elevation, the values of DP/dtmax are recorded as changes compared to the values without leg elevation. The values dropped in all groups with leg elevation. Prior to CABG the change with respect to initial value (ie. without leg raising) was -50+/-11 mmHg (propofol arm), -55+/-12 mmHg (Desflurane arm) and -57+/- 14 mmHg. As can be seen all groups responded in a similar manner to the trial of leg raising pre CABG. After the bypass surgery the value differed slightly, with no leg elevation the values were 645+/-72, 802+/-77, and 823+/-82. With leg elevation, the propofol arm was -138 +/- 18, the desflurane arm was -57 +/- 11, and the sevoflurane arm -49+/-12. This indicates some sluggishness of the heart in the propofol arm as compared to the other two arms. The authors cite this as a significant change in the propofol arm, and feel this represents a significant change in cardiac function.

Hemodynamic data were collected throughout the procedure. The study breaks these down into Baseline, Pre CPB, Post CPB, End of procedure, ICU T3 (hour 3), ICU T12 (hour 12), ICU T24 (hour 24). The data reported were mean arterial pressure (MAP), mean pulmonary arterial pressure, central venous pressure, cardiac index, and systemic vascular resistance index. Of these values the propofol, desflurane, sevoflurane groups were all equivalent in values except in cardiac index both pre and post op. The propofol arm of the study had a decreased cardiac index compared to the other two arms post operatively. The mean value of the propofol CI post CPB was 2.0 +/- 0.4, compared to 2.5 +/- 0.4 with desflurane and 2.7 +/- 0.4 with sevoflurane. The disparity was also present at the end of the procedure with a value in the propofol group of 2.1 +/- 0.4, compared to 2.6 +/- 0.4 with desflurane and 2.8 +/- 0.4 with sevoflurane.

The values came closer at T3, and were no longer impressive by T12. Though the general trend to have lower values in the propofol arm continued. This was not one of the primary outcome measurements of the study.

Another variable measured was the time constant t of isovolumetric relaxation. This value was used with end systolic pressure to calculate R. R quantified changes in t, induced by changes in end systolic pressure and quantified afterload dependence of the rate of left ventricular pressure drop. As expected, these values are dependent on pressure changes in the ventricle and therefore also undergo significant changes. The propofol group shows more dysfunction than the other two

arms. Since R is calculated using tau, and tau is based on pressure this would be expected. However the authors did not cite these values as primary endpoints.

Interestingly, there were no differences noted in the right ventricle that were considered significant.

The other primary endpoint of the study was the troponin levels measured at various times throughout the recovery. As previously stated, troponin I was the measured quantity. Troponin levels were taken pre operatively, at arrival in the intensive care unit T0, at hour 3, hours 12, 24, and 36. The values of these variables were plotted with troponin on the Y axis and time on the X axis. The authors report any value above 2 ng/ml was significant. At hour three the propofol group, on average exceeded this value and was at 3 ng/ml. This value continued to rise and peaked at T24 when the propofol group was at 6 ng/ml. The desflurane group peaked at T12 at 2.25 ng/ml, while the sevoflurane group peaked at 1.7 ng/ml.

## DISCUSSION

The authors come to the conclusion that the use of sevoflurane and desflurane appear to have a cardioprotective effect on the myocardium during CPB, while this effect is not as evident with the use of propofol. As evidence of this, the authors point to the values of DP/dtmax which were worse in the propofol group and the elevated troponin values also noted in the study. De Hert et al. also indicate an increase in inotropic support for the propofol arm in the ICU, however this is poorly quantified in the study and almost becomes an aside.

It is felt that these results help to support the authors' hypothesis that volatile anesthetics are superior to propofol in CABG. They noted that this had also been verified in a previous study involving patients with higher ejection fractions, although the primary author of both studies is the same person. They feel this study indicates the same results and holds true for patients who are deemed higher risk. The authors are noncommittal on why this effect is occurring. They relate several possible mechanisms of cardioprotection that have been forwarded by researchers; several studies 1,2,3,4 are cited. De Hert et al. also recognize that propofol has antioxidant properties which have been deemed cardioprotective in some research. Although the authors of this study report the evidence around this point is conflicting. The reason for this effect is unclear to the authors and they are unable to comment on the protective mechanism of the volatile anesthetics. They note that previous work has indicated that volatile anesthetics provide ischemic preconditioning via the K atp pump on the mitochondria<sup>2</sup>.

The patients in this trial were subjected to a full anesthetic. In most situations, there is more than one drug given during an anesthetic. Is it possible that some of the other drugs may have contributed to the results seen? In actual fact this trial was well controlled with respect to drugs administered during the procedure. The authors mention that opioids have been reported to have a cardioprotective effect in some cases. In this trial, remifenatanil was the only opioid used and all patients received an equivalent dosage. This would tend to rule out an effect caused by this drug. One difference among the groups was the use of diazepam in the desflurane arm. It is possible that some of the effect in the desflurane group may be attributed to this. However the authors cite a study by Zaugg et al<sup>5</sup>. which reported minimal activity of midazolam on the K atp

channel in the mitochondria in rats, which is one of the postulated mechanisms of cardioprotection.

The troponin levels found by the authors support the theory of the cardioprotective effect of desflurane and sevoflurane. The cutoff value decided on by the authors was 2mg/L. They state two other values as well. The first is a value described by Sadony which indicates that 5.2 mg/L represent minor myocardial damage, and 13.4mg/L which is reported by Jacquet as being significant myocardial ischemia and infarction. The propofol arm developed troponin values in the range of the minor myocardial damage. In the authors opinion this supports the theory of the minimal protective effects of propofol.

## CONCLUSIONS

This study adds to the evidence that there is a protective effect of volatile anesthetics on the myocardium. This effect may be beneficial in situations where the heart is stressed such as CABG. It shows that this effect appears to be absent in anesthetics based on propofol. One of the limitations of this study is the small number of patients in each arm. Another limitation is the problem with the clinical relevance of this study. There is a lack of information provided on outcome of the patients except the biochemical marker troponin. There is also no mention of the patient course in the ICU and in hospital, except for some comments on increased inotropic support in the propofol arm. And finally, there is no measurement of outcome after discharge or functional status post discharge.

The study is interesting from a scientific and a knowledge point of view, however it fails to deliver in the clinical relevance side of the picture. The study is very well done and in my opinion is well written and a very detailed paper. The endpoints were achieved and well described. However there are limitations to this study design. For obvious reasons the study is not blind. Unfortunately though, it does not change the fact that the anesthetics were randomized but the anesthetists were not. Due to the fact that the patient had to show some negative changes in DP/dtmax with leg elevation, people could not be put into the study until they were basically primed for being put on pump. How this affected the selection criteria is not clear. Another issue is that all patients received propofol in the ICU for sedation, which in some ways contaminates the collection of troponin values.

Surgical technique and surgeon are not factored into the study at all. Were all grafts done in the same manner? How many surgeons were involved, how many cases did they perform in each arm? These questions are not addressed in the study. These are important variables that should have been addressed in the paper. How many different anesthetists were involved, did one anesthesiologist do all the cases in the propofol arm? Again these important questions are not clarified in the report.

I feel the big question that is left unanswered by this study is whether there is clinically significant outcome differences. The paper obviously adds to the body of knowledge that exists in the cardiac surgery realm but is inconclusive about the use of propofol in cardiac surgery patients. As the authors themselves report there needs to be more studies with increased patient enrollment and with longer follow up, in particular clinical outcomes.

**CRITICAL APPRAISAL**  
**By: Dave Robertson, MD, PGY-1**

**Title of Publication: "Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial."**

**Authors: Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A; Carvedilol Or Metoprolol European Trial Investigators.**

**Lancet 2003;362:7-1**

**BACKGROUND AND PURPOSE OF STUDY**

The COMET (Carvedilol or Metoprolol European Trial) Trial<sup>1</sup> was a superiority trial designed to compare clinical outcomes in chronic heart failure (CHF) patients treated with Carvedilol or Metoprolol. Although both classed as Beta-blockers, the two drugs have differing pharmacologic modes of action. Metoprolol tartrate (the study formulation) is a Beta-1 specific blocking agent. Carvedilol has a blocking action at both the Beta-1 and Beta-2 receptors as well as alpha-adrenergic receptors.

Both Metoprolol and Carvedilol have previously demonstrated significant clinical benefit in patients with CHF in randomized controlled trials. Metoprolol significantly reduced all-cause mortality by 34% and the risk of death or hospitalization by 19% (the primary endpoints) in a large (n = 3991) double-blind, randomized, placebo-controlled study [the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)]<sup>2</sup> involving patients with NYHA class II-IV heart failure (3.4% of Metoprolol recipients and 3.8% of placebo recipients had NYHA class IV heart failure. Carvedilol's clinical benefit was demonstrated in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS)<sup>3</sup> trial. This was a large (n = 2289), multicentre, double-blind, randomized trial involving clinically euvoletic patients with severe heart failure (defined as the presence of dyspnoea or fatigue at rest or with minimal exertion for  $\geq 2$  months and an LVEF of  $\leq 25\%$ , despite treatment with diuretics and an ACE inhibitor or angiotensin II receptor antagonist).

The COMET trial<sup>1</sup> was a multicenter, double-blind, parallel-group study designed to compare the effects of nonselective blockade of the  $\beta_1/\beta_2$  1-adrenergic receptors with Carvedilol to those of selective  $\beta_1$ -blockade with Metoprolol tartrate in 3029 patients with chronic HF (New York Heart Association Class II-IV HF; an LV ejection fraction  $< 35\%$ ; optimally treated with diuretics and angiotensin-converting enzyme inhibitors). The co-primary endpoints were all-cause mortality and the composite of all-cause mortality or all-cause hospital admission. In comparing these two agents, the COMET investigators sought to assess whether the addition of  $\beta_2$  1-blockade with Carvedilol could demonstrate any incremental clinical advantages compared to  $\beta_1$ -blockade alone.

**STUDY DESIGN**

*Inclusion Criteria*

To qualify for enrollment subjects with moderate or severe chronic heart failure (NYHA II-IV) were required to meet the criteria below:

- Subjects were on stable treatment with diuretics at a daily dose of furosemide 40 mg or equivalent (bumetanide 1 mg; torasemide 10 mg; hydrochlorothiazide 100 mg; bendroflumethiazide 10 mg) for at least 2 weeks prior to randomization.
- Subjects were on an ACE-inhibitor for at least 4 weeks, unless there is a contraindication. Digitalis and/or vasodilators were allowed at the discretion of the physician.
- Left ventricular ejection fraction must be  $\geq 0.35$  using echocardiography, radionuclide ventriculography or contrast ventriculography. If ejection fraction was not determined then left ventricular end diastolic diameter  $> 6.0$  cm and a fractional shortening  $< 20\%$  as measured by echocardiography could also qualify patients.
- At least one hospitalization for a cardiovascular reason should have taken place during the last 2 years.
- Written informed consent was obtained.

*Exclusion criteria*

Relating to cardiovascular disease

- Recent change of heart failure therapy defined as the introduction of a new class of drug for heart failure treatment within 2 weeks prior to randomization.
- Treatment with oral  $\alpha$ - or  $\beta$ -adrenergic blockers within the previous 2 weeks prior to randomization.
- Requirement for intravenous inotropic therapy.
- Current treatment with calcium channel blockers of the diltiazem or verapamil class.
- Current treatment with amiodarone  $> 200$  mg per day.
- Unstable angina within the last 2 months.
- Myocardial infarction within 2 months prior to the study.
- Cardiac surgery or angioplasty within 2 months prior to the study.
- Uncontrolled hypertension (systolic BP  $> 170$  mmHg or diastolic BP  $> 105$  mmHg).
- Haemodynamically significant valvular disease.
- Symptomatic and sustained ventricular arrhythmias within the last 2 months not adequately treated with antiarrhythmic drugs or implantation of a defibrillator.

- Class I anti-arrhythmic drugs.

#### Contraindications to beta-blocker therapy

- Heart rate <60 bpm, sitting.
- Peripheral arterial disease, symptomatic at rest.
- Sick sinus syndrome, bifascicular block, second or third degree AV block, unless treated with a pacemaker.
- Sitting systolic blood pressure <85 mmHg.
- History of asthma or other chronic obstructive pulmonary disease.
- Unstable insulin-dependent diabetes mellitus.

#### General exclusion criteria

- Hepatic disease (serum transferase >3 times normal).
- Stroke within the last 2 months.
- Endocrine disorders such as pheochromocytoma, active hyperthyroidism and untreated hypothyroidism.
- Cancer or other serious systemic disease with reduced life expectancy.
- Pregnant women and females with childbearing potential unless adequate contraception.
- Known drug or alcohol abuse or poor compliance with treatment.
- Administration of any study drug within the preceding 30 days.

#### Primary endpoints

- All-cause mortality.
- All-cause mortality or all-cause hospitalization.

#### Secondary endpoints

- Combined endpoint (all-cause mortality or cardiovascular hospitalization).
- Combined endpoint (cardiovascular death, non-fatal acute myocardial infarction, heart transplantation or worsening of heart failure).
- Cardiovascular death.
- NYHA class.
- Worsening of heart failure.
- Hospital admissions and duration of hospitalisations for heart failure and other reasons.
- Discontinuation of study therapy.

#### Dosages of study drugs

The Steering Committee selected 25 mg bid for Carvedilol and 50 mg bid for Metoprolol tartrate to be used as target doses in COMET. These doses were chosen as the existing evidence suggested that such doses would achieve a comparable degree of beta blockade in both groups. This was a departure from the dosing schedule used in previous landmark Metoprolol studies (MERIT HF and the Metoprolol in Dilated Cardiomyopathy (MDC))<sup>4</sup>.

## RESULTS

Of the 3029 enrolled subjects, 1511 were assigned to receive Carvedilol and 1518 Metoprolol. The mean study duration was 58 months. The baseline characteristics of the 2 study groups were similar. The all-cause mortality was 34% in the Carvedilol group and 40% in the Metoprolol group. The difference persisted after adjustment for known prognostic factors, and the distribution according to cause of death was similar between the 2 groups. Total admissions did not differ between the 2 groups (hazard ratio 0.97, 95% confidence interval [CI] 0.89 to 1.05,  $p = 0.45$ ); thus, the difference in composite end point was mainly a result of mortality reduction

in the Carvedilol group. The incidence of side effects and discontinuation of treatment were similar between the 2 groups.

## CRITIQUE

There are two major criticisms that must be addressed in evaluating the reliability and validity of the COMET's findings. These issues, although related, are independently important.

### Medication

The designers of COMET choose immediate-release Metoprolol (Metoprolol tartrate). Although more commonly prescribed in North America, its use in the study creates some problems. The previous landmark study in heart failure and Metoprolol was the MERIT HF2 trial. In fact, the authors of the COMET trial used the design and findings of MERIT HF to support their study design and hypothesis<sup>1</sup>. However, the MERIT HF trial used an extended release form of Metoprolol (Metoprolol succinate). There are previously demonstrated pharmacodynamic and pharmacokinetic differences between these two medications<sup>5</sup>. This significantly limits the generalizability of the COMET findings, as Carvedilol has not been proven superior to extended-release Metoprolol, the proven effective medication in heart failure.

### Dose

The target dose for Metoprolol tartrate was 50mg BID. In the MERIT HF trial the target dose of Metoprolol succinate was 200mg OD. Converting the extended-release to immediate release would result in a dose of 50mg QID. This results in a design that pits a low-dose beta-blocker against a high-dose beta-blocker. This is a contravention of one of the criterion for a valid superiority trial: that the medications be compared at equipotent doses<sup>6</sup>. Not unexpectedly the two medications demonstrated significantly different effects on heart rate and blood pressure, two of the important effects of beta-blockers in the treatment of heart failure. Carvedilol dose resulted in a reduction of heart of 13 beats per minute. This is exactly the same as the reduction noted in COPERNICUS<sup>3</sup>. The Metoprolol arm of the trial resulted in a reduction in heart rate of 11.7 beats per minute. This was significantly less than the Carvedilol are and less than that of the MERIT HF trial (14 beats per minute)<sup>1,2</sup>.

A similar result was noted when examining the blood pressure reductions. The paper states at 4 months there was a reduction of SBP of 3.8 mmHg in the Carvedilol group and 2.0 mmHg in the Metoprolol group<sup>1</sup>. This was a significant difference. The authors never address this point.

## CRITICAL APPRAISAL

Critical appraisal of a superiority trial forces examination of different set of variables than a simple randomized-control trial<sup>6</sup>. McAlister and Sackett have developed a set of criteria to examine the validity of this type of trial.

1. Was the assignment of patients to treatment randomized?

- In the COMET trial patients were randomized.

2. Was the randomization list concealed?

- COMET, Yes

3. Were all the patients who entered the trial accounted for at its conclusion

- COMET, Yes

4. Was analysis by intention to treat?

- COMET, Yes

5. Were clinicians and patients blinded to which treatment they received?

- COMET, Yes

6. Aside from the experimental treatment, were the two groups treated equally?

- This is the point in which the issues around the choice of medication and dose are most relevant. An inferior drug can appear superior if the control medication is given an inadequate dose. As previously proven effective doses of Metoprolol had been established (MERIT HF), then use of a reduced dose results in the study of an unproven regimen. This negates the possibility of truly proving that Carvedilol superiority. A valid trial must pit two proven drug regimens.

7. Were the two groups similar at baseline?

- COMET, Yes

8. Were the study endpoints clinically important?

- Yes, all-cause mortality and hospitalization are obviously important.

#### CONCLUSIONS

The design faults of the COMET study severely limit the utility of its findings. Unfortunately they should not be used to alter clinical practice because a clear superiority of Carvedilol has not been proven.

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