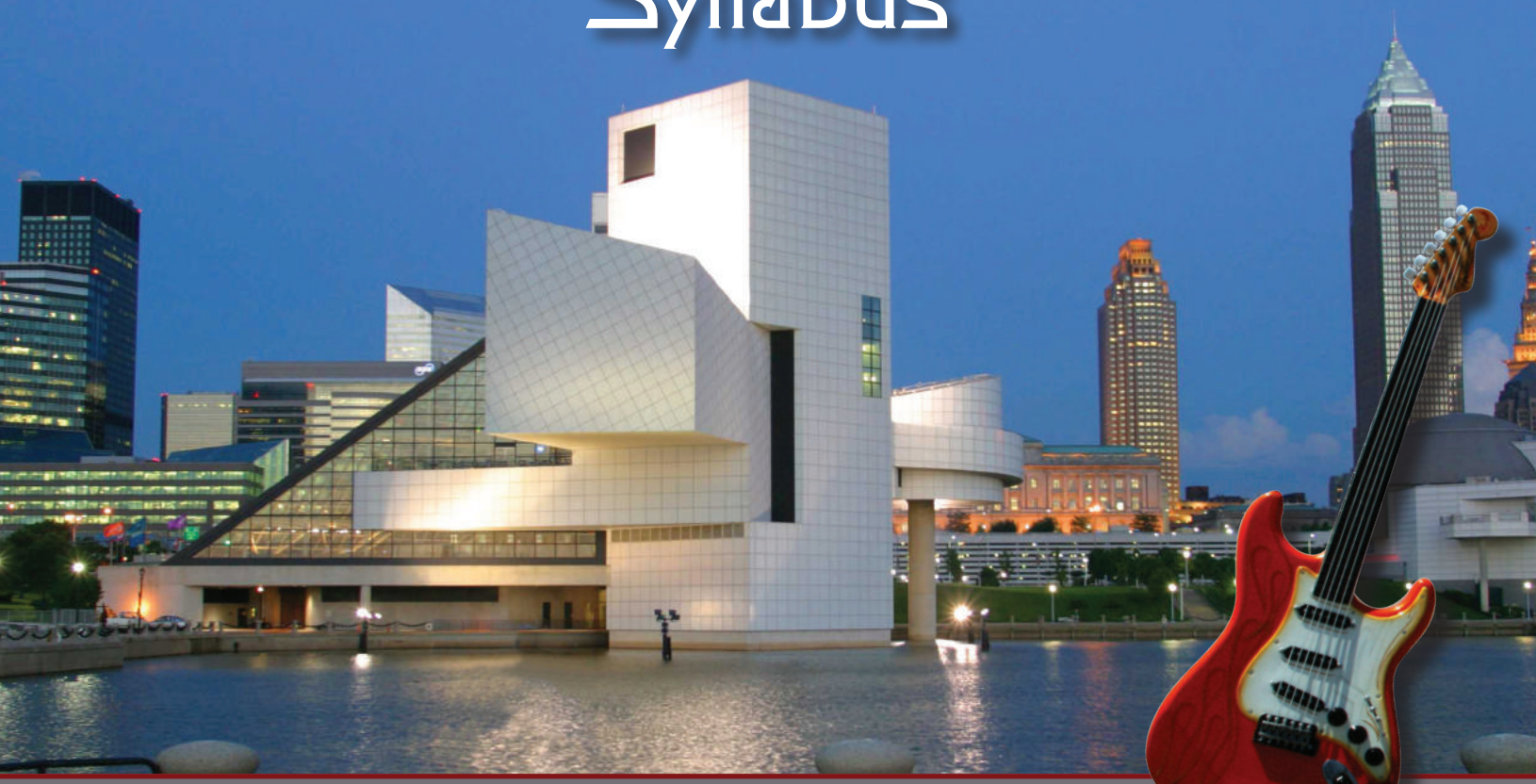
AUA 59th Annual Meeting

May 17-19, 2012 • InterContinental Cleveland • Cleveland, Ohio

Syllabus



Jointly sponsored by Cleveland Clinic and AUA Association of University Anesthesiologists

This activity has been approved for *AMA PRA Category 1 Credits™*.

AUA 59th Annual Meeting

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InterContinental Cleveland

Cleveland, Ohio

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Welcome to the AUA 59th Annual Meeting in Cleveland, Ohio!

Welcome to Cleveland!

We are extremely pleased to host the 2012 Association of University Anesthesiologists' Annual Meeting in Cleveland. The Anesthesiology Institute at Cleveland Clinic is proud to host this meeting for the first time, and we look forward to an exciting program.

We welcome all the AUA members to Cleveland, a city with a great tradition for clinical medicine, research and medical education. Cleveland Clinic sponsors the Cleveland Clinic Lerner College of Medicine, a 5 year program designed to create the physician investigators of the future, and one of the newest medical schools in the country. The Clinic sponsors GME training for more than 900 physicians in residency and fellowship programs. The Cleveland Clinic campus is just minutes from University Circle, with Severance Hall (home of the Cleveland Symphony Orchestra), the Museum of Art, the Botanical Gardens, the Museum of Natural History, and historic Cleveland Auto Museum. A few blocks further is the campus of Case Western Reserve University, which includes the Case School of Medicine and University Hospitals of Cleveland. As you can see, medicine is a major part of the life-blood of Cleveland.

The AUA leadership has again created an exciting program, assembling elements of healthcare dynamics, anesthesiology education, and basic science. The EAB will present a panel describing international anesthesiology education, and a panel on performance assessment during anesthesiology residency. The President's Panel will explore the basic science on consciousness, including the controversial topic of intraoperative awareness. The SAB offers oral presentations and poster discussion sessions, where junior faculty and residents mix with senior faculty presenting a wide array of scientific work. The Host Program is entitled "When Music Sings, the Brain Listens and the Heart Modulates: A Concert-Lecture" and will explore the science of how music stimulates the brain, is created, and can be used therapeutically. The science will be complemented by a performance by a virtuoso pianist, Prisca Benoit. The meeting reception will be Friday night, to allow early departure from Cleveland on Saturday for those who wish to do so. This reception will be held in the world famous Rock and Roll Hall of Fame, where cocktails and a buffet dinner will complement free access to all exhibits in the Rock Hall. There is no better way to come in touch with the origins of rock and roll than a gently stroll through the Rock Hall, and even better- only the AUA guests will be present, promising uncrowded access to all the exhibits.

Great meetings do not just happen. Christine Dionne and her team from the AUA headquarters in Park Ridge, Illinois have made a major commitment to making this a great meeting, handling logistics, challenging scheduling issues and the innumerable critical issues involved in creating a running a meeting of this size. The EAB and SAB have done their usual stellar job of assembling a cutting edge program. The Cleveland Clinic CME office has made positive suggestions, and the leadership of the InterContinental Hotel has planned a warm, comfortable welcome for all AUA attendees. The planning committee gratefully acknowledges the hard work and expertise of all who have contributed to creating this program.

Host Committee:

David L. Brown, M.D.
Andrea Kurz, M.D.
John E. Tetzlaff, M.D.

General Information

Identification Badges
Participants will receive a name badge, which will serve as admission to all scientific sessions, lunches and social events. Your badge must be worn at all times in order to enter all AUA 59th Annual Meeting functions.

Cell Phones and Beepers
Cell phones and beepers should be turned off or on vibrate. We thank you for your cooperation.

Phone Messages
The phone number for the InterContinental Cleveland is (216) 707-4300. Please ask callers to request the AUA 59th Annual Meeting Registration Desk by its full name. All messages will be posted on the message board near the Registration Area. Messages will not be announced, so please check the message board frequently if you are anticipating messages.

Attendee Interaction
Attendee participation is strongly encouraged. Standing microphones will be placed in each aisle to facilitate question and answer sessions. Those attendees asking questions are encouraged to use the microphones.

Meeting Evaluations and Continuing Medical Education Certificates
The Cleveland Clinic Foundation Center for Continuing Education requires that each attendee complete and return the meeting evaluation form as well as the Physicians Verification of Attendance form (both located in the syllabus folder).

Resident and Junior Faculty Meet and Greet Reception
Thursday, May 17, 2012, 6:00 – 6:30 p.m.
(Included in the Resident/Fellow registration fee)
A return feature from last year is the Resident and Junior Faculty Meet and Greet Reception. This reception gives residents and fellows and opportunity to meet their peers and the AUA Council members in an informal settling before the start of the formal program.

Welcome Reception
Thursday, May 17, 2012, 6:30 – 8:30 p.m.
AUA meeting attendees are encouraged to attend the Welcome Reception. This is an ideal opportunity to catch up with friends and colleagues.

Evening Social Event at the Rock and Roll Hall of Fame
Friday, May 18, 2012, 6:00 – 10:00 p.m.
Join your friends and colleagues for a evening of relaxation and nostalgia. The Rock and Roll Hall of Fame and Museum exists to collect, preserve and interpret the impact rock has made on our world. Attendees will have access to the exhibits and galleries. Consider this your backstage pass.

Coach busses have been secured to transport attendees to and from the Rock and Roll Hall of Fame.

Resident Luncheon
Saturday, May 19, 2012, Noon – 1:30 p.m.
(Included in Resident/Fellow registration fee)
A special luncheon for residents, fellows and their sponsoring chair. Members of the AUA Council will be present to meet with these future academic anesthesiology leaders.

Poster Presentations
Poster viewing is scheduled for each coffee break. The Scientific Advisory Board (SAB) will moderate the poster sessions. The following are members of the Scientific Advisory Board:

Dean B. Andropoulos, M.D.
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Houston, Texas

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Accreditation Information

Target Audience
This meeting is designed for anesthesiologists in the clinical and laboratory setting who desire to improve development of anesthesiology teaching methods by engaging in an interchange of ideas as represented in this meeting.

Needs Assessment
Topics for this meeting were derived from evaluations from the 2011 and previous annual meetings. Suggested topics were discussed and developed by educators who attended previous Annual, Council and Advisory Board meetings and by other authorities in the field of anesthesia education.

Accreditation and Credit Designation
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Cleveland Clinic and the Association of University Anesthesiologists. Cleveland Clinic is accredited by the ACCME to provide continuing medical education for physicians.

The Cleveland Clinic Foundation Center for Continuing Education designates this live activity for a maximum of 17.25 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Disclaimer
The information in this educational activity is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in this CME activity are those of the authors/faculty. They do not represent an endorsement by the Cleveland Clinic Foundation. In no event will the Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through this CME activity.

Program Objectives

President's Panel
At the conclusion of the session, the attendee should be able to:
- Describe the neuroscientifi c principles of anesthetic emergence and their relationship to intraoperative awareness and pharmacologic control of recovery.

EAB Panel: High Stakes Performance Assessment: During Residency and for Certification
At the conclusion of the session, the attendee should be able to:
- Determine how various performance measures using simulation, task training and standardized patients are used to assess performance.

EAB Panel – Anesthesia Education: Impact on Global Health
At the conclusion of the session, the attendee should be able to:
- Describe the factors and education solutions that influence maternal, infant and trauma mortality in low income countries and assess the requirements as well as the benefits of resident participation in global health projects.

SAB Oral Sessions
At the conclusion of the session, the attendee should be able to:
- Recognize a broad range of current basic science and clinical research in anesthesiology and critical care.

When Music Sings, the Brain Listens and the Heart Modulates: A Concert- Lecture™
At the conclusion of the session, the attendee should be able to:
- Recognize the neural mechanisms underlying music appreciation, the role of music education in brain development, the parallel between the doctor-patient and musician audience relationship, and the therapeutic effects of music on diseases of the nervous system and mental health.

NIH Session Panel – Translation Nuts and Bolts
At the conclusion of the session, the attendee should be able to:
- Be familiar with the skills and team necessary to move an academic lab discovery into the commercial space, and the types of funding sources available for small businesses.

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It is policy at the Cleveland Clinic Foundation Center for Continuing Education for individuals who are in a position to control the content of an educational activity to disclose to the learners all relevant financial relationships that they have with any commercial interest that provides products or services that may be relevant to the content of this continuing medical education activity. For this purpose we consider relationships of the person involved in the CME activity to include financial relationships of a spouse or partner.

The intent of this policy is not to prevent expert faculty with relevant relationship(s) with commercial interest(s) from involvement in CME, but rather to ensure that the Cleveland Clinic Foundation Center for Continuing Education CME-certified activities promote quality and safety, are effective in improving medical practice, are based on valid content, and are independent of control from commercial interests and free of commercial bias. Peer review of all content was conducted for all faculty presentations whose disclosure information provided to the Cleveland Clinic Foundation Center for Continuing Education was found to contain relationships that created a conflict of interest relative to the topic of their presentation. In addition, all faculty were instructed to provide balanced, scientifically rigorous and evidence-based presentations.

The staff in the Cleveland Clinic Foundation Center for Continuing Education, the Association of University Anesthesiologists, have reported that they have no relevant financial relationships with any commercial interests related to the content of this educational activity.

1= Ownership
2= Grants/Research Support
3= Stock Shareholder
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6= Royalties
7= Honoraria
8= Teaching and Speaking
9= Other

The following program committee members have reported the listed relevant financial relationships with commercial interests related to the content of this educational activity.

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Program Schedule

Thursday, May 17, 2012

10:00 a.m. - 6:00 p.m.	**Registration**	**3rd Floor Foyer**
1:00 - 1:15 p.m.	**Introduction and Welcome to the 59th Annual Meeting** David L. Brown, M.D., Host Chair	**Bank of America Conference Center**
1:15 - 1:25 p.m.	**SAB Program Introduction** Marie E. Csete, M.D., Ph.D.	
1:25 - 2:25 p.m.	**From Discovery to Product** *A panel discussion with anesthesiologists experienced in various stages of the product development pipeline.* • **The Academic Perspective: Finding Partners Needed to Bring a Discovery into the Development Pipeline** Douglas E. Raines, M.D. • **The Pharma Perspective: Evaluating the Commercial Potential of a Novel Therapy From an Academic Lab** Paula Bokesch, M.D. • **The Founder's Perspective: Maintaining the Ethical Divide Between Academic and Industry Labs** Dan E. Berkowitz, M.B.B.Ch. • **Funding Opportunities for Start-Ups** Marie E. Csete, M.D., Ph.D.	
2:25 - 2:55 p.m.	**ASA President's Update** John M. Zerwas, M.D., ASA President-Elect	
2:55 - 3:10 p.m.	**Break with Poster Viewing and Discussion**	**Ballroom A, B**
3:10 - 3:25 p.m.	**FAER Update** Denham S. Ward, M.D., Ph.D.	
3:25 - 4:55 p.m.	**AUA President's Panel – The Emergence of Consciousness** Moderator: George Mashour, M.D. • **Intraoperative Awareness** Michael S. Avidan, M.B.B.Ch. • **Neural Inertia** Max B. Kelz, M.D., Ph.D. • **Inducing Emergence** Ken Solt, M.D.	
5:00 - 6:00 p.m.	**AUA Business Meeting**	**Bank of America Conference Center**
6:00 - 6:30 p.m.	**Resident Meet and Greet Reception – InterContinental Hotel**	**Philips Break Area, 2nd Floor**
6:30 - 8:30 p.m.	**Welcome Reception – InterContinental Hotel**	**Bank of America Conference Center, 3rd Floor Foyer**

Program Schedule

Friday, May 18, 2012

6:30 a.m. - 4:30 p.m.	**Registration**	**3rd Floor Foyer**
7:00 - 8:00 a.m.	**Continental Breakfast**	**Ballroom C**
8:00 - 8:15 a.m.	**EAB Program Introduction** David J. Murray, M.D	
8:15 - 9:45 a.m.	**EAB Program (Part 1)**	
	High Stakes Performance Assessment: During Residency and for Certification Moderator: David J. Murray, M.D.	
	Performance Assessment: Assuring the Measures are Meaningful David J. Murray, M.D.	
	Resident Evaluation: What to Measure and How to Use the Measures Keith H. Baker, M.D., Ph.D.	
	Anesthesiology Certification: Beyond the Multiple Choice Examination Cynthia A. Lien, M.D.	
9:45 – 10:15 a.m.	**SAB Moderated Poster Discussion Session**	**Ballroom A, B**
10:15 - 11:45 a.m.	**EAB Program (Part 2)**	
	Anesthesia Education: Impact on Global Health Moderator: Robert R. Gaiser, M.D.	
	Obstetric Anesthesia: The Kybele Experience Medge D. Owen, M.D.	
	Establishing Trauma Care Training for Developing Countries Maureen McCunn, M.D.	
	Resident Participation in Global Health: Importance, Challenges, and Opportunities Marcel E. Durieux, M.D., Ph.D.	
11:45 a.m. - 1:00 p.m.	**Luncheon**	**Ballroom C**
11:45 a.m. - 1:00 p.m.	**EAB Luncheon**	**Room 204**
	SAB Luncheon	**Room 201**
	Presidents' Luncheon	**Falcon Room**
1:00 - 1:10 p.m.	**SAB Program Introduction** Marie E. Csete, M.D., Ph.D.	
1:10 - 2:40 p.m.	**SAB Oral Session (Part 1)**	
	Hemodynamic Slow Waves Induced With PEEP Oscillation to Measure Cerebrovascular Reactivity *Ken Brady, M.D.*	
Resident Travel Award	***Anesthetics Interfere With Axon Guidance via a GABAA Receptor Mechanism*** *Cyrus D. Mintz, M.D., Ph.D.*	
	Carbon Monoxide Prevents Anesthesia-Induced Neuroapoptosis in Newborn Mice *Richard J. Levy, M.D.*	
Junior Faculty Award	***Switching Microglia to a Neuroprotective Phenotype: A Novel Way to Improve Neuronal Survival After Cardiac Arrest*** *Ines P. Koerner, M.D., Ph.D.*	
	Role of Endothelial CSE/H2S in the Pathogenesis of Hypertension *Gautam Sikka, M.D.*	
	Association of Intraoperative Anesthesia Handovers With Postoperative Adverse Outcomes *Alsparslan Turan, M.D.*	
	The CQR Platform: A Novel Technology to Facilitate Longitudinal Data Collection and Evidence-Based Medicine *Roy C. Levitt, M.D.*	
	Leading Perioperative Change in an Era of Health Care Reform *Sharon Muret-Wagstaff, Ph.D.*	
2:40 - 4:15 p.m.	**SAB Moderated Poster Discussion Session**	**Ballroom A, B**
4:15 p.m.	**Adjournment**	
6:15 - 10:00 p.m.	**Evening Social Event at the Rock and Roll Hall of Fame** *Buses will start to depart from the Main Hotel Entrance at 5:30 p.m.*	

Program Schedule

Saturday, May 19, 2012

6:30 a.m. - 5:00 p.m.	**Registration**	**3rd Floor Foyer**
7:00 - 8:00 a.m.	**Continental Breakfast**	**Ballroom C**
8:00 - 8:15 a.m.	**Host Program Introductions** John E. Tetzlaff, M.D.	
8:15 - 9:05 a.m.	**Music and the Ear** Neil Cherian, M.D.	
9:05 - 9:15 a.m.	**Question and Answer Session**	
9:15 - 10:05 a.m.	**Music Therapy: Where Music and Medicine Meet** Dwyer Conklyn, MM, MT-BC	
10:05 - 10:15 a.m.	**Question and Answer Session**	
10:15 - 10:40 a.m.	**Break/Poster Viewing and Discussion**	**Ballroom A, B**
10:40 - Noon	**When Music Sings the Brain Listens and the Heart Modulates: A Conference-Concert™** Kamal R. Chémali, M.D.; Prisca Benoit	
Noon - 1:30 p.m.	**Luncheon**	**Ballroom C**
Noon - 1:30 p.m.	**Resident Luncheon**	**Room 204**
1:30 - 1:40 p.m.	**SAB Session (Part 2) Introduction** Marie E. Csete, M.D., Ph.D.	
1:30 - 3:00 p.m.	**SAB Oral Session (Part 2)**	
	The Complications of Uncomplicated Acute Type B Aortic Dissection: Refining the Penn Classification to Improve Patient Outcome *John G. Augoustides, M.D.*	
	Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 1 Diabetes Hyperglycemia in Mice *Robert E. Shangraw, M.D., Ph.D.*	
	Obesity Predicts Acute Kidney Injury Following Cardiac Surgery: Role of Oxidative Stress *Frederic T. Billings, M.D., M.Sc.*	
Junior Faculty Award	**An Engineered Water Soluble Variant of Human MU Receptor** *Renyu Liu, M.D., Ph.D.*	
Resident Travel Award	***Identification and Characterization of a Novel Compound That Protects Cardiac Tissue From hERG-Related, Drug-Induced Arrhythmias*** *Amanda N. Lorinc, M.D.*	
	Norepinephrine Blocks Isoflurane-Induced Activation of Firing in Putative Sleep-Promoting VLPO Neurons *Michael R. Chalifoux, M.D.*	
	Optoanesthesia With Meta-Azipropofol in Xenopus Tadpoles *Brian P. Weiser, B.S.*	
	Specific Hypersensitivity to Volatile Anesthetics in a Mouse Lacking Ndufs4, a Subunit of Mitochondrial Complex I. *Margaret M. Sedensky, M.D.*	
3:00 - 4:00 p.m.	**SAB Moderated Poster Discussion Session**	**Ballroom A, B**
4:00 - 5:00 p.m.	**SAB Plenary Session: New Concepts in Pulmonary Hypotension: From Gene to Therapy** Roger A. Johns, M.D.	

Future Meetings

AUA 60th Annual Meeting

April 4-6, 2013
J.W. Marriott Marquis
Miami, Florida

Hosted by
Department of Anesthesiology Perioperative Medicine and Pain Management
University of Miami, School of Medicine

AUA 61st Annual Meeting

April 24-26, 2014
Stanford, California

Hosted by
Stanford University, School of Medicine

Program Material

Thursday, May 17, 2012

From Discovery to Product

A panel discussion with anesthesiologists experienced in various stages of the product development pipeline.

- **The Academic Perspective: Finding Partners Needed to Bring a Discovery into the Development Pipeline**
  Douglas E. Raines, M.D.
- **The Pharma Perspective: Evaluating the Commercial Potential of a Novel Therapy From an Academic Lab**
  Paula Bokesch, M.D.
- **The Founder's Perspective: Maintaining the Ethical Divide Between Academic and Industry Labs**
  Dan E. Berkowitz, M.B.B.Ch.
- **Funding Opportunities for Start-Ups**
  Marie E. Csete, M.D., Ph.D.

The Pharma Perspective: Evaluating the Commercial Potential of a Novel Therapy From an Academic Lab

Paula Bokesch, M.D.

The objectives are of this presentation are:

- Describe the processes and costs of drug development from discovery to launch
- Describe how Pharma evaluates a novel molecule
- Describe the factors and metrics involved in determining the commercial potential

Processes of Drug Development

Nonclinical Development

An important strategy for drug development is to work backwards from the label – that is, what will the label look like? The target label is the basis of the target product profile (TPP). The TPP is applied to a library of compounds during nonclinical development and it serves as guidance for the selection of candidates to file for an Investigational New Drug license (IND) to study the compound in humans. Below is an example of a TPP for a novel, first-in-class oral analgesic for acute perioperative pain.

INDICATION: Management of moderate to severe acute perioperative pain

FREQUENCY: Oral BID

EFFICACY: Sig. decrease in pain scores (SPID, TOPAR, etc.), sig. prolonged time to rescue, and 30-50% reduction in opiate rescue requirements compared to placebo.

SAFETY: No respiratory depression; No platelet dysfx; No osteoclast/blast effects; No Sedation; GI complications (nausea, vomiting, constipation) reduced compared to opiates or NSAID alone or in combinations. No abuse potential. No withdrawal effects.

PK/ADME: Analgesia onset < 30 min; No clinically important interactions with anesthetics, proton pump inhibitors or other drugs typically used during surgery or post-surgery preferred. Potentiating analgesia by opiates or NSAIDs desirable.

CLINICAL USE: Perioperative analgesia for all surgery. Appropriate for surgery requiring postop oral analgesics, outpatient surgery.

CURRENT SOC: IV opioids peri-op in hospital, Ketorolac IV; discharged home on oral analgesics – usually Vicodin or other oral opioid and NSAIDS.

HEOR: Sig. less post-op opioid use and less post-op nausea and vomiting (PONV) in PACU with possible reduction in PACU length of stay or time to discharge home; more Fast-track from OR to step-down.

Based on this TPP, a library of compounds with target engagement for the analgesic mechanism of action are screened for their PK and toxicology. At each step of the way in nonclinical development, a compound advances or development discontinued based on if the compound meets the TPP for target engagement, pharmacology and toxicity. A promising compound can undergo "tweaking" by the chemists to alter solubility, adsorption, distribution and metabolism. At the end of this process (usually one year) several lead candidates are identified and advanced based on further nonclinical toxicology studies including safety pharmacology and pharmacodynamcs of the cardiovascular, CNS, and respiratory systems, phototoxicity, immunotoxicity, genotoxicity, carcinogenicity, reproductive toxicity, juvenile animal and abuse potential studies. The lead nomination undergoes toxicokinetic and PK studies with metabolic and plasma protein binding, *in vitro* CYP and metabolism, characterization of major metabolites and dose limiting toxicity studies to determine maximum tolerated dose. In principle, the duration of the animal toxicity studies conducted in two mammalian species (one nonrodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies.

Repeated-dose toxicity studies in two species (one nonrodent) for a minimum duration of 2 weeks (Table 1) would generally support any clinical development trial up to 2 weeks in duration (i.e. anesthetic drugs and analgesics for acute pain). Clinical trials of longer duration should be supported by repeated-dose toxicity studies of at least equivalent duration. Six-month rodent and 9-month nonrodent studies generally support dosing for longer than 6 months in clinical trials (i.e oral chronic use drugs).

Table 1. Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials (FDA Guidance: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) January 2010.

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials
Rodents	**Nonrodents**
Up to 2 weeks	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial
> 6 months	9 months

In the United States, as an alternative to 2-week studies, extended single-dose toxicity studies can support single-dose human trials. Clinical studies of less than 14 days can be supported with toxicity studies of the same duration as the proposed clinical study.

Clinical Drug Trials

As with nonclinical studies in animals, clinical trials in humans are designed based on the TPP and the desired label. Ideally, particularly for anesthetics and analgesics, the broadest label possible is sought. This can be achieved by several approaches. The first is to study the drug in multiple trials. At the time of the filing of the NDA for propofol 92 trials were submitted in over 3000 patients. Many of these trials were in small numbers of patients, i.e. 20 patients undergoing ECT. The result was the following very broad label for propofol.

Indication	Approved Patient Population
Initiation and maintenance of Monitored Anesthesia Care (MAC) sedation	Adults only
Combined sedation and regional anesthesia	Adults only
Induction of General Anesthesia	Patients ≥ 3 years of age
Maintenance of General Anesthesia	Patients ≥ 2 months of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients	Adults only

Another approach is to design an "all-comers trial". For example, the sNDA for Precedex included only two trials – one in awake fiberoptic intubation and the other for monitored anesthesia care. Both trials enrolled ASA 1- IV patients, including patients with multiple co-morbidities and organ failure. The MAC trial enrolled any surgical or diagnostic procedures in non-intubated patients resulting in everything from eye surgery to bunionectomies (and in-between). The resulting label from this trial is very broad and allows Precedex to be used for sedation of any non-intubated patient undergoing any surgical or "other" procedure anywhere in the hospital.

Precedex Labeled Indications

- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours. (1.1)
- Sedation of non-intubated patients prior to and/or during surgical and other procedures

The difference in cost between these approaches is enormous – 92 vs. 2 trials. An example of too narrow a label in the anesthesia space is the recent Exparel label by Pacira. This bupivacaine liposome injectable suspension is "indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia"…8 ml for bunionectomy and 20 ml for hemorroidectomy. This label limits the use of the product to bunions and hemorrhoids. How much Exparel would you inject for a hernia?

The cost of clinical trials reflects the duration of therapy. In general, drugs for use in the anesthesia space and acute care medicine usually cost less to develop than drugs intended to take indefinitely. The $2 billion to get a compound from discovery to launch is apropos to Lipitor or Plavix but not an IV analgesic, antibiotic or muscle relaxant. The major expenses in IV antibiotic trials are the central lab microbiology assessments and long follow up period for test of cure. In comparison, the Precedex MAC trial followed patients for 24 hours and the cost to conduct the trial was a third the cost of a daptomycin trial. Antibiotics and analgesics for acute care in hospital use in general cost less to develop than chronic use drugs.

Although drugs for acute care (acute pain analgesics, antibiotics) do not cost as much to develop in clinical trials, neither is their return on investment as great as for chronic use drugs. As indicated above, the nonclinical animal toxicity studies for an anesthetic or acute pain analgesic need only be conducted for up to 2 weeks as compared to 6-9 months for drugs intended to be taken for months or years. Similarly, clinical trials and follow up periods are shorter for acute care pharmaceuticals. The FDA may require long term use or follow up periods of 5-7 years for chronic use drugs and sometimes even drugs used for acute pain – i.e. neonatal anesthetics.

Estimating the Return on Investment

When a biotech company or university present their novel compound for consideration of in-licensing, there is nothing more annoying than their first slide which projects this will be a "billion dollar drug" for a compound that will be used for a short period of time in-hospital (anesthetics, IV analgesics, IV antibiotics). There are very few drugs in the anesthesia space that achieve the billion dollar/year milestone.

Revenue estimates are based on epidemiology, unmet medical needs, non-medical needs, and available alternative drugs.

Factor	Description / Examples
Epidemiology	Number of patients, trends, length of therapy
Medical needs	Morbidity, mortality, safety
Non-medical needs	Convenience, tolerability, patient quality of life, economics / pricing
Alternatives	Currently available treatments (drug and non-drug), treatments in development, prevention

These factors work together – for example, high mortality could lead to pricing flexibility and overcome the limitations of a small patient population. A pharmaceutical company can charge more for a drug that saves lives or preserves CV, CNS or renal function. This is one reason that makes orphan drug development so attractive to some companies. Another attraction of an orphan drug for a life-threatening disease is often a shortened time to development because fewer patients are required for safety analysis. Orphan drug compounds are often first-in-class compounds and these are much more attractive – and exciting. Anything after the first-in-class is just another "same old" that can only compete with the first-in-class if it has a significant safety benefit or is cheaper.

When assessing a novel compound to in-license, both the cost and risk of the deal are determined by where the compound is in development. The earlier in development, i.e. still in nonclinical or Phase I, the lower the investment (and cost of the deal) and the higher the risk to the pharmaceutical company acquiring the product. In contrast, drugs already in Phase III trials carry a higher investment premium and lower risk. At this late stage of development only launch and commercialization costs remain to market the product. **Most drugs fail in Phase 2;** the probability of success in Phase 2 is only 34%, whereas 70% of drugs in Phase 3 succeed to approval. The further along in drug development, the less risk and the higher the price tag. *Current corporate strategy of multiple early investments (nonclinical or P-1) may be worth pursuing, even if only one in ten would be fully developed*.

Investment	Impact on Attractiveness
Pre-clinical and clinical trials	Low early investments that generate information about likelihood of success increase attractiveness of a project (i.e. proof of concept early in P-1)
COGS	Helps to determine pricing flexibility / margins (low cost of goods preferable for competing with generics)
Pre and post launch sales and marketing costs	Have a low impact on attractiveness relative to the size of the investment required because the investment only needs to be made once the product has a high probability of launching
Sales force	Determines whether to commercialize internally or out-license

When shopping around for a pharmaceutical company to invest in your novel compound, it is important to find the correct fit. For example, Cubist is an acute care pharmaceutical company. We are focused on drugs and products given in hospitals. We market two IV antibiotics, daptomycin and fidaxomycin, and oral Entereg for post-op ileus. We have several other antibiotics in Phase III and a novel analgesic in Phase 1. Our sales force is hospital based and they call on infectious disease doctors, intensivists, hospitalists, and colo-rectal surgeons, and hopefully anesthesiologists in the future. When we evaluate products to in-license or acquire, we look for products that we can market within the hospital ICU, OR or ER. We are not a good fit for a drug that will be prescribed by internists, family practitioners, or other out of hospital office-based practices.

The probability of success is used to create an expected value for the project and is determined by several factors listed below.

Factor	Description / Example
Standard probabilities	Industry and antibiotic (or analgesic)-specific standards for each phase of development - i.e. FDA "guidance"
Specific barriers	Factors related to specific opportunities, such as formulation challenges, manufacturing difficulty, safety concerns, etc.
Risks	Issues related to specific opportunities, such as potential for resistance/tolerance, class-related toxicities, changes in market needs, etc.

Below is an example of an antibiotic from our discovery group that failed during development due to a safety signal. The projected sales were based on the following assumptions:

- Large and increasing number of potential patients with Gram negative infections
- High unmet needs due to mortality associated with target pathogens and toxicity/limited efficacy of current treatment options (Polymyxin)
- Potential for pricing flexibility due to seriousness of needs
- No other options likely to launch in next several years
- Pre-clinical and clinical Investments required now are low relative to the size of the potential opportunity
- Could commercialize internally with current sales force – hospital based

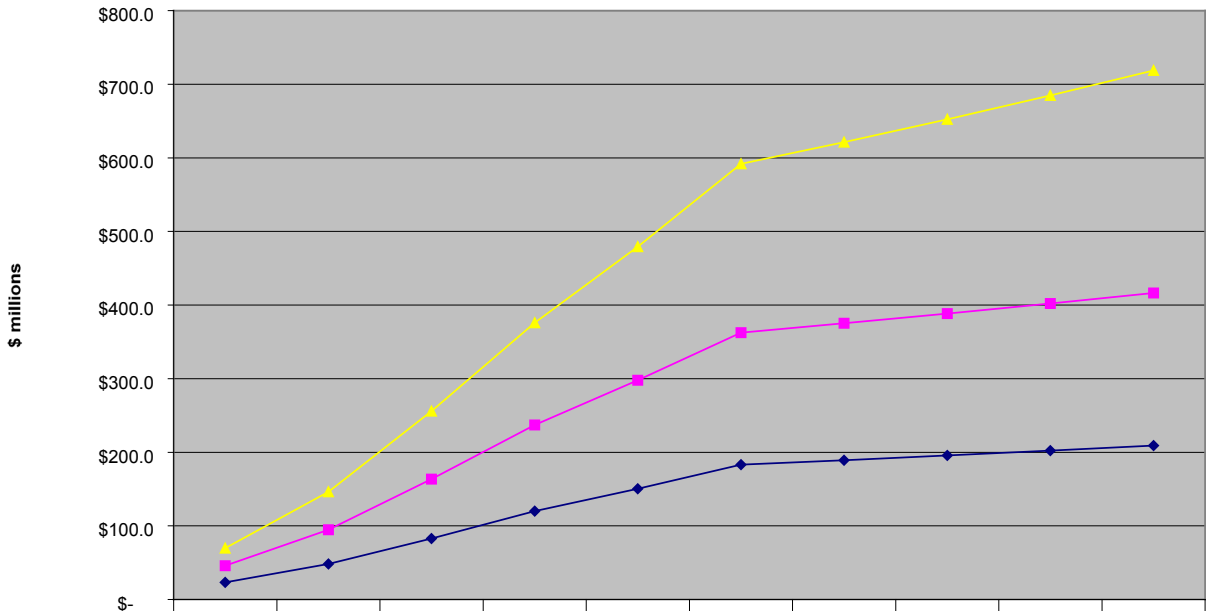
Grail revenue estimates peaked around $400MM. The ROI on this product would have been high had it not failed due to renal toxicity in Phase 1. The pre-clinical and clinical trials investments were low relative to the size of the potential sales. Furthermore, our sale force could commercialize internally with our current hospital based sales force. Grail (Gram negative infections) would not compete with daptomycin (Gram positive infections), which is another important consideration for drug development: don't shoot yourself in the foot or rob from Peter to pay Paul.

Finally non-financial factors are considered for our internal discovery products as indicated in the table below. In addition, luck helps. For example, propofol benefited enormously when sodium pentothal was scheduled in the 90's. Daptomycin (Cubicin) was the right drug at the right time. MRSA rates surged in the mid-2000's prompting the need for other effective antibiotics besides vancomycin which had reports of resistance developing. Daptomycin was launched in 2003 and has a bactericidal mechanism that is novel among antibiotics. It also has once a day dosing and doesn't have the adverse effects of vancomycin on the kidneys. Daptomycin can also be given as a two-minute infusion unlike vancomycin. Daptomycin has exceeded sales projections because it meets the fundamental criteria for success: (1) a first-in-class drug with a novel bactericidal mechanism; (2) better safety profile than the competitors (vancomycin, linezolid); (3) favorable COGS for margins; (4) it met an unmet need.

Factor	Description / Example
Fit with Cubist's capabilities	Commercial focuses on commercial capabilities, including sales force experience and reach, marketing strengths, etc.
Ability to commercialize or out-license the product	If Cubist will not commercialize the product itself, how easy / lucrative will it be to out-license the product; for example, is the product big enough to generate interest from large companies
Upside potential	Upside sales potential can make a marginal product attractive; for example, are there additional markets or indications where the product could be used

The bottom line to enhance the bottom line is to do your homework. What is the unmet need in a therapeutic area? Who/what is the competition addressing this unmet need? Where are they in development? What distinguishes your product from the others: safety; better efficacy; ease of administration; COGS? Finally, hospitals and insurers are very reluctant to put a proprietary drug on the formulary unless it distinguishes itself and has clear patient benefits (FDA requirement also) and can save the hospital/insurers money.

Grail Case Comparisons



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Low case	$23.3	$48.1	$82.9	$119.9	$150.5	$183.0	$189.2	$195.6	$202.2	$209.0
Base case	$45.8	$94.8	$163.5	$236.9	$297.8	$362.6	$375.3	$388.5	$402.2	$416.3
High case	$69.6	$146.2	$255.8	$375.9	$479.2	$591.8	$621.3	$652.2	$684.7	$718.8

Program Material

Thursday, May 17, 2012

ASA President's Update
John M. Zerwas, M.D., ASA President-Elect

AUA President's Panel – The Emergence of Consciousness
Moderator: George Mashour, M.D.

- **Intraoperative Awareness**
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ASA 2012

"*Indispensible to Your Practice*"

John M. Zerwas, MD
President Elect

ASSOCIATION OF UNIVERSITY ANESTHESIOLOGISTS
MAY 2012

American Society of Anesthesiologists

Advancing the Practice, Securing the Future

✓***Financial Security***

✓***Organizational Excellence***

✓***Exceptional Member Benefits***

American Society of Anesthesiologists

2

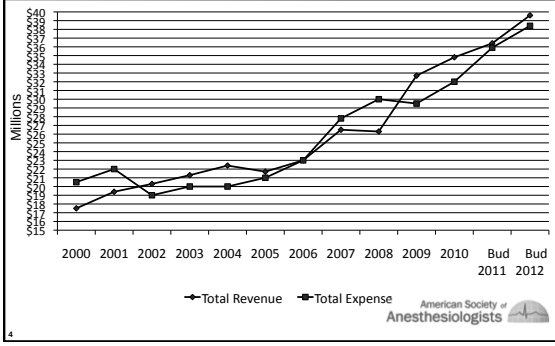
Advancing the Practice, Securing the Future

Financial Security

American Society of Anesthesiologists

3

Operating Revenue and Expense 2000-2010

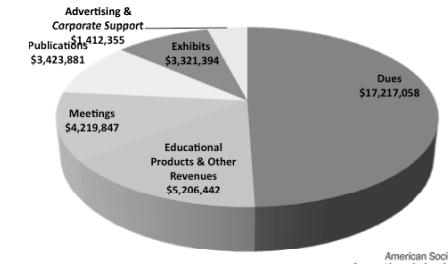


American Society of Anesthesiologists

4

Operating Revenues

2010 Operating Revenue $34,800,977

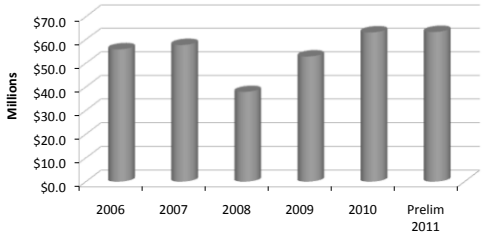


American Society of Anesthesiologists

5

ASA Total Reserves

Preliminary 2011 ASA Total Reserves $63,345,000



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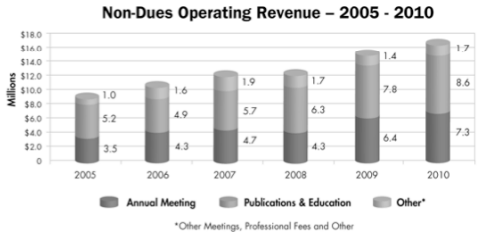
Non-Dues Operating Revenue



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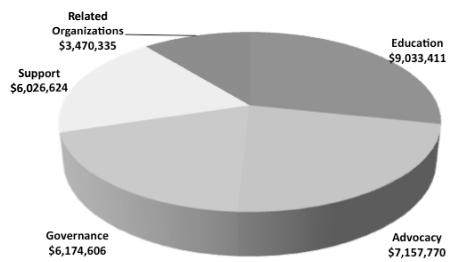
Operating Expenses

2010 Operating Expense $31,862,746



American Society of Anesthesiologists

8

Financial Processes and Systems

Over the past 4 years we have:

- **Hired a CFO**
- **Instituted Generally Accepted Accounting Principles**
- **Created a budget process**
- **Increased revenue**
- **Controlled expenses**
- **Rebuilt reserves**

American Society of Anesthesiologists

9

Advancing the Practice, Securing the Future

Organizational Excellence

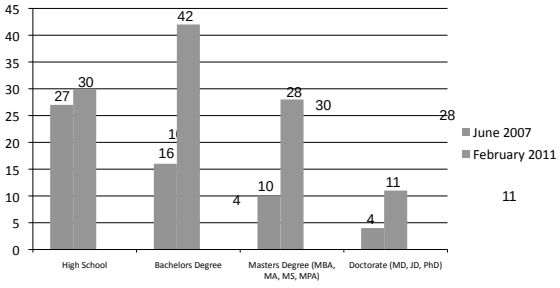
American Society of Anesthesiologists

New Leadership in Park Ridge John P. Thorner, JD

American Society of Anesthesiologists

11

Not Just Quantity, Quality



American Society of Anesthesiologists

12

Our Staff Experience Comes From:

American Hospital Association
AMA AMERICAN MEDICAL ASSOCIATION
NASS
The Joint Commission
AAD
AOA AMERICAN OSTEOPATHIC ASSOCIATION
BOSTROM
TMA
IPTA
RSNA
OSA
AAOS
cap
BlueCross BlueShield Association
AMC
American Society of Anesthesiologists

13

Created an Education Department

- Hired a Chief Learning Officer
- Evaluated educational products
- Determined member needs
- Maintained ACCME accreditation
- Assumed responsibility for Annual Meeting education programs

American Society of Anesthesiologists

14 4/26/12

Chief Learning Officer

- B. Diane Gambill, Ph.D.
- Initial goals will be to work with the education staff and Society leadership to evaluate current programs and identify areas where those programs can be enhanced and/or expanded to meet the educational needs of ASA members, as outlined in the Society's Strategic Plan.

American Society of Anesthesiologists

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Created a Strong Meetings Team

- Hired experienced director with medical meeting and event management experience
- Re-organized and improved the expertise of the meetings and exhibits team
- Focused on customer service, improving process, and superior logistics
- Improved the attendee experience at the Annual Meeting and all ASA meetings
- Introducing the use of today's medical meeting technology into ASA meetings
- Growing revenues and controlling expenses through stronger contract negotiations

American Society of Anesthesiologists

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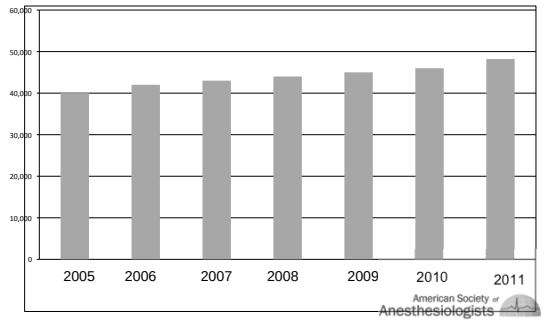
Membership- We Continue to Grow



American Society of Anesthesiologists

Advancing the Practice, Securing the Future

Exceptional Member Benefits

American Society of Anesthesiologists

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A Strategic Education Focus

- Continuous updates and revision of current educational products
- The first of its kind Education Summit pairing leadership and key staff to brainstorm on meeting the education needs of members
- Coordination with MOCA requirements

ANESTHESIOLOGY 2010
AMERICAN SOCIETY OF ANESTHESIOLOGISTS ANNUAL MEETING

A Customized Learning Center …

http://education.asahq.org

- Track CME activities
- Purchase course material
- Take online education
- Manage pre- and post-requirements
- Interact with MOCA

American Society of Anesthesiologists
EDUCATION CENTER
Your Lifeline to Learning

American Society of Anesthesiologists

Advancing *Anesthesiology*

- Utilizing new technology: "Page 2"
- Introduction of an iPad application.
- Building successful press release program attracting top tier media.

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ANESTHESIOLOGY 2012

TRANSFORMING PATIENT SAFETY THROUGH SCIENCE AND INNOVATION

WASHINGTON, D.C. • OCTOBER 13-17, 2012

SAVE THE DATE

A Communications Strategy & Strong Brand

American Society of Anesthesiologists
ASAP
All the News From ASA - As Soon As Possible

NEWSLETTER
Obstetrical Anesthesia

MONITOR
YouTube
facebook
twitter
The ASA Insider

American Society of Anesthesiologists

What are we doing in Michigan?

- A large scale public awareness campaign designed to inform the citizens of Michigan about all aspects of anesthesia.
- This is being accomplished through:
  - Partnering with ally organizations to lend credible third party voices to the messages.
  - Media relations throughout the state.
  - Print and radio advertising.
  - Exploring partnership opportunities with the Governor's wellness initiative.

Only an anesthesiologist can put your body *and* your mind at rest.

Supporting Our Foundations and Related Organizations



Anesthesia Quality Institute

FAER



apsf
ANESTHESIA PATIENT SAFETY FOUNDATION
American Society of Anesthesiologists

ASA Making a Difference

American Society of Anesthesiologists
GLOBAL HUMANITARIAN OUTREACH

lifebox
Saving lives through safer surgery
American Society of Anesthesiologists

Advancing the Practice, Securing the Future

Advocacy Update

American Society of Anesthesiologists

Mr. Ron Szabat, JD
Executive VP, ASA Washington DC


American Society of Anesthesiologists

Our Washington, DC Team













American Society of Anesthesiologists

Congressman Andy Harris, MD
Anesthesiologist & ASA Member


American Society of Anesthesiologists

The Patient Protection and Affordable Care Act (PPACA)

- PPACA is the law of the land.
- A full repeal of the law is unlikely with a Democratic President. Changes to individual pieces of the law are possible.
- As part of the law, a tsunami of regulations will be issued over the coming years impacting anesthesiology and the rest of medicine.
- If successful, current legal challenges to the individual mandate would dramatically change the implementation of the law.

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ASA Top Issue

No Proliferation of Medicare Payment rates – *No public option tied to Medicare rates, No Medicare Buy-in*

aka "33% Problem": *We Win!*

- **Thousands of Key Contacts/Grassroots Contacts**
- **Capitol Hill visits by ASA leadership**
- **Hundreds of Lobbyists Contacts**
- **Work with Democratic Leadership in both the Senate and House**
- **Moderates in the Senate/Blue Dogs in the House**

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ASA Post-Enactment Initiatives

- **Looking for Opportunities to Repeal or Revise Onerous Provisions**

  (Legislative Repeal of Entire Bill is a Non-Starter under Current Democratic Administration)
- **Working with Strong Surgical Coalition**
- **Preparing for Massive Regulatory/ Rulemaking Effort to Implement Law**

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Legislative Advocacy – Key Issues

- **Medicare Physician Payment**
- **IPAB repeal**
- **SGR reform**
- **Rural Pass-through**
- **Truth and Transparency**
- **Drug Shortages**

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Regulatory Advocacy

- **CMS**
  - CoPs
    - Efforts by ASA helped avert a national opt-out of the physician supervision standard. ASA also has led the charge in opposing non-physician providers obtaining hospital staff privileges.
  - Interpretive Guidelines
    - ASA achieves victories in revised IGs
- **HITECH and "meaningful use"**

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Regulatory Advocacy

- **Accountable Care Organizations (ACOs)**
- - Final rule released and analyzed 11/11.
- **Medication Management**
- **FDA**
  - Drug shortages
  - GAO Report
  - Sedation Initiative

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Perioperative or "Surgical" Home

"The perioperative or "surgical" home is a new concept and reflects the great potential that coordination and management of surgical patients have to reduce complications and improve efficiencies and cost-effectiveness of perioperative care."

"Because anesthesiologists care for patients with a variety of co-morbid conditions from admission to discharge, they are uniquely suited to help healthcare organizations improve the quality of care that patients receive."

- "The Perioperative or Surgical Home" concept paper released as part of the 2011 Legislative Conference, now being further developed by a new ASA Committee lead by Dr. Norm Cohen

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Advisory Group on Health Policy

- **Established as a result of HoD action 2010**
- **Intended to help drive policy regarding anesthesiology as opposed to always being reactionary**
- **Staffed by Mr. Ron Szabat**
- **Currently in search for director**

American Society of Anesthesiologists

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Advocacy—Your role

- ✓ **Join the ASA Grassroots Network**
- ✓ **Join ASAPAC**
- ✓ **Know the issues**
- ✓ **Get your colleagues involved**

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2012 Legislative Conference

Theme: "Campaign 2012: ASA Signifies Advocacy"

Former CMS Administrator, Don Berwick, MD, MPP, slated to address attendees.

Calendar Dates:
April 30 – May 2, 2012
JW Marriott Washington, DC

How does positive change happen? The politics of getting and giving

- **ASAPAC raised and spent nearly $3 million per last election cycle (2 years) making it the largest physician PAC**
- **ASAPAC is now among the top 35 of the *4,000* PACs nationally**
- **FY 2011 Total: $1,668,425 (record year)**
- **ASA is force to be reckoned with**

American Society of Anesthesiologists Political Action Committee ASAPAC

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2011 Final Contributions Totals

	2010	*2011**
Donors:	5,617	6,781
Amount:	$1,543,909	$1,668,425
Participation Rate:	16.5%	19.7%

* ASAPAC All-Time Record

American Society of Anesthesiologists

Others are Fully Engaged.

CRNA-PAC $1.36 M

AAJPAC $6 M

AMPAC $2.35 M

AHAPAC $3.9 M

ASAPAC $3.2 M

AAOSPAC $3.03 M

Source: Federal Election Commission filings for 2009- 2010 Election Cycle

American Society of Anesthesiologists

Do we want a seat at the table?

American Society of Anesthesiologists

Or do we want to be on the menu?

American Society of Anesthesiologists

Thank You
Association of University Anesthesiologists!

American Society of Anesthesiologists

AUA President's Panel – The Emergence of Consciousness

Moderator: George Mashour, M.D.

Intraoperative Awareness

Michael S. Avidan, M.B.B.Ch.

Prevention of Intraoperative Awareness

"Notwithstanding weaknesses of current devices, **a window into the anesthetized brain, albeit a foggy one, may still be useful**, in conjunction with information from other monitors, as a generic, all-purpose index of the brain's response to powerfully sedating drugs." - Gregory Crosby.[1]

As early as 1937, Gibbs, Gibbs and Lennox proposed, "The anesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of both heart and brain." Heuristically, this notion is compelling for several reasons. Although the brain is a primary target organ of general anesthesia, the field has not established a standard monitor for the brain. The EEG provides useful information during anesthesia, including surrogacy of unawareness. Today, EEG plug and play modules are available for most intraoperative monitors. However, a practitioner cannot spend all her time scrutinizing a complex EEG trace and most anesthesia practitioners have not received formal instruction in EEG interpretation. The introduction of processed EEG devices that displayed a scaled index from 100 to 0 to reflect anesthetic depth was therefore appealing and enjoyed widespread and perhaps uncritical adoption among practitioners. With limited evidence of clinical utility, processed EEG devices garnered FDA approval, which legitimized their use in clinical practice. An important question that many asked was whether the use of processed EEG devices during general anesthesia would prevent unintended intraoperative awareness.

An important observational study suggested that routine processed EEG monitoring might be associated with a dramatic 82% reduction in awareness,[2] but, as an observational cohort study, the results had to be interpreted with caution. The B-Aware investigators argued that in order to adopt processed EEG devices in routine anesthesia practice, convincing proof of efficacy was necessary.[3] They suggested that short of yielding a 0.9% reduction (minimum clinically important effect) in awareness in high-risk (for awareness) patients, such devices could not be recommended for routine use. The B-Aware trial randomized 2,500 patients to a protocol based on a currently used processed EEG monitoring or to routine clinical practice.[3] The processed EEG protocol was associated with a 0.74% (95% CI, 0.14% to 1.4%) reduction in awareness.[3] Thus the B-Aware trial did not demonstrate a reduction commensurate with the pre-specified minimum clinically important effect. Furthermore, it was difficult to know whether the reduction in awareness was attributable to the monitor or to a protocol that increased clinical vigilance in the experimental group. Finally, about half the patients in the B-Aware trial received total intravenous anesthesia, which is associated with a higher risk for intraoperative awareness.

The B-Unaware and the BAG-RECALL clinical trials enlarged on the results of previous studies. The single center 2,000 patient B-Unaware trial tested a protocol based on a currently used processed EEG device against a protocol based on end tidal anesthetic concentration (ETAC).[4] There was no difference in the incidence of definite awareness between the protocols (0%; 95% CI, -0.56% to 0.57%). Similar to the B-Aware trial, the B-Unaware trial was imprecise (i.e., had wide confidence intervals around the point estimate), which meant that it could rule out potentially clinically relevant benefit (in terms of awareness) of either protocol. However, the results of the B-Unaware trial did suggest that compared with a protocol based on ETAC, a protocol based on processed EEG would not decrease awareness by the minimum clinically important effect pre-specified by the B-Aware investigators. Interestingly, the B-Unaware trial was heavily criticized for its imprecision, whereas the B-Aware trial, which was similarly imprecise, did not face similar censure. This is probably because the B-Unaware trial was a "negative" trial, while the B-Aware trial was a "positive" study. In the B-Unaware trial fewer patients had possible awareness in the ETAC group than in the processed EEG group.

The 6,000 patient, multi-center BAG-RECALL trial was methodologically similar to the B-Unaware trial.[5] This follow-up study showed convincingly that for patients at high risk for awareness, a protocol based on a currently used processed EEG device was not superior to a protocol based on ETAC.[6] Interestingly, and contrary to the hypothesis of the trial, there was a higher incidence of definite awareness, possible awareness and traumatic awareness among patients who were randomized to the processed EEG group.[6]

The Michigan Awareness Control Study (MACS) was a 20,000 (approximately) patient study that different from previous studies in that it tested interventions to prevent awareness in an unselected surgical patient population.[7] Unlike previous studies, MACS was an effectiveness trial. The results of MACS have not yet been published, but it reinforces the findings of previous clinical trials. Consistent with B-Unaware and BAG-RECALL, MACS found that a protocol based on a currently used processed EEG was not superior in preventing awareness to a protocol based on anesthetic concentration. However, in a post-hoc analysis, the protocol based on processed EEG was found to be superior to routine clinical practice, which is consistent with the results of the B-Aware study.

To help complete the picture somewhat, a recent multi-center study from China showed that for patients receiving total intravenous anesthesia, a protocol based on processed EEG was associated with a dramatic decrease in the incidence of awareness.[8] However, similar to the B-Aware trial, it is unclear how much of the benefit in this trial was attributable to the monitor, and how much to a protocol designed to increased clinical vigilance. Taking all the studies together, it is likely that a protocol based on processed EEG is effective in reducing awareness, especially compared to routine care and in patients receiving total intravenous anesthesia. On the other hand, a processed EEG based protocol is not superior to a protocol based on ETAC in preventing intraoperative awareness.

There are several possible explanations for the lack of an advantage of a processed EEG based protocol over an ETAC based protocol. Conceptually, it is not clear that anesthesia deepens smoothly or linearly, in which case "depth of anesthesia" might be a problematic concept. In a recent study, Whitlock and colleagues showed that the processed EEG index does not always change predictably with changes in ETAC. This could mean that titrating volatile anesthetic administration according to currently used processed EEG indices might be inappropriate. Other potential reasons why a protocol based on currently available processed EEG devices might be imperfect in preventing awareness include:

- Current devices are not designed based on neurobiological principles of anesthesia or unconsciousness.[9]
- Awareness can occur when processed EEG indices suggest that patients are unaware.[4,6]
- There is lack of intra-patient reproducibility in currently used processed EEG indices, which brings into question their reliability.[10]
- There is lack of inter-patient reproducibility in currently used processed EEG indices, which also brings into question their reliability. For example young people and older people can have shifts in levels of consciousness at very different values of the processed EEG indices.[11]
- Ketamine and NMDA antagonists (e.g., nitrous oxide) do not produce the typical EEG changes that are seen during general anesthesia.
- As single or dual channel devices, limited montage EEG and currently available processed EEG monitors are unable to assess relational assessments among brain regions (e.g., by transfer entropy).

- State transitions occur rapidly; however, currently used processed EEG devices have a median delay of about 1 minute before they reflect state shifts (e.g., unaware to wakeful).[12]

- Currently available monitors are not specific for anesthesia (e.g., they cannot distinguish general anesthesia from sleep). As such they cannot predict whether a patient will responde to a particular stimulus.

- Electromyography and other artifacts contaminate the EEG trace and might confound clinical interpretation.

In concluding my talk I will present unpublished evidence on patients with natural red hair and patients with a history of intraoperative awareness. We hypothesized that these patients would require and receive more (higher doses of) anesthesia and that they would have a higher incidence of intraoperative awareness.

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Neural Inertia

Max B. Kelz, M.D., Ph.D.

“Barriers Impeding Anesthetic Emergence”

The forward and reverse processes through which the state of general anesthesia arises and dissipates are not mirror images of each other.[1] Rather, using population dose-response curves, we have demonstrated that the hysteresis loop separating volatile anesthetic induction and emergence unmasks a behavioral state barrier that impedes transitions from the unconscious back to the conscious state.[2] Evidence for such a barrier had been previously hypothesized.[3-5] Based upon our studies in invertebrates and mammals, we demonstrate that the behavioral state barrier, which we term “neural inertia” is amenable both to genetic and pharmacologic manipulation. Using genetic engineering in the fruit fly, *Drosophila Melanogaster*, we can demonstrate that it is possible to dissociate anesthetic induction from anesthetic emergence. By restricting the expression of a single gene to subsets of the fly brain we show that it is also possible to induce parallel or asymmetric leftward or rightward shifts in both induction and emergence curves either with or without altering the inertial barrier separating the two states. We thus demonstrate that induction sensitivity cannot be used to predict emergence sensitivity. In cases of collapsed neural inertia, we hypothesized that individuals could be at increased risk for anesthetic awareness.

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Inducing Emergence

Ken Solt, M.D.

Accumulating evidence suggests that ascending arousal pathways in the brain play important roles in emergence from general anesthesia.[1-3] Cholinergic,[4-6] noradrenergic,[7] histaminergic,[8,9] and orexinergic[10,11] arousal pathways have been implicated in emergence from general anesthesia, but the roles of other arousal-promoting neurotransmitters such as dopamine remain unclear. We recently reported that methylphenidate (Ritalin), an inhibitor of dopamine and norepinephrine reuptake transporters, induces emergence from isoflurane general anesthesia in rats.[12] During continuous isoflurane anesthesia at a dose sufficient to maintain loss of righting, intravenous administration of methylphenidate reliably restored the righting reflex and produced EEG changes consistent with arousal, despite no change in the isoflurane dose. Pretreatment with intravenous droperidol inhibited the arousal-promoting effects of methylphenidate, suggesting that methylphenidate promotes arousal primarily by activating a dopaminergic pathway.

Methylphenidate also induces emergence from general anesthesia with propofol.[13] Methylphenidate reduced the time to emergence after an induction dose of propofol, and restored the righting reflex during a continuous target-controlled infusion of propofol. Methylphenidate has a well-established safety profile in humans, and may be clinically useful as a reversal agent for propofol and other general anesthetics. Because isoflurane and propofol likely have distinct molecular mechanisms of action,[14] these results support the idea that methylphenidate induces arousal at the circuit level by stimulating dopaminergic and noradrenergic neurotransmission, rather than blocking the actions of general anesthetics at the molecular level.

We recently found that selective activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia.[15] The D1 agonist chloro-APB reduced time to emergence from isoflurane anesthesia, and restored the righting reflex during continuous isoflurane general anesthesia. Pre-treatment with the D1 antagonist SCH-23390 inhibited the arousal-promoting effects of chloro-APB. Finally, the D2 agonist quinpirole failed to elicit an arousal response during isoflurane anesthesia. Taken together, these results demonstrate that activation of D1 dopamine receptors is sufficient to induce emergence from general anesthesia, and suggest that methylphenidate-induced arousal during general anesthesia is mediated, at least in part, by activation of D1 receptors.

Dopamine is well known to be involved in behavioral arousal.[16] However, its precise role has been controversial and the specific dopaminergic circuits in the brain that promote arousal have yet to be clearly defined. Stimulating dopaminergic neurotransmission may provide a novel approach to induce emergence from general anesthesia, with fewer peripheral side effects compared to cholinergic stimulation.

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Program Material

Friday, May 18, 2012

EAB Program (Part 1)

High Stakes Performance Assessment: During Residency and for Certification
Moderator: David J. Murray, M.D.

- **Performance Assessment: Assuring the Measures are Meaningful**
  David J. Murray, M.D.
- **Resident Evaluation: What to Measure and How to Use the Measures**
  Keith H. Baker, M.D., Ph.D.
- **Anesthesiology Certification: Beyond the Multiple Choice Examination**
  Cynthia A. Lien, M.D.

EAB Program (Part 1)

High Stakes Performance Assessment: During Residency and for Certification

Moderator: David J. Murray, M.D.

Performance Assessment: Assuring the Measures are Meaningful

David J. Murray, M.D.

Performance Assessment: Assuring the Measures are Meaningful

David J Murray MD
Carol B. and Jerome T. Loeb Professor of Medicine
Director, Howard and Joyce Wood Simulation Center
Washington University School of Medicine
Anesthesiologist-in-Chief
St Louis Children's Hospital,
St Louis, MO

Performance Assessment: Assuring the Measures are Meaningful

- **An Overview of the Link between Quality and Performance**
- **Performance and Peer Review**
- **Performance and Practice Skills**
- **Designing Performance Assessments for Anesthesia Practice**
- **Considerations in Scoring Performance Assessments**

Performance Assessment: Assuring the Measures are Meaningful

Establishing the Link between Quality and Safety in Anesthesia Practice and Measures of Performance.

Establishing the Link between Quality and Safety in Anesthesia Practice and Performance Assessment

The evidence that assessment protects the public from poor-quality care is both indirect and scarce; it consists of a few studies that show correlations between assessment programs that use multiple methods and relatively crude estimates of quality such as diagnostic testing, prescribing, and referral patterns.

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Quality and Safety Indicators in Anesthesia

Anesthesiology 2009; 110:1158–75.

Guy Haller, M.D., M.Sc., Ph.D., Johannes Stoelwinder, M.B.B.S., M.D., F.R.C.A.M.A., F.A.C.H.S.E., F.F.P.H.M.,† Paul S. Myles, M.B.B.S., M.P.H., M.D., F.C.A.R.C.S.I., F.A.N.Z.C.A.,‡ John McNeil, M.B.B.S., Ph.D., F.R.A.C.P.*

The majority of the clinical indicators identified in order to be directed to physician performance relied on follow-up expert opinion.

Quality and Safety Indicators in Anesthesia

Anesthesiology 2009; 110:1158–75.

Guy Haller, M.D., M.Sc., Ph.D., Johannes Stoelwinder, M.B.B.S., M.D., F.R.C.A.M.A., F.A.C.H.S.E., F.F.P.H.M.,† Paul S. Myles, M.B.B.S., M.P.H., M.D., F.C.A.R.C.S.I., F.A.N.Z.C.A.,‡ John McNeil, M.B.B.S., Ph.D., F.R.A.C.P.*

'108 anesthetic clinical indicators, of which 53 related also to surgical or postoperative ward care. Most were process (42%) or outcome (57%) measures assessing the safety and effectiveness of patient care'

Quality and Safety Indicators in Anesthesia

Anesthesiology 2009; 110:1158–75.

Guy Haller, M.D., M.Sc., Ph.D., Johannes Stoelwinder, M.B.B.S., M.D., F.R.C.A.M.A., F.A.C.H.S.E., F.F.P.H.M.,† Paul S. Myles, M.B.B.S., M.P.H., M.D., F.C.A.R.C.S.I., F.A.N.Z.C.A.,‡ John McNeil, M.B.B.S., Ph.D., F.R.A.C.P.*

Clinical indicators are used as indirect measures. Once an indicator is present, further steps need to be taken (usually a formal peer-review process) to confirm a potential quality issue of anesthetic care.

'knowledge of the outcome of an adverse event influences their thinking and assessment of the event.'

'fondness for retrospective techniques (such as morbidity and mortality conferences, malpractice claims analysis, error reporting systems, chart reviews) for investigating adverse events that harm patients.'

Hindsight bias, outcome knowledge and adaptive learning.

Henriksen K, Kaplan H. Qual Saf Health Care 2003;12(Suppl II):ii46–ii50

Quality of Care, Performance Assessment and Expert Opinion

- Caplan RA, Posner KL, Cheney FW, et al. Effect of outcome of physician judgments of appropriateness of care. JAMA 1991; 265:1957–60.
  - 112 anesthesiologists were presented with identical clinical scenarios but differing outcomes.
    - Reviewers were more likely to judge anesthesia care as appropriate if the injury was temporary; conversely, reviewers were more likely to judge anesthesia care as substandard or impossible to judge if the injury was permanent.

Quality of Care, Performance Assessment and Expert Opinion

- Posner KL, Caplan RA, Cheney FW. Variation in expert opinion in medical malpractice review. Anesthesiology 1996; 85:1049-1054.
  - Was the anesthesia care appropriate, less than appropriate, or impossible to judge?
  - Thirty anesthesiologists reviewed 103 claims. Reviewers agreed on 62% of claims and disagreed on 38%. They agreed that care was appropriate in 27% and less than appropriate in 32%.

Are Bad Outcomes From Questionable Clincal Decisions Preventable Medical Errors? A Case of Cascade Iatrogenesis

Hofer TP, Hayword RA: Ann Intern Med 2002; 137: 327-333

- Recognize that not all errors are "system errors"
- More emphasis on research rather than initiatives and isolated case analysis
- Investigate cognitive and procedural errors
- Foster individual skills and expertise
- Increase physician responsibility and accountability

Methods to achieve a performance consensus: Simulation-derived algorithm

- Expectations based on overall goals and considerations rather than isolated case or an adverse outcome
- An algorithm with attention to timing and sequence of each step in a 'real time' simulation environment.
- If experts are required to participate in managing the resulting scenario:
  - An expert's often Inordinately high performance expectations can be modulated
  - The algorithm developed can based on what expert actually 'does' rather than 'expects' in a peer review setting

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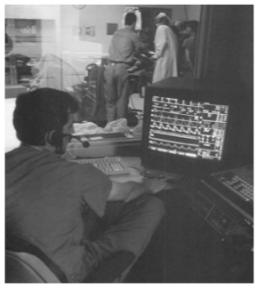
Performance Assessment: Assuring the Measures are Meaningful

- Psychomotor Skills
- Clinical Judgments (Recognition, Diagnosis and Treatment)
- Communication and Teamwork Skills



Performance in Practice: Psychomotor Skills Training for Practice
What preparation is appropriate prior to conducting a supervised procedure?
What are the steps required to effectively accomplish each procedure?
Are there technical milestones that could be measured for each step?
Are there common misadventures in performing this procedure?
Can these errors be programmed in a simulated environment?
What is the range of resident skill prior to and following simulation training?
Can the 'learning curve' be predicted from simulation training?
How many 'mentored' or training procedures are needed before a trainee possesses the expertise to function independently?
How can proficiency be measured for the procedure?
In order to meet minimum qualifications, how many procedures are needed? How many procedures are needed to maintain requisite skill?

Failure Modes and Failure Mode Analysis: Central Line (Pneumothorax, Arterial Puncture, Retained Guidewires; Bloodstream Infections)

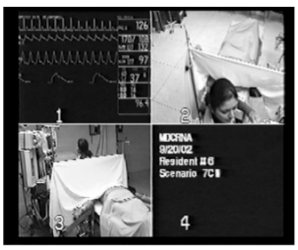
- **Attention to training steps that effectively reduced the most serious failure modes.**
  - **Arterial puncture and pneumothorax:**
    - **Practice in Ultrasound guidance**
  - **Retained Guidewires:**
    - **Practice in Seldinger Technique**
  - **Blood Stream Infection:**
    - **Practice in aseptic technique, wire and catheter management**

Patient Safety Implications: Failure Mode and Effects Analysis (FMEA)

- Failure Mode and Effects Analysis (FMEA) to identify high-priority failure modes
  - Training directed to reduce the frequency, decrease the severity and improve the detection and correction of failure modes prior to harm.

Assessment in Medical Education. Epstein RM. N Engl J Med 2007;356:387-96.

Clinical expertise implies the practical wisdom to manage ambiguous and unstructured problems, balance competing explanations, avoid premature closure, note exceptions to rules and principles, and — even when under stress — choose one of the several courses of action that are acceptable but imperfect.



Performance-based Curriculum: Problem-based (scenario or events)

Common Skill Deficits:

- *setting priorities,*
- *generating hypothesis,*
- *processing knowledge,*
- *assigning probabilities,*
- *recognizing important, from unimportant information,*
- *integrating competing issues,*
- *recognizing limits,*
- *learning when to call for assistance*

The transition out of medical school-a qualitative study of descriptions of borderline trainee interns.
Wilkinson TJ, Harris P. Medical Education 2002; 36: 466-72

Clinical Expertise: Defining the Skills and Choosing the Appropriate Tasks

Scenario is the fundamental building block of the simulation-based assessment.

- Selecting competence domains that are amenable to a simulation environment,
- Defining the expected skills that are needed to diagnose and manage the crisis
- Designing a scenario that has the skills required embedded into the framework
- Establish instruments and metrics to conduct the assessment

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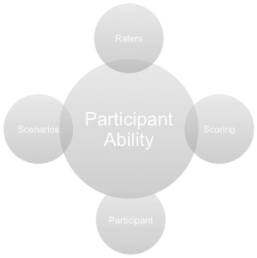
Building the Simulation Assessment

The Simulation Centers at Washington University School of Medicine

Performance Assessment: Assuring the Measures are Meaningful

- *Scores require faculty to define expectations and commit to the required and essential clinical management*
- *Participants' scores used to analyze quality of scenarios (difficulty, content, construct and scoring)*
- *Ability measure provide curriculum affirmation (or reproof) (Validation)*
- *Potential to direct curriculum effort to performance deficits, the need for an adaptive curriculum*
- *Individual score assures feedback directed to strengths and weaknesses*
- *Motivation to acquire and exceed performance expectations (the secondary learning outcome)*

Analysis of Participant Scores



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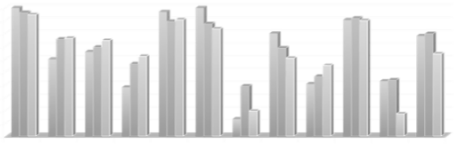
Expert Opinion: Objective versus Qualitative Scoring

Scenario Score Variance: Rationale for the Multiple Scenario Assessment

Performance of Residents and Anesthesiologists in a Simulation-based Skill Assessment

David J Murray M.D., John R. Boulet Ph.D., Michael Avidan M.D., Joseph F. Kras, M.D., Bernadette Henrichs, C.RNA, Julie Woodhouse RN

Anesthesiology 2007; 107:705–13



'Task sampling variability usually has the most impact on the reproducibility of scores'

Reliability and Validity of a Simulation-based Acute Care Skills Assessment for Medical Students and Residents
Boulet JR, Murray DJ, Kras J, Woodhouse J, McAllister JD, Ziv A
Anesthesiology 99: 1270-1280, 2003.

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'The most effective method to improve the ability measure is to increase the number of scenarios/stations/tasks that the participant manages '

Reliability and Validity of a Simulation-based Acute Care Skills Assessment for Medical Students and Residents
Boulet JR, Murray DJ, Kras J, Woodhouse J, McAllister JD, Ziv A
Anesthesiology 99: 1270-1280, 2003.

The Simulation Centers at Washington University School of Medicine

The relationship between competence and performance: implications for assessing practice performance.

Rethans JJ, Norcini JJ, Baro´ n-Maldonado M, Blackmore D, Jolly BC, LaDuca T, Lew S, Page GG, Southgate LH. Med Educ 2002;36:901–9

Performance (what we do in clinical practice) is a product of competence (what we demonstrate under controlled conditions), systems factors (resources, organizational factors), and individual (fatigue, mood) factors.

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Resident Evaluation: What to Measure and How to Use the Measures

Keith H. Baker, M.D., Ph.D.

Determining resident physician performance in a valid and reliable manner has challenged medical educators for years. The Accreditation Council for Graduate Medical Education (ACGME) has stated that each residency and its faculty must demonstrate, via outcome measures, that each trainee is competent to practice in an independent manner. Since trainees practice in a supervised setting, often in a team model, it can be difficult to untangle precisely what the trainee is able to competently manage in an independent fashion. Objective structured clinical exams (OSCEs) offer the hope of determining what a trainee might do when left to their own devices. However, it was shown that what physicians do under testing conditions (such as an OSCE) and what they do in actual practice (termed performance) may not relate to each other (1). Furthermore, OSCEs and simulators only sample a small sphere of practice, are infrequently used and are expensive to run. The need for a valid assessment of daily physician performance in still needed.

We developed a performance assessment system which addresses many of the gaps in current methods (2). Our system has the following ten features: 1) direct observation of clinical performance, 2) broad systematic sampling, 3) multiple raters, 4) ACGME Core Competency framework, 5) separation of formative feedback and evaluative numbers, 6) encourages weekly evaluation, 7) occurs in a naturalistic setting with relatively unobtrusive observation, 8) corrects for grade inflation (bias) and differential grade range use, 9) relates to high stakes medical knowledge tests (In-Training Exams) and referral to a clinical competency committee, 10) uses only 5 or 7 rating choices per item and specifies meaning of ratings.

Anesthesia residents were evaluated confidentially on a weekly basis by faculty members who supervised them. Our electronic evaluation form has five sections, including a rating section for absolute and relative-to-peers performance under each of the six ACGME core competencies, clinical competency committee questions, rater confidence in having the resident perform cases of increasing difficulty, and comment sections. Residents and their faculty mentors were provided with the resident's formative comments on a biweekly basis. Over a two year period, 140 faculty members returned 14,469 evaluations on 108 residents. The faculty scores were pervasively positively biased and were affected by idiosyncratic score range usage. These effects were eliminated by normalizing each performance score to the unique scoring characteristics of each faculty member (Z-scores). Individual Z-scores had low amounts of performance information, but signal averaging allowed determination of reliable performance scores. Average Z-scores were stable over time, related to external measures of medical knowledge, identified residents referred to the clinical competency committee, and scores increased when performance improved after an intervention. This approach demonstrates a reliable and valid clinical performance assessment system for residents at all levels of training.

References:

1. Rethans JJ, Sturmans F, Drop R, van der Vleuten C, Hobus P: Does competence of general practitioners predict their performance? Comparison between examination setting and actual practice. BMJ 1991; 303:1377– 80.

2. Baker K: Determining Resident Clinical Performance: Getting Beyond the Noise. Anesthesiology 2011; 115:862-78.

Anesthesiology Certification: Beyond the Multiple Choice Examination

Cynthia A. Lien, M.D.

Graduate medical education is replete with high stakes examinations. Admission into medical school requires that applicants take the MCATs. Graduation from medical school may require passing a component of the USMLE. Licensure to practice medicine requires passing each of the components of the USMLE. In some cases, candidacy for a residency program is determined, at least in part, by scores on the USMLE. In many residency programs, acquisition of knowledge during residency is monitored in part through performance on an in-training examination. For each of the 24 ABMS Boards, certification requires, in addition to satisfactory completion of a residency, passing at least one certifying examination.

Our residents and graduates of our programs are very well-versed in taking multiple choice examinations. They have had a lot of practice. Through the USMLE (Step 1, Step 2 CK and Step 3) they are exposed to multiple choice questions. The structure and purpose of the multiple choice examinations varies with the examination. Step 1 assesses understanding of the science of basic scientific principles and their application to the practice of medicine. Principles and mechanisms underlying health, disease and modes of therapy are emphasized. Step 2 CK assesses application of medical knowledge, skills and understanding of clinical science essential for the provision of patient care in supervised practice. This exam emphasizes health prevention and disease promotion. Step 3 assesses application of medical knowledge and understanding of biomedical and clinical science essential for the unsupervised practice of medicine. Emphasis in this exam is on patient management in the ambulatory setting. These assessments are made through responses to a combination of multiple choice questions of different types and case simulations – with case simulations being most important in the Step 3 examination.

When looking at the types of questions used for these different purposes, it is difficult to perceive a change significant enough to determine whether or not someone can practice effectively and independently. A review of sample items available on the USMLE website shows that each exam has multiple choice questions with one single best answer. Step 1 and 2 have, in addition to the typical single question: single answer problems, sequential item sets – where a clinical vignette is followed by a series of 2 or 3 single best answer questions related to that vignette. The Step 2 exam also has matching sets of questions – where a single list of answers is provided for a set of questions. Each response may be correct for none, one or more than one of the questions. There is only one correct response to each item. The step 3 exam has multiple choice multiple item sets of questions. Again, each question has only one correct answer. However, once a response is submitted for the first question in that set, it cannot be reviewed or revised as looking at subsequent questions. In addition to these questions, there are computer-based simulations. Many of these question formats are currently used on the in-training and Part 1 examinations of the ABA as well as other Boards.

While unable to assess all of the qualities required for effective, independent practice of medicine, multiple choice questions endure for a number or reasons. Essay responses – which may better assess understanding of choices made in an examination are difficult to score. Different raters score the same essay differently and the same rater will score the same essay differently when subsequently reviewed several months later. Additionally, the standard of the rater varies over a single prolonged period of grading.

Multiple choice examinations eliminate the same rater and inter-rater variability encountered when scoring essay responses. They provide an efficient way to test knowledge over a wide range of topics, with reliable scoring that is not subject to human error or interpretation. Responses are consistently marked as either correct of incorrect – amongst examinees and over time. Multiple choice examinations, though, regardless of how creative the question format, cannot reliably assess many of the characteristics important in patient care such as judgment and clinical ability.

While the Part 2 or oral exam of the ABA is designed to assess candidates judgment through their responses to changing clinical scenarios, it cannot test what someone will actually do in a scenario. When considering the constellation of requirements of a physician, this piece of information is exceptionally important in terms of actually knowing whether or not someone can practice independently. Data gathered through the use of the Objective Structured Clinical Examination has demonstrated that it is effective in assessing these higher levels of competency. OSCEs comprise the Clinical Skills (CS) portion of the USMLE Step 2 exam and they are used to determine whether or not medical students and graduates can gather information from patients, perform physical exams and communicate their findings to colleagues. In anesthesiology, simulation has provided an effective tool for education. Use of standardized performance measures in a simulator may effectively test for the higher levels of competency not assessed in multiple choice examinations. The Royal College of Anaesthetists has incorporated the OSCE into its certification process. In exposing candidates to multiple OSCE stations allows candidates to be tested on many different topics including anatomy, equipment, resuscitation, interpreting x-ray results, obtaining a pertinent history, and technical skills such as ultrasound-guided placement of a central line catheter. Results of performance in these different scenarios as well as in a structured oral examination are the final steps in certification in this system.

In addition, the Israeli Board of Anesthesiology has incorporated simulation-based OSCE into its certification process. Candidates are assessed in trauma management, resuscitation, operating room crisis management, mechanical ventilation and regional anesthesia. Participants in the process reported that they found the difficulty of the scenarios reasonable. Moreover, reliability between examiners was good and candidate satisfaction with the process high.

There are multiple options available for examinations – certifying and otherwise. Multiple choice questions, while they provide a valid assessment of a physician's knowledge base, do not test many of the qualities expected of independently practicing physicians. Other exam formats, such as the Script Concordance Test, computer-based simulation and simulation-based OSCE, may provide alternatives for exam formats that would better assess the competency of physicians.

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2. Ben-Menachem E, Ezri T, Ziv A, Sidi A, Brill S, Berkenstadt H. Objective Structured Clinical Examination-based assessment of regional anesthesia skills: the Israeli National Board Examination in Anesthesiology experience. Anesth Analg. 2010;112:242-5

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4. Bull GM. An examination of the final examination in medicine. Lancet. 1956;271:368-72

5. Charlin B, Roy L, Brailovsky C, Goulet F, van der Vleuten C. The Script Concordance test: a tool to assess the reflective clinician. Teach Learn Med. 2000;12:189-95.

6. Hodges B. Validity and the OSCE. Med Teach. 2003;25:250-4

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Program Material

Friday, May 18, 2012

EAB Program (Part 2)

Anesthesia Education: Impact on Global Health
Moderator: Robert R. Gaiser, M.D.

- **Obstetric Anesthesia: The Kybele Experience**
  Medge D. Owen, M.D.
- **Establishing Trauma Care Training for Developing Countries**
  Maureen McCunn, M.D.
- **Resident Participation in Global Health: Importance, Challenges, and Opportunities**
  Marcel E. Durieux, M.D., Ph.D.

EAB Program (Part 2)

Anesthesia Education: Impact on Global Health

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Obstetric Anesthesia: The Kybele Experience

Medge D. Owen, M.D.

Obstetric Anesthesia:
The Kybele Experience

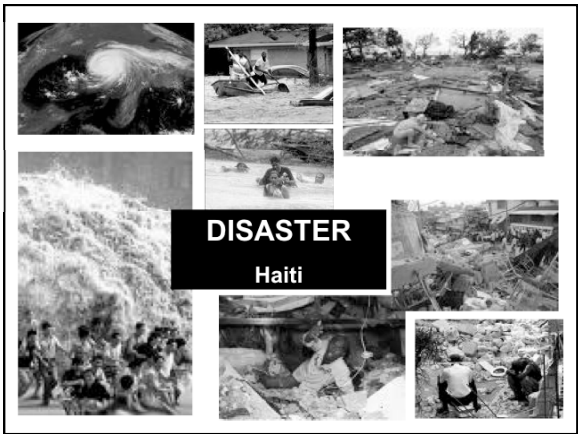
Medge D. Owen, MD
Professor, Obstetric Anesthesia
Director Maternal & Infant Global Health Programs
Wake Forest School of Medicine
President, Kybele, Inc.

WAKE FOREST UNIVERSITY SCHOOL of MEDICINE

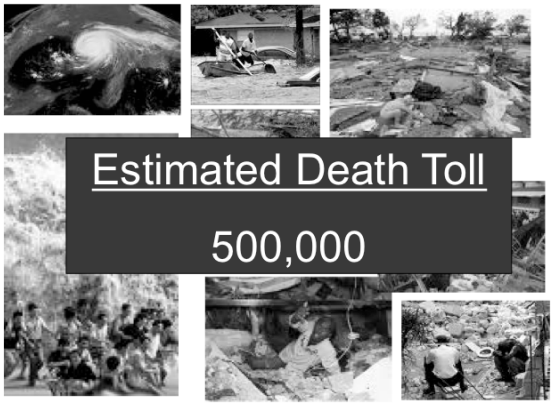
Kybele

DISASTER
Katrina

DISASTER
Tsunami



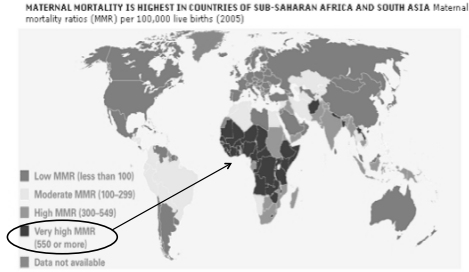
DISASTER
Haiti



Estimated Death Toll

500,000

Childbirth mortality: The "silent" disaster

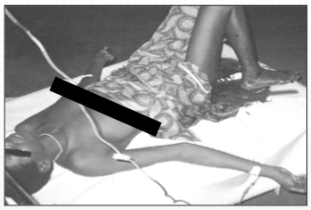


- 350,000-500,000 maternal deaths/year
- Most maternal deaths avoidable

Dying Mothers – WHO 2008

Country	Life time death risk 1 in :
Afghanistan	11
Nigeria	23
Ghana	66
India	140
Brazil	860
US	2,100
Ireland	17,800

Childbirth – The "Silent" Disaster



"Women and babies in some parts of the world are not dying because of diseases we cannot treat… They are dying because society has yet to make decisions that their lives are worth saving" Dr M. Fathalla

Founded in 2001

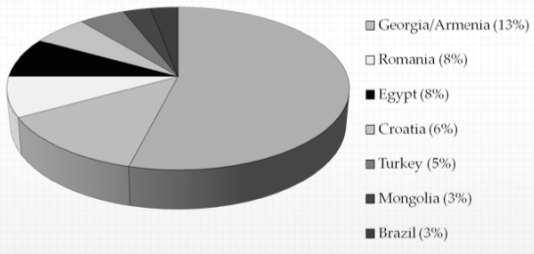
Kybele incorporated …for safe childbirth worldwide

Non-profit 501 (c)(3) organization to promote safe childbirth worldwide through medical education partnerships

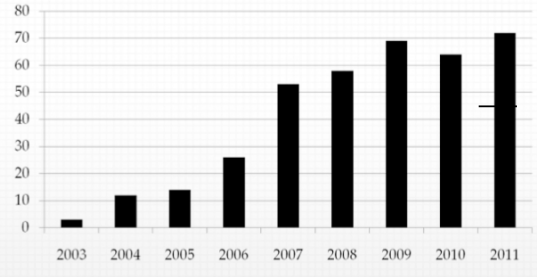
Kybele Profile since 2003

- **Total Faculty Participation = 370**
  - **64 institutions, 10 countries**
  - **28 medical, nursing & other disciplines**
- **Target Countries = Turkey, Croatia, Ghana, Rep. of Georgia, Armenia, Brazil, Egypt, Romania, Mongolia**
- **In-country Programs = 44**
- **Major Meetings Hosted = 17**
- **Individuals Sponsored = 18**

% Participants/Country



Participants/Year



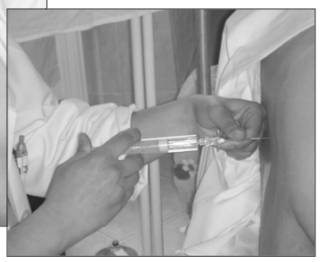
Kybele's Educational Model

- On-site Education
- Cost Efficient
- International Trainers
- Multidisciplinary Teams
- Leadership Involvement / Development
- Monitoring / Evaluation

Kybele – fertility goddess 7,000 BC

Spinal anesthesia placed at high levels

Without sterile gloves



Beer break in the OR

Turkey September 2004: Creating the Model

Dr. Clyne WFU Fellow

★ Indicates Kybele Visits

7/10 Hospitals changed clinical practice

Anesthesiology 2005;102(1)A-94

Croatia September 2005: Testing the model

★ Indicates Kybele Visits

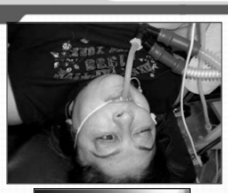
85% ↑ in Regional Anesthesia for C-Section one year after program

Anesth 2007;106:A29

IJOA 2009;18:4-9 with editorial

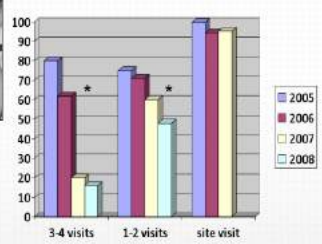
Rep. of Georgia Sept 2006: Extending the model

- Interesting "indications" for c-section
- No bupivacaine
- General anesthesia inadequate
- Few monitors
- Evidence based practices introduced



Rep. of Georgia – Bupivacaine is approved !

General Anesthesia for CS (%)



Anesth Analg 2008;106:A-128
Int J Gynecol Obstet (submitted)

*p<0.001 compared to BL

Ghana Jan 2007: 5 yr collaboration

Dr. George Yankee, Ghana Health Minister
with Dr. Medge Owen, WFUSM

Objective: To create a "Center of Excellence" for 50% Reduction of Maternal & Newborn Mortality

Introduction: Ghana

- Maternal & infant mortality = basic indicators of adequacy of healthcare systems
- 60% maternal deaths in Accra are in hospitals[1]
- 36% increase in hospital-based maternal death 1997-2007[2]

[1]Zakarian AY. Reprod Health. 2009 June; 6(7):1-6.
[2]Ghana Health Service Annual Report, 2007;1-74.

Why Mother's Die

#1 Delays in recognizing need for medical care

Herbal remedies tried first

Why Mother's Die

#1 Delays in recognizing need for medical care

Faith healing for obstructed labor

Why Mother's Die

#2 Delays in reaching hospitals

Taxi = Emergency Medical Service

Why Mother's Die

#3 Delays in receiving care within hospitals

Overcrowded…Urban Hospital

Why Mother's Die

#3 Delays in receiving care within hospitals

Understaffed…Rural Hospital

3rd Largest OB unit in Ghana

Causes Maternal Death
Ridge Regional Hospital, Accra 2006

Condition	Percent
Pre-Eclampsia	33%
Hemorrhage	27%
Anemia/malaria	10%
Unsafe abortion	7%
HIV/pneumonia	7%
Ectopic	3%
Other	13%
23 maternal deaths in 4,793 births	**MMR: 479/100,000**

Jan 2007

17 member team

- Anesthesia
- OBGYN
- Neonatology
- Nurse anesthesia
- Labor nurse
- Midwife
- Neonatal Nurse

Entrance to Labor Ward

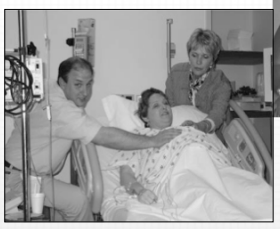
Forsyth Medical Center

Ridge Regional Hospital

Labor

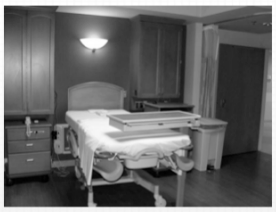
Ridge Regional Hospital

Forsyth Medical Center



Delivery

Forsyth Medical Center



Ridge Regional Hospital

Post Partum

Forsyth Medical Center

Ridge Regional Hospital

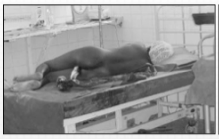
Methods

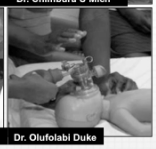
Jan 2007

Observed Needs:

- **Better emergency management**
- **Improve technology**
- **Multidisciplinary teamwork**

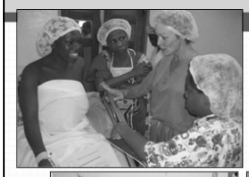
Dr. Hickman Canada Dr. Chimbura U Mich

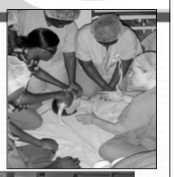




Dr. Wood UNC Dr. Olufolabi Duke

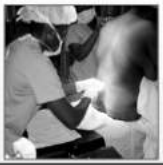
Education



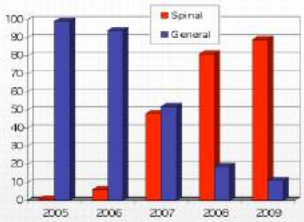


Education

M. Reiker CRNA



- Monitoring
- Spinal anesthesia for C/S



Skinny Patients = Easy Spinals

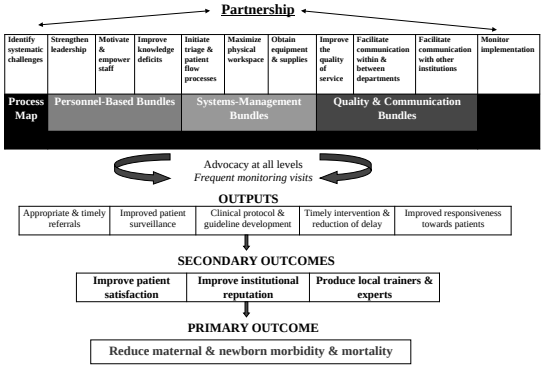
Skinny Patients ≠ Easy Spinals

Clinical Care Improvements

- Morning report
- Triage system
- Protocol driven care
- High dependency unit
- Neonatal resuscitation
- Fetal monitoring / ultrasound

Dr. Damasio NY

Srofenyoh, et al. Int J Gynecol Obstet 2012;116:17-21



Advocacy

- **Sponsorship of key physician & midwives**
- **Nurse anesthesia training program**

Outcomes: Delivery Trends

Year	Total deliveries	Maternal deaths	MMR - Maternal deaths/100,000 live births
2007	6049	30	**496**
2008	7465	29	**388**
2009	8230	27	**328**
2010	8133	31	**380**
2011	9357	36	**380**

23 % drop in maternal death

Srofenyoh, et al. Int J Gynecol Obstet 2012;116:17-21

Results: ⬇Pre-eclampsia-related maternal deaths

	Pre-eclampsia			
Year	# Cases	Deaths	Prevalence (%)	Case Fatality Rate (%)
2007	321	10	5.3	**3.1**
2008	581	8	7.9	1.3
2009	994	11	12.1	**1.1***
2010	1031	11	12.8	1.1
2011	1360	15	14.5	**1.1***

- ***P*< 0.05** for 2011 compared to 2007 using Fisher's exact test
- 65% overall reduction in mortality from pre-eclampsia

Srofenyoh, et al. Int J Gynecol Obstet 2012;116:17-21

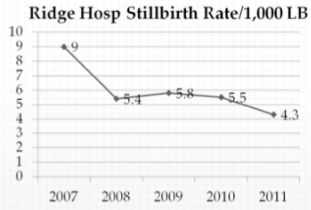
Results: ⬇Hemorrhage-related maternal death

	Hemorrhage			
Year	# Cases	Deaths	Prevalence (%)	Case Fatality Rate (%)
2007	54	8	.08	**14.8**
2008	99	5	1.3	5.1
2009	319	6	3.9	1.9#
2010	343	7	4.2	2.0
2011	485	8	5.2	1.6

- ***P* < 0.001** for 2011 compared to 2007 using Fisher's exact test
- 89% overall reduction in mortality from hemorrhage

Srofenyoh, et al. Int J Gynecol Obstet 2012;116:17-21

NEONATAL RESUCITATION
Stillbirth Mortality: 52 % decrease



Srofenyoh, et al. Int J Gynecol Obstet 2012;116:17-21

Conclusion: Future direction

- Childbirth standards can be improved in resource-poor countries when appropriate educational methods are developed and employed
- Need to determine which interventions are most important, especially in sub-Saharan Africa
- Need to validate and replicate

Conclusion:

Education is the most powerful weapon which you can use to change the world

Nelson Mandela

.

www.kybeleworldwide.org

Establishing Trauma Care Training for Developing Countries

Maureen McCunn, M.D.

Objectives:

- To present the global burden of disease from injury
- To review the current literature on trauma care training and the effectiveness of trauma care education
- To suggest strategies which address the gap between (1.) the high burden of injury/death due to poor access to surgery and anesthesia, and (2.) available solutions for training, education, policy and advocacy in low and middle income countries (specific country examples such as an NIH study in Egypt, volunteerism in India, and trauma training in Ecuador and Tanzania will be included)

GLOBAL BURDEN OF DISEASE FROM INJURY

Traumatic injury is the leading cause of death under the age of 45 in the U.S. and worldwide. Approximately 5.8 million people die each year as a result of injuries. This accounts for 10% of the world's deaths, more than the number of fatalities from malaria, tuberculosis and HIV/AIDS combined. Ninety percent of these injury deaths occur in low and middle income countries (LMICs).

In 1966, the United States (U.S.) National Academy of Sciences published the influential report titled *Accidental Death and Disability: The Neglected Disease of Modern Society*, more commonly known as "The White Paper". This landmark report was vital in the development of the emergency medical services system in the U.S., leading to significant improvement in prehospital care, coordination of care within trauma systems, as well as a focus on functional rehabilitation. Trauma and emergency care systems have continued to mature over the past five decades in the U.S. and other highly-developed nations, in contrast to low and middle income countries where such organization and infrastructure is virtually non-existent.

Estimates suggest that 11% of the world's disability adjusted life years, or DALYs (an estimation of years of healthy life lost due to disease or disability), are due to conditions that could be adequately treated with emergency surgery. The worldwide DALYs burden is felt disproportionally by LMICs.

Death and DALYs estimates for 2004. WHO, Geneva.

The World Health Organization (WHO) Global Burden of Disease project ranks self-inflicted and road-traffic injuries in adults aged 15-59 among the leading causes of mortality and disability-adjusted life years in high-, middle- and low-income countries. In the past 30 years, many governments, non-governmental organizations (NGOs), and institutions have developed trauma training courses to address this escalating burden of disease.

A number of factors in LMICs contribute to the significant morbidity and mortality associated with injury and emergency, and is reflective of the problems with access to care. Potential barriers to providing surgery, emergency and anesthesia care to the world's poorest include a lack of effective political advocacy, insufficient resources (both personnel and consumables), and a perception that surgical intervention is not cost-effective by population-based measures.

Organizational resources

Trauma surgery has a long history of incorporating performance improvement efforts into clinical practice, but many LMIC do not have this organizational infrastructure in place. The WHO provides guidelines for trauma care resources through the *Global Initiative for Emergency and Essential Surgical Care* and *Guidelines for Essential Trauma Care* which have been implemented in several countries. Implementation of basic performance improvement efforts to identify preventable deaths and address patient care issues has been shown to decrease mortality. The importance of establishing and attaining benchmarks is a better understanding of the processes of patient care, and lies at the foundation of improving quality of care for all patients. There are shortfalls in trained personnel, infrastructure, and anaesthesia equipment.

Anesthesia delivery requires training, functioning equipment, drugs, and disposables. The avoidable mortality rate attributable to anaesthesia in some countries is high (1:150 in Togo, 1:504 in on Central Hospital in Malawi and 1:1923 in another in Zambia) when compared to rates of 0.55 per 100,000 in the United States. In Afghanistan (population of 32 million), there are 9 physician anaesthetists, 8 in Bhutan (population less than 700,000), and 13 excluding expatriates in Uganda (population of 27 million). In sub-Saharan Africa the majority of anaesthetics are provided by non-physician anaesthetic providers working alone, unsupervised, and with limited training.

Our own preliminary data demonstrates that 35% of health care facilities in LMICs have no access to oxygen, approximately half of facilities do not have continuous access to anesthesia machines or pulse oximetry, and the majority of personnel providing anesthesia are nurses or clinical assistants. Anesthesia machines must be designed to endure harsh climates, adaptation with oxygen concentrators, and interrupted power supplies. At present, it is unrealistic to expect that a trained physician anesthetist can staff every remote health care facility. Task shifting through the teaching of nurses, paramedics, and medical officers to administer basic anesthetic needs at the health center or district hospital level, while staffing physician anesthetists at the secondary and tertiary care level, is a viable solution. Infrastructure and health systems should be robust enough to incentivize newly trained anaesthesiologists to stay and practice in their home countries. Global anesthesia outreach in education and local training of anesthesia providers in trauma care is a short-term strategy supported by the WHO to improve the quality and quantity of providers in countries with insufficiently met needs.

Trauma Training

The American College of Surgeons Advanced Trauma Life Support (ATLS®) course offers a basic foundation in the principles and practice of trauma care - with an unknown impact on outcome. ATLS which is considered to be the gold standard of trauma care training courses has not been adequately tested by a systematic review in either high- or low- income countries as noted by recent Cochrane database reviews.

Institution of ATLS in Trinidad was associated with a decrease in mortality from 67% to 34% for severely injured patients. Other efforts to provide additional training as well as further opportunity for exchange between surgeons across countries have demonstrated some benefit, but often as measured in differences between pre- and post-test scores as opposed to patient outcomes. Commonalities in knowledge, training, and previous experiences may allow for formation of interdependent multidisciplinary teams; and trauma team training, as occurs in the military and in high-income nations, has also be implemented in hospitals in LMICs.

There is even less data from LMIC regarding effectiveness of trauma training. A recent study compared written test scores after ATLS™ of medical officers (MO's) in India to those in Australia and found that MO's who had taken the course in both countries had higher passing rates, compared to MO's with clinical experience but no ATLS™ training. A basic trauma care (BTC ©) course in Ecuador, based on local resources and location of injury including the jungle, rural hospitals, and definitive referral centers, evaluated effectiveness of trauma training. In addition to pre- and post- test scores, this study incorporated objec-

tive structured clinical exams (OSCEs) to aid in the evaluation of the effectiveness of training. In rudimentary health posts, management was adequate for hemorrhage control, immobilization, and early transfer to rural hospitals, but prehospital communication was inadequate. Findings also suggest that rural hospital management was adequate for primary evaluation and resuscitation but poor in secondary patient evaluation and transfer to definitive referral centers.

Due to the high cost of ATLS and nearly 2 year wait for course delivery, many countries have developed, or partnered with high income countries to develop, trauma care training. A study assessed the impact of Trauma Team Training (TTT) on trauma knowledge and performance of Tanzanian physicians and nurses, and validated a questionnaire assessing trauma knowledge using simulation. After the TTT course, subjects improved their individual scores, and team performance scores for the simulation were all >80%. Seventy-five percent of subjects were very satisfied with TTT and 90% would strongly recommend it to others and would agree to teach future courses.

A systematic review investigating resuscitation training in developing countries sought to evaluate whether the inclusion of any specific resuscitation training educational strategy improves outcomes. 38 studies that provided support for the use of resuscitation training programs in developing countries were included. All studies that examined self-efficacy (15 studies) and student satisfaction (8 studies) reported improvement. Increased patient survival after resuscitation training was variable, with an absolute risk reduction that ranged from 0% to 34%, similar to those following introduction of ATLS™ training. There was no consistent testing method for educational outcomes across studies and few studies examined both educational outcomes and patient outcome.

Our own data show that 71% percent of trauma training courses are developed in high-income countries (HICs), as the burden of disease following injury is the greatest in LMICs. 60% of the courses developed in HICs are implemented in LMIC and 45% are implemented in LIC.

CONCLUSION

What value is there in trauma training? If we assume that most trauma care courses cover the initial identification and management of life-threatening injury, perhaps this is of greatest value in lives saved. There is little evidence that an improvement in test scores pre- versus post- training translates into improved patient care, yet this is the premise upon which much of the global medical education system is based. There is variability in the cost to run courses and higher costs may be attributed to transportation, housing and per diem costs to bring Western faculty to LMICs for course delivery.

There is a lack of trained medical personnel to provide trauma services, including anesthesia, in low and middle income countries based upon available data. Life expectancy is low, DALYs requiring anesthesia and surgery are high, and the death rate from anesthesia is high - due in part to a lack of well-trained anesthesia providers. The level of training needed may be controversial but the need for education is not. In an effort to improve life quality and expectancy of inhabitants of these countries, programs increasing the numbers trained and improving the specific training should be addressed.

Key Points:

- **Trauma is the leading cause of death under the age of 45 worldwide.**
- **There are shortfalls in trained personnel, infrastructure, and anaesthesia equipment.**
- **Global anesthesia outreach in education and local training of anesthesia providers in trauma care is a short-term strategy supported by the WHO to improve the quality and quantity of providers in countries with insufficiently met needs.**
- **ATLS is considered to be the gold standard of trauma care training courses but has not been adequately tested by a systematic review in either high- or low- income countries as noted by recent Cochrane database reviews.**
- **Many smaller trauma care training courses have developed around the world to meet local needs.**
- **There are no standards for trauma training nor evaluation of it's effectiveness.**
- **Establishing emergency, surgery and anesthesia care requires effective political advocacy, and sufficient human and consumable resources.**

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Resident Participation in Global Health: Importance, Challenges, and Opportunities

Marcel E. Durieux, M.D., Ph.D.

Training in anesthesiology tends to occur in a single institution, and as a result residents will finish their education with a somewhat myopic view of our specialty. Rotations in other institutions may mitigate this problem to some degree, but it is participation in global health efforts that really does show residents how profoundly different the practice of anesthesiology may be in locations other than their home institution.

Practicing, and particularly teaching, in austere environments forces one to rethink many of our "givens". We use "standard monitoring" on everyone without thinking about it – but if one has to determine which patient gets the sole capnograph and which one the sole EKG machine, selecting monitors becomes a clinical decision process. Inducing anesthesia with thiopental and maintaining it with ketamine provides new pharmacologic experiences for residents, and providing anesthesia for neurosurgery using halothane shows that some dogmas of our trade may require rethinking as well.

In addition to these basic and somewhat technical issues, many other aspects of healthcare tend to be dramatically different in global health settings, and being confronted by these differences helps residents not to take our US approaches for granted. Not only limitations in equipment and supplies, but also differences in access to healthcare; attitudes of both providers and patients toward illness and death, particularly in the context of surgery and anesthesia; outcomes of surgery; and interactions between healthcare providers (1) are items that force themselves on western anesthesiologists working in the developing world. The result of dealing with these issues is a more rounded anesthesiologist with a broader view of the specialty, as well as a larger "bag of tricks". The feeling of being able to provide service to a population in need, and of making use of the skills acquired during training, add to the benefits.

In 1969, an editorial in JAMA stated: "If, as a routine, young American doctors were encouraged to spend some months working in a developing country before they became tied to the responsibilities of practice, the result could only be better medicine at home and abroad."(2) This has not changed in the last 40 years. In fact, there is now some data to show that participation in global health work does change attitudes of residents, as exemplified by a recent study that reported reduced use of laboratory testing, and improved physical examination skills as a result of participation in global health efforts (3).

But where for practicing anesthesiologists it is relatively easy to participate in global health work, additional rules are imposed on residents who wish to do such work while in training. An overseas trip can be counted toward residency requirements if it is approved by the home program, as well as by the Accreditation Council on Graduate Medical Education (ACGME) and the Anesthesiology Residency Review Committee (RRC). A full description of this process can be found on the website of the American Board of Anesthesiology (4) and on the Global Humanitarian Outreach pages of the American Society of Anesthesiologists (5). Most importantly, the overseas program must either have an RRC-approved affiliation or integration with the home institution (which will rarely be the case) or an anesthesiologist needs to be present who supervises the resident overseas – this will often be a faculty member from the home institution. Overseas rotations may not take place in the first year of anesthesia training, nor in the final 3 months of training. Also, residents need to keep in mind that the can not spend more than 6 month away from their home institution in 3 years.

The home institution that employs the resident (usually the training hospital) also needs to approve the rotation. Since the hospital pays the resident, and since the resident will not be doing productive work for the hospital during the rotation, some institutions will not pay salary during trips. This unfortunate practice can obviously make it much more difficult for a resident to participate in global health work.

A frequently asked question from residents is: where do I start? If faculty at the home institution are involved in global health work, that is the obvious place. Otherwise, there are various resources available to get underway. The American Society of Anesthesiologists Global Humanitarian Outreach committee is constructing a searchable database of organizations (6). Similarly, the Society for Pediatric Anesthesia has an extensive on-line database (7). Part of the decision making process will pertain to the type of work one wishes to do: patient care (which often entails short-term trips with own equipment and a high volume of procedures) or teaching (which often requires longer stays, working with local equipment, and fewer cases). Also, not all organizations take residents. The Table lists some groups that do. One organization of particular interest is the Society for Education in Anesthesia, which partners with Health Volunteers Overseas and provides grants for residents to assist in overseas teaching efforts.

Group	Website
Medical Missions for Children	http://www.mmfc.org/waystovolunteer.htm
Global Partners in Anesthesia and Surgery	http://www.globalpas.org/
ReSurge International	http://www.resurge.org/home/home.cfm
Operation Smile	http://www.resurge.org/home/home.cfm
Rotaplast	http://www.rotaplast.org/volunteers/medical.php
Society for Pediatric Anesthesia	http://www.pedsanesthesia.org/vmsa_search.iphtml
Doctors Without Borders	http://www.doctorswithoutborders.org/
The Society for Education in Anesthesia – SEA/HVO Traveling Fellowship Rotation	http://www.seahq.net/index.php?option=com_content&view=article&id=54&Itemid=77

In short, participation by residents in global health efforts is a highly valuable extension of their training in anesthesiology. As with anything in the residency process, there are rules to be followed before it can become a reality. But the opportunities are there, and training programs should be encouraged to assist their residents as much as they can in these very worthwhile efforts.

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5. http://www.asahq.org/GHO/Residents.aspx

6. http://www.asahq.org/GHO/Volunteer.aspx?m=k

7. http://www.pedsanesthesia.org/vmsa_search.iphtml

Program Material

Friday, May 18, 2012

SAB Oral Session (Part 1)

- *Hemodynamic Slow Waves Induced With PEEP Oscillation to Measure Cerebrovascular Reactivity*
  Ken Brady, M.D.

Resident Travel Award

- *Anesthetics Interfere With Axon Guidance via a GABAA Receptor Mechanism*
  Cyrus D. Mintz, M.D., Ph.D.
- *Carbon Monoxide Prevents Anesthesia-Induced Neuroapoptosis in Newborn Mice*
  Richard J. Levy, M.D.

Junior Faculty Award

- *Switching Microglia to a Neuroprotective Phenotype: A Novel Way to Improve Neuronal Survival After Cardiac Arrest*
  Ines P. Koerner, M.D., Ph.D.
- *Role of Endothelial CSE/H2S in the Pathogenesis of Hypertension*
  Gautam Sikka, M.D.
- *Association of Intraoperative Anesthesia Handovers With Postoperative Adverse Outcomes*
  Alsparslan Turan, M.D.
- *The CQR Platform: A Novel Technology to Facilitate Longitudinal Data Collection and Evidence-Based Medicine*
  Roy C. Levitt, M.D.
- *Leading Perioperative Change in an Era of Health Care Reform*
  Sharon Muret-Wagstaff, Ph.D.

SAB Oral Session (Part 1)

Hemodynamic Slow Waves Induced With PEEP Oscillation to Measure Cerebrovascular Reactivity

Ken Brady, M.D.[1]; Kathleen Kibler, B.S.[1]; David Kaczka, M.D.[2]; Dean Andropoulos, M.D.[1]; Blaine Easley, M.D.[1]; Craig Rusin, Ph.D.[1]
Texas Children's Hospital, Baylor College of Medicine[1]; Harvard Medical School[2]

Background: The Pressure Reactivity Index (PRx) is a correlation between arterial blood pressure (ABP) and intracranial pressure (ICP). PRx is useful to identify cerebral perfusion pressures (CPP) associated with cerebrovascular autoregulation, and favorable outcome after trauma. Precision of the PRx is rate limiting and due to variable spontaneous low frequency hemodynamic activity. We sought to improve PRx precision by causing a fixed-frequency ABP oscillation by varying positive end-expiratory pressure (PEEP). We hypothesized that PRx precision would improve with induced low-frequency ABP waves (iPRx), and that iPRx precision would be replicated by analysis of the phase angle difference between ABP and ICP at the input frequency ($\Delta\phi$AI).

Methods: Anesthetized neonatal swine (n=10) with ABP, ICP, and intracranial laser-Doppler monitors were ventilated with PEEP at 5 cmH2O, and then with PEEP that oscillated between 5 and 10 cmH2O over a 60-second period. The PRx was recorded as a moving correlation coefficient between ABP and ICP from spontaneous slow wave activity (0.05 – 0.003 Hz), during static PEEP. The iPRx was similarly recorded with oscillating PEEP. $\Delta\phi$AI was recorded as the phase angle difference between ABP and ICP at the PEEP oscillation input frequency. Precision measurements of the PRx, iPRx, and $\Delta\phi$AI were done as [standard deviation]/[range of possible values] (S.D./RPV). ABP was reduced by hemorrhage. Accuracy of the iPRx and $\Delta\phi$AI were assessed after averaging in 5mmHg bins of CPP and dichotomizing above and below the lower limit of autoregulation (LLA). LLA was determined using laser-Doppler scatter plots across CPP at the intersection of two best-fit lines.

Results: PEEP oscillation increased the precision of autoregulation monitoring. S.D./RPV for the PRx, iPRx and $\Delta\phi$AI were 0.16 (0.13 – 0.20), 0.10 (0.07 – 0.11), and 0.08 (0.07 – 0.15) respectively (median and IQR; p=0.0006). Values of iPRx above and below the LLA were -0.42 (-0.37 to -0.47) and 0.43 (0.34 to 0.52; Arbitrary Units, mean and 95% C.I.). Values of $\Delta\phi$AI above and below the LLA were 144° (139° to 150°) and 55° (46° to 64°). Receiver-operator characteristics (ROC) showed similar accuracy for both iPRx and $\Delta\phi$AI with area under ROC curve of 0.988 (95% C.I. 0.97-1.00) for both indices. An iPRx value of -0.04 was 95% sensitive and 95% specific for loss of autoregulation. A $\Delta\phi$AI of 116° was 95% sensitive and a $\Delta\phi$AI of 102° was 95% specific for loss of autoregulation.

Conclusion: Oscillating PEEP reduced noise in the PRx. $\Delta\phi$AI replicates the correlation analysis of PRx with similar precision and accuracy. Safe application of these findings in a clinical environment may yield faster, more accurate delineation of optimal CPP.

Figure 1: Accuracy of iPRx and $\Delta\varphi$AI. A) Using laser-Doppler defined lower limits of autoregulation (LLA), iPRx of -0.04 (dashed horizontal line) was 95% specific and 95% sensitive for delineating cerebral perfusion pressure (CPP) below the LLA. B), the area under receiver-operator characteristic curve (AUC) using the laser-Doppler derived LLA demarcation was 0.988 for the iPRx. C) $\Delta\varphi$AI of 115° was 95% sensitive for delineating CPP below LLA. $\Delta\varphi$AI of 103° was 95% specific for delineating CPP below LLA. D) $\Delta\varphi$AI monitoring yielded the same AUC as iPRx.

Resident Travel Award

Anesthetics Interfere With Axon Guidance Via a GABAA Receptor Mechanism

Cyrus D. Mintz, M.D., Ph.D.[1]; Kendall M. S. Barrett[1]; Sarah C. Smith, M.D.[1]; Deanna L. Benson, Ph.D.[2]; Neil L. Harrison, Ph.D.[1]
Columbia University Medical Center[1]; Mount Sinai School of Medicine[2]

There is a growing concern that exposure to general anesthetics (GAs) in childhood may increase rates of behavioral disorders and learning disabilities (1). Previous work on this topic has focused primarily on the finding that GAs enhance the process of neuronal apoptosis in early brain development (2). In contrast, little attention has been directed towards the possibility that deficits may arise from dysfunction of the surviving neurons. Brain function is critically dependent on the generation of appropriate circuits, a complex developmental process in which axons follow guidance cues to their dendritic targets.

We observed substantial errors in axon targeting in an ex vivo mouse neocortex model exposed to isoflurane. Neurons adhered to cultured mouse neocortex slices normally send their axons ventrally under the influence of the guidance cue, Semaphorin 3A (Sema3A) (Fig A example of tracings of trajectories from one slice, Fig C summary of all trajectories). By contrast treatment with isoflurane results in randomly oriented trajectories, indicating a striking loss of axon guidance (Fig B example, Fig D summary).

Further experiments in primary cultured cortical neurons showed that this deficit may result from a disruption of the axonal growth cone (AGC) response to Sema3A. When exposed to Sema3A growth cones normally switch from an extended (Fig E) to a collapsed morphology (Fig F), thus allowing the response to Sema3A to be quantified by counting the percentage of collapsed AGCs. Treatment with isoflurane results in a marked loss of the Sema3A collapse response (Fig G) that is concentration dependent (Fig H). Similar results are obtained with propofol (Fig J, K). Interestingly, both volatile (Fig I) and intravenous (Fig L) agents with allosteric activity at GABAA receptors interfere with the AGC collapse response to Sema3A, but agents completely lacking activity at GABAA receptors leave the response intact (n.b. fentanyl and dexmedetomidine in Fig L). The selective GABAA agonist muscimol also blocks Sema3A induced AGC collapse in a concentration-dependent manner (Fig M), and the collapse response that is lost with either muscimol or isoflurane can be restored when picrotoxin, a GABAA receptor anatagonist, is co-administered with these agents (Fig N, O).

In summary, our data show that GAs that act on GABAA receptors can prevent the appropriate targeting of growing axons by interfering with the AGC response to the guidance cue Sema3A. The finding that GAs interfere with axon guidance represents a novel form of anesthesia neurotoxicity in brain development with potentially serious implications, given that axon guidance is necessary for the formation of brain circuits.

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Carbon Monoxide Prevents Anesthesia-Induced Neuroapoptosis in Newborn Mice

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Introduction: Volatile anesthetics cause wide-spread neuroapoptosis in the developing brain. Carbon monoxide (CO) has ant-apoptotic properties and exhaled endogenous CO is commonly re-breathed during low-flow anesthesia in infants and children resulting in sub-clinical CO exposure. We hypothesized that low concentrations of CO inspired during volatile anesthetic exposure would prevent anesthesia-induced neuroapoptosis. We aimed to quantify the number of activated caspase-3 cells and TUNEL positive nuclei in the developing brain following concomitant exposure to CO and isoflurane.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. 7 day old male CD-1 mice underwent 1-hour exposure to 0 ppm (air), 5 ppm, or 100 ppm CO in air with or without isoflurane (2%). Thus, six different cohorts were evaluated. Five hours after exposure, brains were harvested and immunohistochemistry for activated caspase-3 and TUNEL assays were performed. Three to four slices per animal were assessed and three mice per cohort were evaluated. In a separate cohort, carboxyhemoglobin levels (COHb%) were measured immediately after exposure. Change in COHb% was assessed with T-test and significance set at $P<.05$. The number of caspase-3 positive cells and TUNEL positive nuclei were determined in primary somatosensory neurocortex, hippocampus, and hypothalamus/thalamus. Significance was assessed with ANOVA and post hoc Tukey's Test.

Results: COHb% increased significantly following exposure to 5 ppm and 100 ppm CO in a concentration-dependent manner compared to air exposed controls. Isoflurane significantly increased the number of activated caspase-3 positive cells and TUNEL positive nuclei in all regions of the brain examined in air-exposed mice. CO exposure abrogated isoflurane-induced increases in activated caspase-3 and TUNEL positive nuclei in each brain region in a dose-dependent manner.

Discussion: Consistent with prior reports, 1-hour isoflurane exposure increased neuroapoptosis in several regions of the developing brain. Exposure to 5 ppm and 100 ppm CO increased COHb% confirming time-weighted exposure. Both concentrations of CO prevented isoflurane-induced neuroapoptosis in each brain region in a dose-dependent manner. Thus, low-flow anesthesia designed to result in re-breathing of specific concentrations of CO may be a desired strategy to prevent anesthesia-induced neurotoxicity in infants and children.

Junior Faculty Award

Switching Microglia to a Neuroprotective Phenotype: A Novel Way to Improve Neuronal Survival After Cardiac Arrest

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Background: While the introduction of therapeutic hypothermia has improved survival after cardiac arrest (CA) and cardiopulmonary resuscitation (CPR), many survivors are disabled by severe loss of memory and executive cognitive function. No specific treatment is available to reduce neuronal death and improve functional outcome. The brain's inflammatory response to ischemia can exacerbate injury and provides a potential treatment target that remains understudied. While activated microglia, the brain's resident immune cells, are thought to contribute to injury after ischemic stroke, little is known about their role after global ischemia during CA/CPR. We hypothesized that microglia are activated by CA/CPR and contribute to neuronal loss and functional deficit. We used a well-characterized mouse model to determine whether pharmacologic inhibition of the pro-inflammatory enzyme soluble epoxide hydrolase (sEH) after CA/CPR alters microglial activation and neuronal death in the ischemia-sensitive hippocampus.

Methods: Male adult C57Bl/6 mice underwent 8 minutes of CA followed by CPR. The sEH inhibitor 4-phenylchalcone oxide (4-PCO; 5 mg/kg ip) or vehicle were administered at 5 minutes after CA/CPR and repeated daily. Trace fear conditioning was used to test memory 10 days after CA/CPR. Microglial activation was assessed by immunostaining for the activation marker Mac-2 at 1, 3, and 10 days after CA/CPR. Surviving CA1 hippocampal neurons were counted at 3 or 10 days. Microglia where isolated from brains 1 or 3 days after CA/CPR using magnetic beads (Miltenyi Inc.). Expression of inflammatory cytokines in isolated microglia and in hippocampal tissue was measured by quantitative RT-PCR.

Results: Delayed death of CA1 neurons was evident as early as 3 days after CA/CPR and continued to day 10. Context, but not cued, freezing after trace fear conditioning was severely compromised 10 days after CA/CPR (42±8% after CA/CPR vs 72±5% in sham-operated animals), indicating loss of hippocampus-dependent memory acquisition. Activated (Mac-2 positive) microglia appeared in the hippocampus as early as 1 day after CA/CPR, before significant neuronal death was present, and persisted at 10 days. Concurrently, expression of pro-inflammatory tumor necrosis factor (TNF)-α and interleukin (IL)-1β increased. 4-PCO significantly increased hippocampal expression of anti-inflammatory IL-10 (2-fold vs. vehicle), while TNF- α and IL-1 β expression was unchanged. Analysis of isolated microglia confirmed that microglia were the main source of increased IL-10. Subsequent death of CA1 neurons was significantly reduced after 4-PCO (34 ± 4%) vs vehicle (52 ± 7%), whereas the number of Mac-2 positive microglia was unchanged.

Conclusions: Post-CPR treatment with 4-PCO selectively induced expression of anti-inflammatory and neuroprotective IL-10 in hippocampal microglia and reduced subsequent neuronal death without affecting microglial numbers. This suggests that sEH inhibition can alter the transcription profile in activated microglia to protect neurons and maintain function. IL-10 may be a signature gene of this beneficial microglial phenotype. Switching microglial gene expression towards a neuroprotective phenotype is a promising new therapeutic approach for ischemic brain injury.

Role of Endothelial CSE/H2S in the Pathogenesis of Hypertension

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One in every three Americans is affected by HTN (hypertension). HTN increases the risk for cardiac disease and stroke. Endogenous H2S (hydrogen sulfide), which plays a prominent role in a multitude of pathologies like inflammation/sepsis, hypertension, peripheral and cerebro-vascular disease and coronary artery disease, is now well characterized as a physiologic vasodilator. H2S is predominantly produced by CSE (cystathionin-γ-lyase) in the vascular endothelium. It caters to relaxation, primarily, through sulfhydration (a novel post-translational modification)[2] of IK, SK and KATP channels, resulting in vascular smooth muscle cell hyperpolarization. This effect is independent of the NO (Nitric Oxide) / cGMP/PKG axis. In 2003 Tang et. al studied H2S in spontaneously hypertensive rats (SHRs) and demonstrated a loss of CSE/H2S in HTN and a decrease in blood pressure (BP) on substitution of H2S.

Objective: To elicit if loss of endogenous H2S contributes to the pathogenesis of hypertension.

Methods and Results: Tail cuffs were used to measure BP in SHRs and control Wistar Kyoto rats (WKYs) starting at 4 weeks (w) of age until the time SHRs became hypertensive.

Infusion of intravenous glybenclamide (20mg/Kg) a KATP channel blocker, revealed a significant increase in systolic BP (SBP) in 4w old SHR (ΔSBP= 43.16 ±24.24%, n=5) and 4w WKY (ΔSBP= 89.97 ±41.40%, n=4), while little change was demonstrated in hypertensive 90w SHR (ΔSBP= 24.07 ±21.99%, n=4), as measured invasively via aortic catheterization.

In a separate set of experiments, aortic rings isolated from age matched SHRs (n=5) and WKYs (n=5), were mounted on a DMT myograph, optimally stretched, prepared in physiologic buffer at 37ºC, and constricted with phenylephrine (1μM), for assessment of endothelial function. Acetylcholine (ACH) dependent maximum relaxation after treatment with L-Name (eNOS inhibitor) was modestly attenuated in aortas of 4w WKY (92.79 ±2.64 to 83.26 ±3.35%), 4w SHR (83.50 ±4.47 to 59.48 ±8.75%) and 90w old WKYs (71.39 ±15.06 to 15.77 ±5.16%). Contrary to that, this response was completely blocked in 90w SHRs (35.32 ±5.16 to 0.24 ±3.17%). Treatment with propargylglycine (CSE blocker) did not affect ACH mediated maximum relaxation in 90w SHR (35.32 ±5.16 to 29.40 ±5.86%), but it significantly attenuated the responses in 4w WKYs (92.79 ±2.64 to 56.30 ±4.55), 4w SHRs (83.50 ±4.47 to 71.63 ±12.25) and 90w SHRs (71.39 ±15.06 to 8.13 ±4.61%). Strikingly, rings from normotensive 16w SHR had a complete L-Name sensitive attenuation of endothelial relaxation (63.25 ±5.15 to 2.74 ±1.75%).

Progress and Conclusion: There appears to be a NO independent component of endothelial relaxation in normotensive blood vessels, which is sensitive to CSE inhibitors and blockage of KATP channels. This NO independent component of relaxation is absent in hypertensive and pre-hypertensive vessels; hence implying that loss of the CSE/H2S/KATP axis could be a primary mechanism preceding HTN. This ongoing project aims to measure CSE activity and sulfhydration of Kir 6.1-Cysteine 43 and GAPDH in normotensive/pre and post hypertensive blood vessels from different animal models of HTN to elicit if the CSE/H2S/KATP axis is a potential new target for the treatment of hypertension.

Association of Intraoperative Anesthesia Handovers With Postoperative Adverse Outcomes

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Cleveland Clinic

Introduction: Recent studies have evaluated patient-care handovers between paramedics and Emergency Department personal, shift handovers between critical care nurses, and handovers between housestaff for overnight and weekend coverage. However, intraoperative handovers between anesthesia providers have not been systematically explored. We therefore tested the hypothesis that the total number of intraoperative handovers between anesthesia providers during surgery is associated with increased postoperative complications.

Methods: We used data from 96,337 patients in the Cleveland Clinic Perioperative Health Documentation System registry. Our outcome was a collapsed composite (any versus one) of in-hospital mortality and 6 morbidities: serious cardiac, respiratory, gastrointestinal, urinary, bleeding, and infection. Total number of anesthesia handovers includes number of handovers between anesthesia staff and between non-staff including certified registered nurse anesthetist (CRNA), resident/fellow, and student registered nurse anesthetist (SRNA). We assessed the associations between the outcome and (1) total number of handovers, (2) number of staff and non-staff handovers, as well as (3) number of CRNA and resident/fellow handovers, each using a multivariable logistic regression.

Results: The observed incidence of the composite outcome was 13.5%. We found that increased number of anesthesia handovers was associated with increased odds of experiencing any major in-hospital morbidity / mortality (OR (95% CI): 1.05 (1.02-1.07) for a one unit increase in the total number of handovers; P < 0.001). Increased number of non-staff handovers was associated with worse outcome (OR (95% CI) of 1.07 (1.04, 1.10) for an increase of one handover; P < 0.001), while number of staff handovers was not associated with outcome (1.0 (0.96, 1.04), P = 0.99), each factor adjusted for the other. However, the association between the number of non-staff handovers and the outcome depended significantly on the number of staff handovers (staff-by-non-staff interaction: P = 0.001; Figure 1), and vice versa.For CRNAs, the odds of having the outcome increased as the number of handovers increased (odds ratio (95% CI) of 1.10 (1.05, 1.14); P < 0.001); however, no such association was observed for number resident/fellow handovers (1.02 (0.97, 1.07); P = 0.44). There was no interaction between number of CRNA handovers and staff handovers (P=0.13), but the odds ratio for resident/fellow handovers decreased from 1.07 to 0.83 as number of staff handovers increased from 0 to 3 (interaction P= 0.01). Furthermore, there was no significant interaction between CRNA and resident/fellow handovers on the outcome (P = 0.85).

Conclusions: More anesthesia handovers was associated with increased odds of having in-hospital morbidity/mortality. Overall, number staff handovers did not matter, while non-staff did. Interestingly, though, the relationship between staff handovers and outcome depended on the number of non-staff handovers, and vice-versa. Results might be affected by more handovers occurring among CRNAs compared with anesthesia staff or residents/fellows.

Figure 1. Odds ratios of having any in-hospital morbidities/mortality for a unit increase in the number of non-staff (including certified registered nurse anesthetist, resident / fellow, and student registered nurse anesthetist) handovers, at each level of staff handovers. There was a significant interaction effect between staff and non-staff handovers on the outcome (P = 0.001). We adjusted for age, gender, race, American Society of Anesthesiologist physical status, start time of surgery, duration of surgery, and principal diagnosis and procedure.

The CQR Platform: A Novel Technology to Facilitate Longitudinal Data Collection and Evidence-Based Medicine

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Background: Longitudinal data collection in the clinical area is costly and complicated by the lack of patient-centric care and resource limitations. The collection of longitudinal data can improve patient care and the patient experience by facilitating quality assessments and continuous improvement, and treatment decisions based on comparing outcomes, assessing patient satisfaction, and supporting approved outcomes research. To facilitate longitudinal patient data collection in and outside the healthcare system, we have developed the CQR Platform (Clinical Quality and Research Platform) representing a wireless data collection tool (utilizing a touch screen application for tablets, smart phones, etc.). The CQR Platform is capable of high dimensional secure data collection on patients over time from any site (home, office, clinics, etc.). CQR data is collected in a proprietary secure database of self-reported and healthcare worker submitted patient data (via modules including validated questionnaires focused on pertinent clinical data) designed to communicate with electronic medical records. Our pilot data modules are focused on patient data collection in our pain treatment clinics.

Methods: The CQR Platform App provides a wireless tablet to collect medical history, medications, referring physicians, vital signs, responses to validated pain assessment questionnaires, as well as patient satisfaction data on each clinic visit. This information is updated by visit and stored on a secure server. The system is designed to facilitate the extraction of key clinical data for clinical assessment on each visit. Clinical data are submitted to the electronic medical record after each entry, where it may be reviewed by the treating healthcare provider(s). Over the course of time, patient outcomes can be assessed to obtain a high-level view of the cases being treated and develop quality reports comparing treatments, assessing performance, guiding future treatment selection, and to track and improve patient satisfaction across large numbers of patients. After ethics committee approval, clinical research may also be facilitated by extraction of longitudinal data where relevant.

Results: The CQR Platform is currently being launched in the Multidisciplinary Pain Clinics at the University of Miami Miller School of Medicine. A demonstration of the App and detailed description of the technology will be provided at the AUA session using a wireless tablet. We expect to report the progress of this technology toward reaching the outlined goals at the meeting.

Conclusions: The CQR Platform is a wireless touch screen supported electronic data collection tool that has the potential to facilitate convenient longitudinal patient data collection across the entire healthcare system (clinics, physician offices, etc.) and outside.

Leading Perioperative Change in an Era of Health Care Reform

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Background: The changing landscape of health care reform affords anesthesiologists new opportunities to lead transformative change in perioperative quality and safety, patient experience, and efficiency. However, new models are needed for today's anesthesiologists to develop effective leadership skills for tomorrow's healthcare environment. We sought to create and test a novel organizational platform to (1)support interdisciplinary learning, innovation, and improvement; and (2)foster critical leadership capability needed to sustain the model at individual, departmental, and institutional levels.

Methods: We launched Faculty Hour in 2010, an interdisciplinary partnership for performance excellence uniting Anesthesia, Surgery, Nursing, and others at a large teaching hospital. OR start time is moved 30 min. later each Tuesday to provide protected time, and a Steering Committee guides efforts along with Patient-Family Advisory Council input. Staff participate voluntarily at 6:45 AM in parallel 90-day chartered teams, cross-discipline division meetings, and faculty development sessions. Key elements include joint leadership by an anesthesiologist, surgeon, and nurse; leader prep sessions and toolkit; innovation discovery teams; data review; broad recognition; and short improvement cycles. In addition to immersion as team and session leaders, faculty devote a 90-day cycle each year to leadership skill seminars.

Results:

Individual: In the first 24 months, 153 individuals from anesthesia, surgery, nursing, and other groups served on chartered teams. Meanwhile, 11 cross-disciplinary divisions met quarterly, alternating with faculty development sessions (e.g., 74 anesthesiologists participated in clinical innovation workshops and leadership, scholarship, and education series). 40 of 74 (54%) Anesthesia faculty served in a leadership role.

Departmental: Organizational performance for the Anesthesia Dept. before and 12 months after introduction of Faculty Hour improved overall ($p<.0001$) with 9-38% point gains on Baldrige-based survey items (Fig. 1), e.g., improvements in % of faculty who reported they were encouraged and enabled to develop skills ($p=.05$) and to generate innovative ideas ($p=.0001$).

Institutional: Sample results from 15 chartered teams: Optimized OR layout to reduce surgical infection risk; improved patient flow with 1,200 annual miles saved in staff walking between sites; reduced instruments opened in robotics by 53%; launched monthly simulation-based OR team training; designed peer support program; created effective communication videos; implemented perioperative computerized physician order entry; improved communication with trauma patients and families. Importantly, on-time OR starts are best on Tuesdays.

Conclusions: We have instituted a replicable, sustainable platform for collaborative learning, innovation, and improvement in the OR environment. Anesthesiologists participate in leadership development and most have held new leadership roles. The Department shows striking evidence of change in organizational performance. Institutionally, early project results show improved efficiency and patient experience, and the Anesthesia Department is newly identified as an institutional leader in innovative care improvement.

Muret-Wagstaff S, Simon BA. Leading Perioperative Change in an Era of Health Care Reform. AUA 2012.

Program Schedule

Saturday, May 19, 2012

Music and the Ear
Neil Cherian, M.D.

Music Therapy: Where Music and Medicine Meet
Dwyer Conklyn, MM, MT-BC

When Music Sings the Brain Listens and the Heart Modulates: A Conference-Concert™
Kamal R. Chémali, M.D.; Prisca Benoit

Music and the Brain

Music and the Ear

Neil Cherian, M.D.

Music Therapy: Where Music and Medicine Meet

Dwyer Conklyn, MM, MT-BC

Music Therapy is an expanding field combining the knowledge of physiological systems with the application of musical stimuli for improved well being. Music can be utilized in the treatment of a variety of disorders; from relaxation and guided imagery for anxiety, to functional singing for patients with acquired speech disorders, to distraction and relaxation for chronic pain patients, to utilizing rhythm to improve gait dysfunction, to name a few. Music therapists provide a bridge between the medical field and the arts and are trained to work individually as well as in collaboration with other disciplines. This presentation will explore some of the basics of music therapy and the potential for collaboration.

-Dwyer Conklyn MM MT-BC
Neurologic Music Therapist

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When Music Sings the Brain Listens and the Heart Modulates: A Conference-Concert™

Kamal R. Chémali, M.D.; Prisca Benoit

Therapeutic properties of music have been intuitively perceived since the dawn of humanity. Today's technological advancements allow scientists and researchers to qualify and quantify the physiological changes that music produces in different body organs. Music perception is a highly complex phenomenon starting with sound waves causing vibration of the tympanic membrane and ending with an elaborate decoding process at the auditory cortex. The brain integrates this input, and other associated inputs, in order to create a musical emotion, which, in turn, modulates basic bodily functions, including cardiovascular responses, breathing, cerebral blood flow and sweat output, to name a few. The series of physiological changes that music can produce in our organism feeds back into the musical emotion and becomes the basis of the therapeutic properties of this art. Touching and transforming ("haptonomizing", from the Greek haptein=touch and make contact) the listener during a live performance enables one to draw a parallel between the artist-audience relationship and the doctor-patient relationship. Through an interactive approach and alternation of scientific talk and live piano performance, Dr. Kamal Chémali and Ms. Prisca Benoit bring a lively demonstration of a collaboration between a physician-scientist and a professional musician aiming at creating awareness of the impact of music on human physiology and triggering new research ideas in the field of the neuroscience of music.

Program Schedule

Saturday, May 19, 2012

SAB Oral Session (Part 2)

- *The Complications of Uncomplicated Acute Type B Aortic Dissection: Refining the Penn Classification to Improve Patient Outcome*
  John G. Augoustides, M.D.
- *Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 1 Diabetes Hyperglycemia in Mice*
  Robert E. Shangraw, M.D., Ph.D.
- *Obesity Predicts Acute Kidney Injury Following Cardiac Surgery: Role of Oxidative Stress*
  Frederic T. Billings, M.D., M.Sc.

Junior Faculty Award

- **An Engineered Water Soluble Variant of Human MU Receptor**
  Renyu Liu, M.D., Ph.D.

Resident Travel Award

- *Identification and Characterization of a Novel Compound That Protects Cardiac Tissue From hERG-Related, Drug-Induced Arrhythmias*
  Amanda N. Lorinc, M.D.
- *Norepinephrine Blocks Isoflurane-Induced Activation of Firing in Putative Sleep-Promoting VLPO Neurons*
  Michael R. Chalifoux, M.D.
- *Optoanesthesia With Meta-Azipropofol in Xenopus Tadpoles*
  Brian P. Weiser, B.S.
- *Specific Hypersensitivity to Volatile Anesthetics in a Mouse Lacking Ndufs4, a Subunit of Mitochondrial Complex I.*
  Margaret M. Sedensky, M.D.

SAB Oral Session (Part 2)

The Complications of Uncomplicated Acute Type B Aortic Dissection: Refining the Penn Classification to Improve Patient Outcome

John G. Augoustides, M.D.; Prakash A. Patel, M.D.; Edward Y. Woo, M.D.; Wilson Y. Szeto, M.D.; Ron M. Fairman, M.D.; Joseph E. Bavaria, M.D.
University of Pennsylvania

Introduction: Acute type B aortic dissection (ATBAD) involves the descending thoracic aorta,beginning with an intimal tear distal to the left subclavian artery and presenting within 2 weeks of onset.

The management of ATBAD depends on clinical presentation, traditionally classified as uncomplicated or complicated. Although uncomplicated ATBAD is typically managed medically, there are still patients at excessive risk for serious aortic complications that may be preventable by endovascular intervention. In an effort to address this quality gap, we have recently derived the University of Pennsylvania (Penn) classification of ATBAD. In this classification, uncomplicated ATBAD presentations are classified as Class A, since they are characterized by an Absence of malperfusion or aortic rupture. The purpose of this study was to identify the risk factors in Penn Class A ATBAD that predict for downstream aortic complications, including mortality.

Methods: An English language literature search was conducted utilizing PubMed for all relevant studies since 2000, utilizing standard search terms. The identified risk factors were considered in three categories: medical therapy, aortic anatomy, and dissection extent (DeBakey IIIA - ATBAD limited to the descending thoracic aorta; DeBakey IIIB - ATBAD involving both the descending thoracic and abdominal aorta) .

Results: Although 12 trials adequately described outcomes out to the long-term, there were only 2 high-quality trials that examined the details of medical therapy, suggesting that tight medical management significantly protected against downstream aortic risk, especially if therapy included beta-adrenergic and calcium channel blockade. There were 12 trials that assessed aortic anatomy to identify the following significant predictors for late aortic complications: aortic diameter > 40mm, patent or partially thrombosed false lumen,large false lumen, and ulcer-like projections. There were no trials identified that examined aortic complications as a function of dissection extent as defined by DeBakey.

Conclusions: Uncomplicated ATBAD presentations are a misnomer and should be more precisely defined as Penn Class A presentations. This study has identified three therapeutic opportunities in Penn Class A ATBAD. Firstly, further trials should define the optimal conduct of medical therapy, including drug therapy, follow-up, and contemporary survival. Secondly, adequately powered prospective randomized trials should evaluate whether endovascular intervention can reduce mortality in patients with high-risk anatomic factors on presentation. Thirdly, further trials should examine whether the extent of ATBAD on presentation determines downstream aortic complications. Penn Class A presentations represent a major therapeutic opportunity from both the medical and interventional perspectives.

Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 1 Diabetes Hyperglycemia in Mice

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Oregon Health & Science University

Hyperglycemia worsens stroke, yet rigorous glycemic control in outpatient diabetic populations does not improve either the incidence or outcome from stroke (1). Failure of tight glucose control to improve neurologic outcome was also reported in critically-ill hyperglycemic patients (2). Attenuating hyperglycemia once a stroke has initiated has not improved neurologic outcome, and may be counterproductive (3). An alternative approach is to interfere with downstream molecular mediator(s) triggered by hyperglycemia but ultimately acting independent of prevailing glycemia. Soluble epoxide hydrolase (sEH), a product of the gene EPHX2, is abundant in brain and a potential mediator of ischemic injury via its removal of neuroprotective epoxyeicosatrienoic acids (EETs) (4,5). We tested the hypothesis that hyperglycemia exacerbates cerebral injury, at least in part, by up-regulating EPHX2 mRNA expression and increasing brain sEH activity in mice. Type 1 diabetes mellitus (T1D) was produced by STZ 50 mg/kg/day i.p, x 5 days in male C57/BL6 mice. At 4 wks, T1D and control mice were subjected to 45-min middle cerebral artery occlusion (MCAO) with or without sEH blockade by trans-4- [4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (t-AUCB) (6). The t-AUCB regimen was 1 mg/kg i.p. x final 6 days before MCAO. Study measures were plasma glucose concentration, EPHX2 mRNA expression, cerebral blood flow, and brain infarct size at 24 hrs. Hyperglycemic T1D mice exhibited 1.8-fold up-regulation of EXPH2 expression, and sustained brain diffuse regional infarct size 47-77% larger than in controls. Pretreatment with t-AUCB improved infarct size in both groups, and eliminated the difference between T1D and control infarct size, without altering glycemic status in either group. We conclude that T1D hyperglycemia upregulates EXPH2 mRNA expression coding for sEH, stimulates sEH production and worsens stroke, an effect obviated by sEH blockade. It remains to be determined whether similar findings occur in the more common Type 2 diabetes setting.

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Fig 5. MCAO-induced hemispheric brain infarct size in T1D and control mice, with or without sEH blockade by t-AUCB (n=5/group). T1D mice received STZ 50 mg/kg i.p. q d x 5 days starting at day zero, and controls received vehicle only, and mice were exposed to MCAO at 4 wks. Brains were harvested at day 1 post-MCAO, and infarct size measured by TTC staining as described in methods. Left panel shows the results in the absence of t-AUCB. Right panel shows pretreatment with t-AUCB 1 mg/kg i.p. q d x 6b days immediately before MCAO testing. Asterisk (*) indicates difference from matched controls, and cross (V) indicates difference from no t-AUCB, at $P<0.05$.

Obesity Predicts Acute Kidney Injury Following Cardiac Surgery: Role of Oxidative Stress

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Vanderbilt University

Background: The prevalence of obesity in cardiac surgery patients has increased. Obesity increases oxidative stress, endothelial dysfunction, and inflammation, but the effect of obesity on postoperative acute kidney injury (AKI) is not known.

Methods and Results: We examined the relationship between body mass index (BMI) and AKI, defined using AKIN consensus criteria for AKI diagnosis (at least a 0.3 mg/dl or 50% increase in serum creatinine within 72 hours of surgery), in 445 cardiac surgery patients. We further examined whether oxidative stress (F2-isoprostanes), inflammation (interleukin-6), or anti-fibrinolysis (plasminogen activator inhibitor (PAI)-1) contribute to any relationship between BMI and AKI.

One hundred and twelve subjects (25.2%) developed AKI, and these subjects stayed in the hospital longer, were more likely to develop postoperative atrial fibrillation or pneumonia, and had an increased risk of 30-day death. Adjusted for preoperative and intraoperative risk factors for postoperative AKI, BMI independently predicted postoperative AKI (28.7% increases in the odds of AKI per 5 kg/m2 increases in BMI, 95% CI: 5.9-56.4, P=0.01). Baseline F2-isoprostane (23.4% higher odds of AKI per 50% increase in biomarker concentrations, P=0.04), intraoperative F2-isoprostane (38.1% higher, P=0.003), and intraoperative PAI-1 (18.1% higher, P=0.04) concentrations also independently predicted AKI. A trend was observed between intraoperative interleukin-6 concentrations and increased odds of AKI (7.3% higher, P=0.07), but baseline interleukin-6 and baseline PAI-1 concentrations had no association with AKI. BMI no longer predicted AKI after adjusting for the effect of F2-isoprostanes, suggesting that obesity affects AKI via the effects of obesity on oxidative stress. Adjustment for interleukin-6 or PAI-1 concentrations did not affect the association between BMI and AKI. Further, deconstruction of the obesity-kidney injury relationship into direct effects (independent of oxidative stress, inflammation, or anti-fibrinolysis candidate pathways) and indirect effects (effect of BMI on AKI via each candidate pathway) indicated that F2-isoprostanes but not interleukin-6 or PAI-1 partially mediate the relationship between obesity and AKI (P=0.03 for baseline oxidative stress and P<0.001 for intraoperative oxidative stress mediation).

Conclusions: Obesity independently predicts AKI following cardiac surgery. Oxidative stress may partially mediate the effect of obesity on AKI.

Junior Faculty Award

An Engineered Water Soluble Variant of Human MU Receptor

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Background: Despite of addiction, lethal respiratory depression, and countless other side effects, the therapeutic use of opioids has soared worldwide(1). The μ opioid receptor (MUR) is the major target of opiates and is linked to most of the notorious side effects. Studying the structure function relationship (SFR) of the MUR is limited because it is an intrinsic membrane protein and lacks high resolution structural data. Here, we present a water soluble variant of human μ receptor (WSMUR) over-expressed in E-coli system as a potential novel tool for further SFR studies.

Methods: While water soluble variants of membrane proteins have been successfully engineered in our group using published structures as templates(2), no crystal structure of μ- receptor is available. A comparative (homology) model of the human mu-receptor (P35372) was built as an alternative starting point using the structure of β2-adrenergic receptor (2RH1)(3) and bovine rhodopsin (1U19)(4) since they belong to the Class A G-protein coupled receptor family. The WSMUR was then engineered by redesigning highly exposed hydrophobic residues on the surface of transmembrane domain with hydrophilic residues in a manner consistent with the model structure. The WSMUR model was then evaluated with molecular dynamic simulation in an aqueous environment and with a docking algorithm (Autodock). The protein was: expressed in an E. coli system and purified. WSMUR was characterized using electrophoresis, mass-spectrometry, dynamic light scattering, circular dichroism (CD), and a time resolved fluorescence based opioid binding assay.

Results: During a 200 ns (300 K) molecular dynamic simulation, WSMUR retained its initial structure similar to the (Figure 1A). Agonists and antagonists were docked into the model with the results in agreement with the published mutagenesis studies. The protein was successfully expressed in E-coli with high yield, purified and the sequence confirmed using mass-spectrometry. The solubility of the protein was more than 5 mg/ml in sodium phosphate buffer. The CD spectra indicated that WSMUR is predominantly alpha helical (Figure 1B: 47% alpha helical, 15% beta turn, and 24% random coil), which is consistent with the secondary structure of the native protein. The CD spectra are invariant over a wide range of pH (6~9). Dynamic light scattering studies indicated that WSMUR is predominantly a monomer (93% of the mass). The affinity of WSMUR with naltrexone is 53 ± 16 nM (mean ± SD) as indicated in figure 1C, which is close to that of its native protein (around 8nM).

Conclusions: A WSMUR was engineered, over-expressed, purified and characterized. Results so far find it to be consistent with existing structural and binding information. This provides a potential novel tool to further investigate the SFR for human MUR.

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Resident Travel Award

Identification and Characterization of a Novel Compound That Protects Cardiac Tissue From hERG-Related, Drug-Induced Arrhythmias

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Sudden cardiac death due to ventricular arrhythmias is a global health issue and accounts for 10-20% of adult deaths in the US alone. Ion channel modulation is a major target for cardiovascular therapeutics. The hERG-encoded K+ current, IKr, is essential for cardiac repolarization but also a source of cardiotoxicity because unintended hERG inhibition by diverse pharmaceuticals can cause arrhythmia and sudden cardiac death. Inhibition of IKr, either through class III antiarrhythmic drugs or through unintended block by agents prescribed for non-cardiac conditions, including over-the-counter drugs, can lead to acquired long QT syndrome (LQTS). Arrhythmias associated with the acquired LQTS present a serious clinical problem that has led to the withdrawal of several otherwise successful drugs from the market. In response, the FDA issued guidelines that require evaluation of novel chemical entities for their potential to induce QT prolongation early in drug development. It has been estimated that 50-70% of all lead compounds are eliminated at early stages due to hERG related safety issues thereby limiting the number of drugs that enter the development pipeline. For these reasons, development of a small molecule that could be co-administered to decrease the risk of arrhythmias in response to hERG inhibitors would improve public health, patient care, and greatly facilitate the drug discovery process.

We hypothesized that IKr reduction in response to a known inhibitor could be prevented by a small molecule. We identified and characterized a small compound, VU0405601, (“601”) that reduces the sensitivity of hERG to the prototypical inhibitor, dofetilide and other known blockers. In isolated, Langendorff-perfused rabbit hearts, 601 reduced the incidence of dofetilide-enhanced arrhythmias. In addition to arrhythmia incidence, additional information regarding the mechanism of dofetilide-induced ventricular arrhythmias was obtained using voltage sensitive dyes and a CCD camera. In regards to arrhythmia mechanism, we found that prolongation of the action potential duration (a surrogate for QT measurement) does not correlate to arrhythmia incidence, 601 does not affect the magnitude or incidence of alternans, nor does it protect against dofetilide-mediated nodal line formation. However, 601 decreases the nodal line length and alternans gradient. Calcium handling and conduction block appear to have a role in arrhythmia formation which are currently under investigation along with the effect of 601 on droperidol-induced arrhythmia.

Norepinephrine Blocks Isoflurane-Induced Activation of Firing in Putative Sleep-Promoting VLPO Neurons

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Introduction: The ventrolateral preoptic nucleus (VLPO) of the hypothalamus has emerged as the prototypic natural sleep-promoting site and an intriguing target for anesthetics.1,2 Reciprocal inhibitory connections have been identified between VLPO and the major monoamine centers of the brain, forming the basis of a "flip-flop" switch.3 Electrophysiological studies have shown that the sleep-promoting neurons of VLPO are hyperpolarized by norepinephrine, a major neurotransmitter responsible for CNS arousal.4 We have previously demonstrated that sleep-promoting VLPO neurons characteristically display low threshold spiking (LTS) and are also depolarized by the volatile anesthetic isoflurane.5 Here we hypothesize that ex vivo and in vivo administration of norepinephrine will reverse the excitation of sleep-promoting VLPO neurons produced by isoflurane and should antagonize anesthetic hypnosis.

Methods: Hypothalamic brain slices containing VLPO were prepared from wild-type mice similar to that previously described.6,7 VLPO neurons were identified as the putative sleep-promoting type by the presence of low threshold spiking (LTS).4,8-9 Hypothalamic slices were exposed to 330μM isoflurane under current clamp conditions and subsequently exposed to a combination of 330μM isoflurane plus 100μM norepinephrine.10 The effects upon membrane characteristics including membrane potential and firing rates were measured. In parallel in vivo experiments, mice were chronically implanted with bilateral cannulas directed at VLPO. After 2 weeks of recovery, mice were stably anesthetized with 1.0% isoflurane. Over a 1-minute period 25nL of 5.75mM norepinephrine and 100μM reboxetine, a norepinephrine reuptake inhibitor, were infused bilaterally into VLPO. Behavioral responsiveness was continuously monitored in the gas-tight chamber.

Results: Whole cell recording demonstrated that isoflurane induced a significant 13.3±1.3mV depolarization and increased the firing rate of putative sleep-promoting LTS VLPO neurons. The isoflurane-induced excitation of these neurons was completely reversed by the concomitant administration of norepinephrine. While being exposed to a constant concentration of isoflurane, norepinephrine caused the putative sleep-promoting LTS VLPO neurons to cease firing and return to -55.8±1.8mV, a level indistinguishable from their baseline resting potential. Preliminary results from mice infused with norepinephrine/reboxetine, in which the cannula successfully targeted VLPO, suggest that a partial antagonism of the anesthetic state occurred. Prior to infusion, mice remained immobile. At a constant concentration of isoflurane, norepinephrine/reboxetine led to purposeful limb and tail movements and efforts to regain the righting reflex.

Conclusions: Exposure of putative sleep-promoting VLPO neurons to norepinephrine both ex vivo and in vivo counteracts the excitatory effects of isoflurane on these cells. The mechanisms by which isoflurane depolarized and norepinephrine hyperpolarized putative sleep-promoting LTS VLPO neurons are currently under investigation. Our data supports the notion that improved understanding of the neural circuits regulating arousal may lead to novel strategies for facilitating or delaying emergence from general anesthesia.

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Animals Studies were conducted in accordance with NIH guidelines and approved by the University of Pennsylvania School of Medicin

Optoanesthesia With Meta-Azipropofol in Xenopus Tadpoles

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General anesthetics are among the most promiscuous drugs used, and the molecular binding partners that contribute to hypnosis, amnesia, and analgesia remain unproven. The identification of anesthetic targets is hindered by low affinity interactions (μM KD values) with numerous proteins, which has motivated the design of pharmacologically active photolabels. Combined with mass spectrometry, these have allowed the confirmation of suspected, and identification of previously unsuspected, targets and binding sites. m-Azi-propofol (Azi-Pm; Hall et al. (2010) J Med Chem 53:5667-5674) is a photoactive mimic of the intravenous anesthetic propofol (2,6-diisopropylphenol). Azi-Pm is physicochemically similar to propofol and pharmacologically comparable in terms of induction and recovery when administered to tadpoles. The photolysis of azi-Pm occurs at 370 nm (UVA), limiting damage to cellular macromolecules upon exposure. The resulting carbene radical is reactive and non-selective, and reliably reports anesthetic binding sites. We hypothesized that organisms exposed to UVA while anesthetized with azi-Pm would show prolonged recovery as anesthetic sites remain irreversibly occupied. We equilibrated albino Xenopus tadpoles with 4 μM azi-Pm in Petri dishes, exposed them to UVA, and monitored recovery of mobility after changing their water. Azi-Pm prolonged the recovery period of tadpoles in a manner dependent on duration of UVA exposure (two to ten-fold after three to twenty minutes UVA, respectively) with no toxicity up to 96 hours later. Control tadpoles exposed to propofol +/- UVA or azi-Pm alone recovered within 25 minutes with no significant differences. Armed with this new knowledge that azi-Pm-adducted targets contribute to immobility, we initiated a campaign to identify Xenopus neuronal proteins bound by tritiated azi-Pm at clinically relevant concentrations through in vivo photolabeling and mass spectrometry. Only a small number of neuronal targets are adducted, suggesting the combination of optoanesthesia and proteomics will become a valuable tool in the elucidation and verification of anesthetic mechanisms on the molecular level in tadpoles and ultimately the systems level as it is adapted to higher vertebrates. (supported in part by GM55876)

Specific Hypersensitivity to Volatile Anesthetics in a Mouse Lacking Ndufs4, a Subunit of Mitochondrial Complex I

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Introduction: The mechanism of action of volatile anesthetics (VAs) remains incompletely understood. In earlier studies, we found that defects specifically in complex I of the mitochondrial electron transport chain altered sensitivity to VAs in the nematode C. elegans (1,2). We previously reported hypersensitivity to isoflurane in a mouse carrying a knockout (KO) mutation in a subunit of mitochondrial complex I (Ndufs4) (3,4). A role for mitochondrial function underlying VA action was corroborated by studies showing that children with mitochondrial dysfunction in complex I are also sensitive to sevoflurane, using BIS recordings as an endpoint (3). We have now extended our studies of the Ndufs4 KO mouse to include sensitivities to halothane, propofol and ketamine using the righting reflex as an endpoint. We find strikingly specific responses by the Ndufs4 KO mouse to these anesthetics indicating that the effects of mitochondrial mutations do not cause a nonspecific depression of the CNS.

Methods: Young (P23-27) Ndufs4 KO mice were compared to age-matched, wild-type littermates at an age before any severe CNS phenotype is apparent. Genotypes were confirmed by PCR for all mice. Mice were anesthetized with incremental doses of isoflurane or halothane in a closed chamber. Anesthetic concentrations were determined by gas chromatography. Lack of response to a non-crushing tail clamp stimulus was the anesthetic endpoint. The EC50 was determined as described by Sonner (4). Studies of propofol and ketamine were done by peritoneal injection and tested for loss of righting reflex (LORR). All mice were either studied under a warming lamp such that ambient temperature was maintained at 36oC or on a warming blanket to maintain body temperature.

Results: Ndufs4-KO mice were very hypersensitive to isoflurane and halothane, with an EC50s of 0.44+.07(SD)% and 0.52 +.11(SD)%, respectively. Wild-type, control mice had an EC50 of 1.23+.13% and 1.28+.07%, similar to previously published reports for this strain of mouse (4). Ndufs4 KO mice were mildly hypersensitive to propofol (ED50 37 + 5 mg/kg KO; ED50 67 + 5 mg/kg WT). Surprisingly, Ndufs4 KO mice were resistant to ketamine (ED50 105 + 7 mg/kg KO; ED50 66 + 6 mg/kg WT).

Discussion: The mice with mitochondrial dysfunction have a change in VA sensitivity that is the largest reported to date for a mammal. The differences in the sensitivities to anesthetics indicate that these responses are not the result of nonspecific defects in CNS function in the KO animal. These data reinforce the concept that mitochondrial complex I contributes specifically to VA sensitivity. We are now studying cell specific Ndufs4 KO animals to identify the mechanism underlying these changes.

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Poster Presentation Abstracts

Anesthetic Toxicity

Anesthetic Toxicity #1 (45)

Resident Travel Award

Anesthetics Interfere With Axon Guidance Via a GABAA Receptor Mechanism

Cyrus D. Mintz, M.D., Ph.D.[1]; Kendall M. S. Barrett[1]; Sarah C. Smith, M.D.[1]; Deanna L. Benson, Ph.D.[2]; Neil L. Harrison, Ph.D.[1]
Columbia University Medical Center[1]; Mount Sinai School of Medicine[2]

Anesthetic Toxicity #2 (14)

Carbon Monoxide Prevents Anesthesia-Induced Neuroapoptosis in Newborn Mice

Richard J. Levy, M.D.; Ying Cheng, B.S.
Children's National Medical Center

Anesthetic Toxicity #3 (20)

Anesthetic-Induced Developmental Neuroapoptosis; Is Anesthesia Bad for the Newborn Brain?

Zeljko J. Bosnjak, Ph.D.; Xiaowen Bai, M.D., Ph.D.
The Medical College of Wisconsin

Anesthetic Toxicity #4 (47)

Propofol Induces Apoptosis Via Over Activation of Inositol 1,4,5-Trisphosphate Receptors

Huafeng Wei, M.D., Ph.D.; Yi Peng, M.D.; Ge Liang, M.D.; Kevin Foskett, Ph.D.; Don-On Daniel Mak, Ph.D.; Horia Vais, Ph.D.
University of Pennsylvania

Anesthetic Toxicity #5 (61)

The Effect of Isoflurane on the Developing Hypoxic Rat Brain

Lisa Wise-Faberowski, M.D.
Stanford University, Palo Alto, CA

Anesthetic Toxicity #6 (90)

Metabolic Status of Neonatal Rat Brain in Response to General Anesthesia Differs From the Young Rat Brain: Role of Glutamate

Rany Makaryus, M.D.[1]; Hedok Lee, Ph.D.[1]; Zvi Jacob, M.D.[1]; Mei Yu, B.S.[2]; Tian Feng, B.S.[1]
Stony Brook University[1]; Brookhaven National Lab[2]

Anesthetic Toxicity #7 (77)

Junior Faculty Award

Switching Microglia to a Neuroprotective Phenotype: A Novel Way to Improve Neuronal Survival After Cardiac Arrest

Ines P. Koerner, M.D., Ph.D.; Jianming Wang, M.D.; Tetsuhiro Fujiyoshi, M.D., Ph.D.; Jonathan D. Raybuck, Ph.D.; K. Matthew Lattal, Ph.D.
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Anesthetic Toxicity #1 (45)

Resident Travel Award

Anesthetics Interfere With Axon Guidance Via a GABAA Receptor Mechanism

Cyrus D. Mintz, M.D., Ph.D.[1]; Kendall M. S. Barrett[1]; Sarah C. Smith, M.D.[1]; Deanna L. Benson, Ph.D.[2]; Neil L. Harrison, Ph.D.[1]
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There is a growing concern that exposure to general anesthetics (GAs) in childhood may increase rates of behavioral disorders and learning disabilities (1). Previous work on this topic has focused primarily on the finding that GAs enhance the process of neuronal apoptosis in early brain development (2). In contrast, little attention has been directed towards the possibility that deficits may arise from dysfunction of the surviving neurons. Brain function is critically dependent on the generation of appropriate circuits, a complex developmental process in which axons follow guidance cues to their dendritic targets.

We observed substantial errors in axon targeting in an ex vivo mouse neocortex model exposed to isoflurane. Neurons adhered to cultured mouse neocortex slices normally send their axons ventrally under the influence of the guidance cue, Semaphorin 3A (Sema3A) (Fig A example of tracings of trajectories from one slice, Fig C summary of all trajectories). By contrast treatment with isoflurane results in randomly oriented trajectories, indicating a striking loss of axon guidance (Fig B example, Fig D summary).

Further experiments in primary cultured cortical neurons showed that this deficit may result from a disruption of the axonal growth cone (AGC) response to Sema3A. When exposed to Sema3A growth cones normally switch from an extended (Fig E) to a collapsed morphology (Fig F), thus allowing the response to Sema3A to be quantified by counting the percentage of collapsed AGCs. Treatment with isoflurane results in a marked loss of the Sema3A collapse response (Fig G) that is concentration dependent (Fig H). Similar results are obtained with propofol (Fig J, K). Interestingly, both volatile (Fig I) and intravenous (Fig L) agents with allosteric activity at GABAA receptors interfere with the AGC collapse response to Sema3A, but agents completely lacking activity at GABAA receptors leave the response intact (n.b. fentanyl and dexmedetomidine in Fig L). The selective GABAA agonist muscimol also blocks Sema3A induced AGC collapse in a concentration-dependent manner (Fig M), and the collapse response that is lost with either muscimol or isoflurane can be restored when picrotoxin, a GABAA receptor anatagonist, is co-administered with these agents (Fig N, O).

In summary, our data show that GAs that act on GABAA receptors can prevent the appropriate targeting of growing axons by interfering with the AGC response to the guidance cue Sema3A. The finding that GAs interfere with axon guidance represents a novel form of anesthesia neurotoxicity in brain development with potentially serious implications, given that axon guidance is necessary for the formation of brain circuits.

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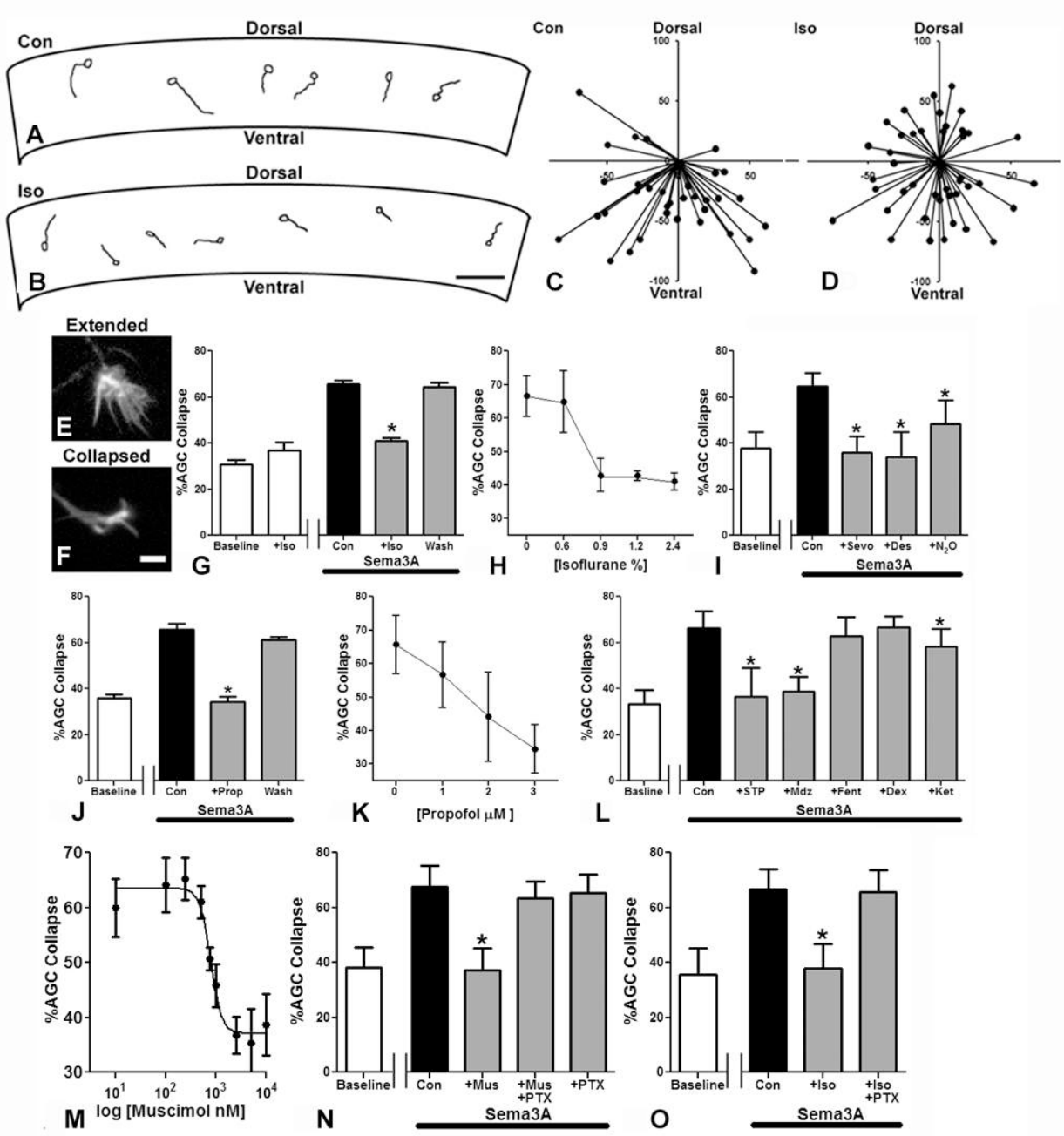


B, D: Iso = Isoflurane 1.2% for 8 hours, Con = carrier gas control for 8 hours

G-O: One hour exposure to vehicle or anesthetic, followed by 20 minutes Sema3A at 100 ng/mL

G, I, J, L, N, O: Baseline = no treatment, Con = Sema3A + vehicle

G, J: Wash = 4 hour wash in cell culture media after anesthetic application

G, O: +Iso = Isoflurane 2.4%

I: +Sevo = Sevoflurane 4%, +Des = Desflurane 12%, N2O = Nitrous Oxide 70%

J: +Prop = Propofol 3uM

K: +STP = Sodium Thiopental 50 uM, +Mdz = Midazolam 1 uM, +Fent = Fentanyl 100 nM, +Dex = Dexmedetomidine 40 nM +Ket = Ketamine 20 uM

N: Mus = Muscimol 10 uM

N, O: PTX = Picrotoxin 50 uM

* Indicates $p < 0.05$, Error bars are standard deviation of mean, and scale bar in F is 10 um

Anesthetic Toxicity #2 (14)

Carbon Monoxide Prevents Anesthesia-Induced Neuroapoptosis in Newborn Mice

Richard J. Levy, M.D.; Ying Cheng, B.S.
Children's National Medical Center

Introduction: Volatile anesthetics cause wide-spread neuroapoptosis in the developing brain. Carbon monoxide (CO) has ant-apoptotic properties and exhaled endogenous CO is commonly re-breathed during low-flow anesthesia in infants and children resulting in sub-clinical CO exposure. We hypothesized that low concentrations of CO inspired during volatile anesthetic exposure would prevent anesthesia-induced neuroapoptosis. We aimed to quantify the number of activated caspase-3 cells and TUNEL positive nuclei in the developing brain following concomitant exposure to CO and isoflurane.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. 7 day old male CD-1 mice underwent 1-hour exposure to 0 ppm (air), 5 ppm, or 100 ppm CO in air with or without isoflurane (2%). Thus, six different cohorts were evaluated. Five hours after exposure, brains were harvested and immunohistochemistry for activated caspase-3 and TUNEL assays were performed. Three to four slices per animal were assessed and three mice per cohort were evaluated. In a separate cohort, carboxyhemoglobin levels (COHb%) were measured immediately after exposure. Change in COHb% was assessed with T-test and significance set at $P<.05$. The number of caspase-3 positive cells and TUNEL positive nuclei were determined in primary somatosensory neurocortex, hippocampus, and hypothalamus/thalamus. Significance was assessed with ANOVA and post hoc Tukey's Test.

Results: COHb% increased significantly following exposure to 5 ppm and 100 ppm CO in a concentration-dependent manner compared to air exposed controls. Isoflurane significantly increased the number of activated caspase-3 positive cells and TUNEL positive nuclei in all regions of the brain examined in air-exposed mice. CO exposure abrogated isoflurane-induced increases in activated caspase-3 and TUNEL positive nuclei in each brain region in a dose-dependent manner.

Discussion: Consistent with prior reports, 1-hour isoflurane exposure increased neuroapoptosis in several regions of the developing brain. Exposure to 5 ppm and 100 ppm CO increased COHb% confirming time-weighted exposure. Both concentrations of CO prevented isoflurane-induced neuroapoptosis in each brain region in a dose-dependent manner. Thus, low-flow anesthesia designed to result in re-breathing of specific concentrations of CO may be a desired strategy to prevent anesthesia-induced neurotoxicity in infants and children.

Anesthetic Toxicity #3 (20)

Anesthetic-Induced Developmental Neuroapoptosis; Is Anesthesia Bad for the Newborn Brain?

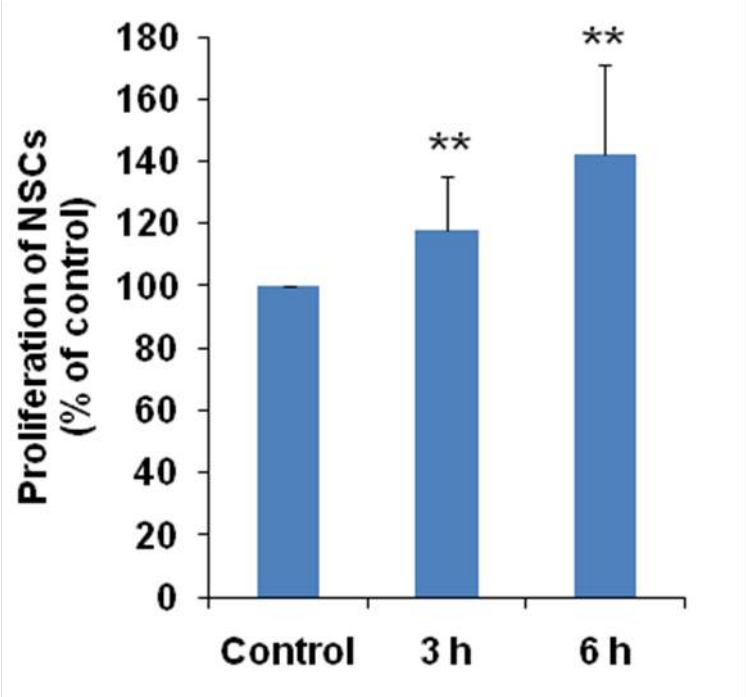
Zeljko J. Bosnjak, Ph.D.; Xiaowen Bai, M.D., Ph.D.
The Medical College of Wisconsin

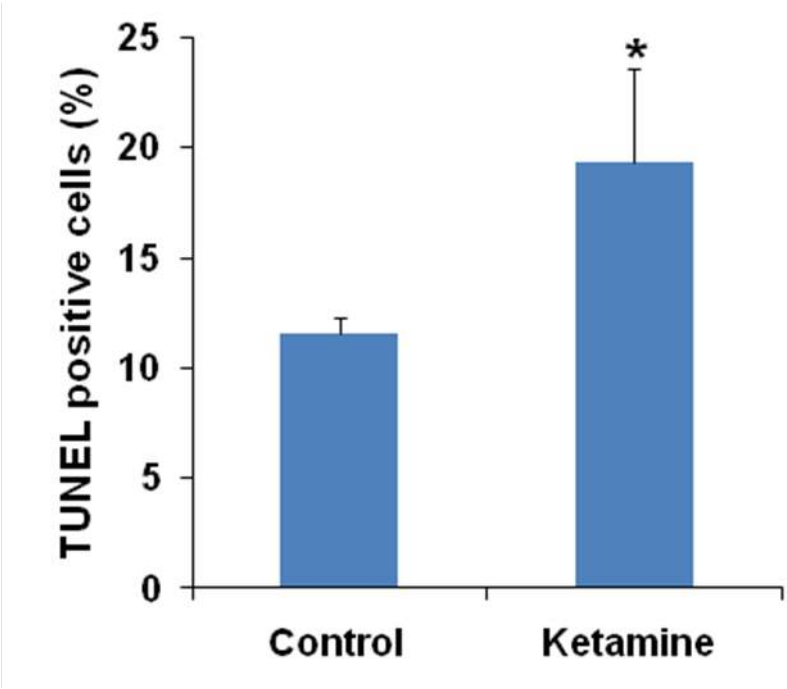
Introduction: Ketamine has been shown to cause neurotoxicity in developing animal models, leading to a serious concern regarding the safety of pediatric anesthesia. However, if and how ketamine induces human neurotoxicity is unknown. Some epidemiological studies show that a single anesthesia administration early in life was associated with learning disabilities later in life, while others found no significant differences. Thus, it is imperative to find a good model to study anesthetic-induced developmental toxicity in human neurons. We have developed an in vitro model of human embryonic stem cell (hESC)-derived neural cell lines so that we can, under control conditions and during intense synapse formation, test the toxic effects of commonly used anesthetics. The goal of this study was to determine the influence of ketamine on human neural stem cell (NSC) proliferation and the toxic effect of ketamine on the neurons differentiated from hESCs.

Methods: hESCs were directly differentiated into neurons via NSC step. NSCs and two-week-old neurons were treated with varying doses of ketamine (20 to 200 μM) for different durations (3 to 48 h). NSC proliferation capacity was analyzed by BrdU assay. Cell viability was examined by MTT assay. Neuron apoptosis were analyzed by TUNEL staining and caspase 3 activity measurement. Mitochondria-related neuron apoptosis pathway including mitochondrial membrane potential, cytochrome c distribution within cells, mitochondrial fission, and reactive oxygen species (ROS) production were also investigated.

Results: Ketamine (100 μM) increased human neural stem cell proliferation by 18% and 43%, after 3 and 6 h exposure, respectively (Fig. top). However, significant neuron apoptosis was only observed in the culture 24 h after ketamine treatment (Fig. middle). In addition, ketamine decreased mitochondrial membrane potential and increased cytochrome c release from mitochondria into cytosol. Ketamine also enhanced mitochondrial fission (Fig. bottom) as well as ROS production compared with no-treatment control. Importantly, Trolox, a ROS scavenger, significantly attenuated the decrease of ketamine-induced cell viability.

Conclusions: Our data suggest that 1) ketamine potentially causes neurotoxicity via both perturbation of neuronal progenitor proliferation and induction of neuron apoptosis; 2) ketamine-induced neuron death can be prevented by ROS scavenger; and 3) hESC-related neurogenesis system may provide a simple and promising in vitro experimental model for screening anesthetic neurotoxicity. In addition, this high throughput approach will be sensitive enough to examine various compounds that have shown varying degrees of brain protection in animal models.




TUNEL positive cells (%)
25
20
15
10
5
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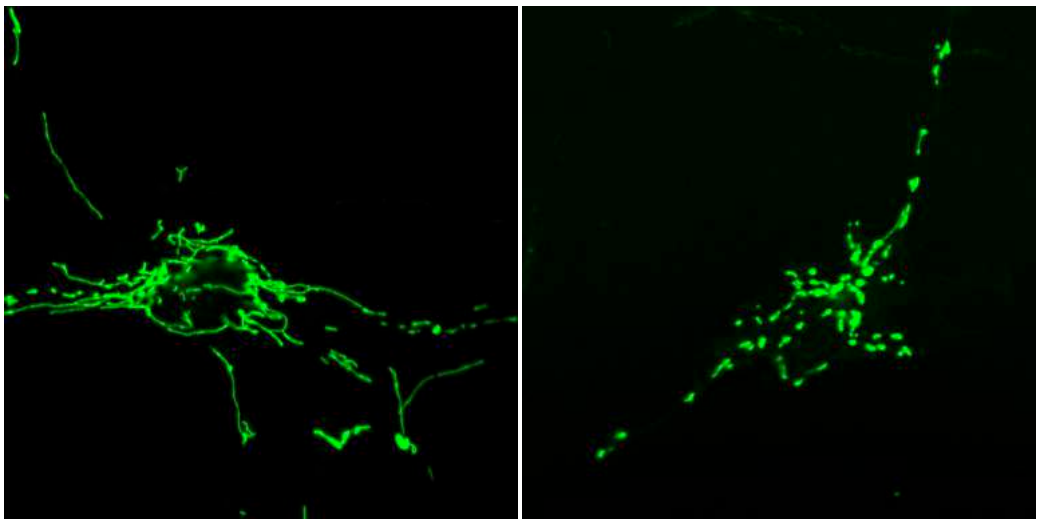
*
Control
Ketamine



Anesthetic Toxicity #4 (47)

Propofol Induces Apoptosis Via Over Activation of Inositol 1,4,5-Trisphosphate Receptors

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University of Pennsylvania

Background: Propofol causes cell apoptosis and widespread neurodegeneration in developing brains of newborn rodents through unclear mechanisms. We hypothesized that propofol may cause cell apoptosis by disruption of intracellular calcium (Ca2+) homeostasis via over-activation of inositol 1,4,5-trisphosphate receptor (InsP3R) Ca2+ release channels.

Methods: At the molecular level, we used single channel patch clamping to study the effects of propofol on types 1 and 3 InsP3R (InsP3R-1; InsP3R-3) located on DT40 chicken lyM.P.H.ocyte nuclear membranes. At the cellular level, we treated chicken B lyM.P.H.ocytes with all three InsP3R isoforms knocked out (DT40-TKO) or wild type (WT) control cells with various concentrations of propofol and then determined the extent of apoptosis by examining caspase-3 activity. We also studied the propofol mediated changes of cytoplasmic Ca2+ concentration using fura-2 imaging.

Results: Propofol activated InsP3R-1 and InsP3R-3 channels at low concentrations but was inhibitory at high concentrations. The lowest propofol concentration that activated InsP3R-3 was 20 μM, a clinically relevant concentration. Both InsP3R-1 and InsP3R-3 channel activation by propofol was abolished by the InsP3R antagonist heparin (Figure 1). Propofol caused significant apoptosis in a dose dependent manner in DT40 WT cells, but not in DT40-TKO cells. In addition, propofol (20 μM) increased cytosolic Ca2+ concentration in DT40 WTcells but only minimally in DT40-TKO cells (Figure 2).

Conclusion: Propofol induces cell apoptosis by causing abnormal Ca2+ release from the endoplasmic reticulum via direct activation of the InsP3R.

Anesthetic Toxicity #5 (61)

The Effect of Isoflurane on the Developing Hypoxic Rat Brain

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Introduction: Both oxygen and isoflurane have effects on the NM.D.A 2B (NR2B) receptor subunit composition. The NR2B subunit composition and hypoxia inducible factor 1-alpha (HIF1-α) both, independently, allow the brain to tolerate hypoxic conditions. NR2B is also necessary in early brain development because of its ability to promote brain derived neurotrophic factor (BDNF) and thereby inhibit apoptosis. We hypothesized that exposure to chronic hypoxia during development would increase NR2B, BDNF and HIF1-α and be protective against exposure to isoflurane when compared to normoxic controls.

Methods: According to NIH guidelines and after institutional approval, OHS were prepared from postnatal day (PND) 4, 7 and 14 normoxic and hypoxic pups. Hypoxic rat pups were housed in an OxycyclerTM (Biospherix; United Kingdom) Hypoxia A Chamber with damns at PND2 and maintained at 12% oxygen for 2, 5 and 12 days respectively. The OHS prepared from normoxic and hypoxic rat pups were exposed to 1.5% isoflurane or air/control for 5 hours. Hippocampal neuronal survival in areas CA1, CA3 and DG was assessed immediately, 24 and 72 h after exposure using Sytox staining. In addition, NM.D.A 2B receptor subunit expression, BDNF and HIF1-α were determined using western blot analysis.

Results: Chronic hypoxia increased cell death as compared to all postnatal age matched normoxic controls (Figure 1). Isoflurane had minimal effect on cell death in OHS prepared from hypoxic rat pups. Isoflurane decreased cell death in normoxic PND 14 OHS but increased cell death in OHS prepared from PND7 normoxic rat pups (Figure 1). The duration of chronic hypoxia was inversely related to NR2B subunit composition (Figure 2) BDNF expression was increased in hypoxic PND 7 rat pups. (Figure 3) HIF1-α expression increased in normoxic PND4 and hypoxic PND7 control rat pups. Isoflurane further increased HIF 1-α in the same control animals (Figure 4). In both hypoxic and normoxic animals (Figures 1, 2, 3 and 4) NR2B subunit composition and BDNF were decreased but HIF1-αexpression was increased by exposure to 1.5% isoflurane for 5 hours.

Discussion: Increased NR2B subunit composition, BDNF and HIF1-α associated with chronic hypoxia in PND7 rat pups may protect the developing hypoxic brain from isoflurane-induced cell death. This may have age–related implications in children with chronic hypoxia, such as children with congenital heart disease, who experience prolonged anesthesia exposure during surgical repair of their heart defect.

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Anesthetic Toxicity #6 (90)

Metabolic Status of Neonatal Rat Brain in Response to General Anesthesia Differs From the Young Rat Brain: Role of Glutamate

Rany Makaryus, M.D.[1]; Hedok Lee, Ph.D.[1]; Zvi Jacob, M.D.[1]; Mei Yu, B.S.[2]; Tian Feng, B.S.[1]
Stony Brook University[1]; Brookhaven National Lab[2]

Proton magnetic resonance spectroscopy (1HMRS) can be used to detect abnormalities in the brain, which may reveal neuronal injuries, ischemia, inflammation, and even possibly neurogenesis and apoptosis. We previously showed that cerebral metabolomic patterns depend on anesthetic regimen used.(1) The main differences seen in adult animals are an increase in the levels of glutamate and lactate in response to inhalational agents as compared to intravenous agents.(1) We sought to determine if these differences would also be seen in younger animals, particularly those undergoing synaptogenesis (rats at PND 6 – 11) and slightly older animals (rats at PND 21 – 36).

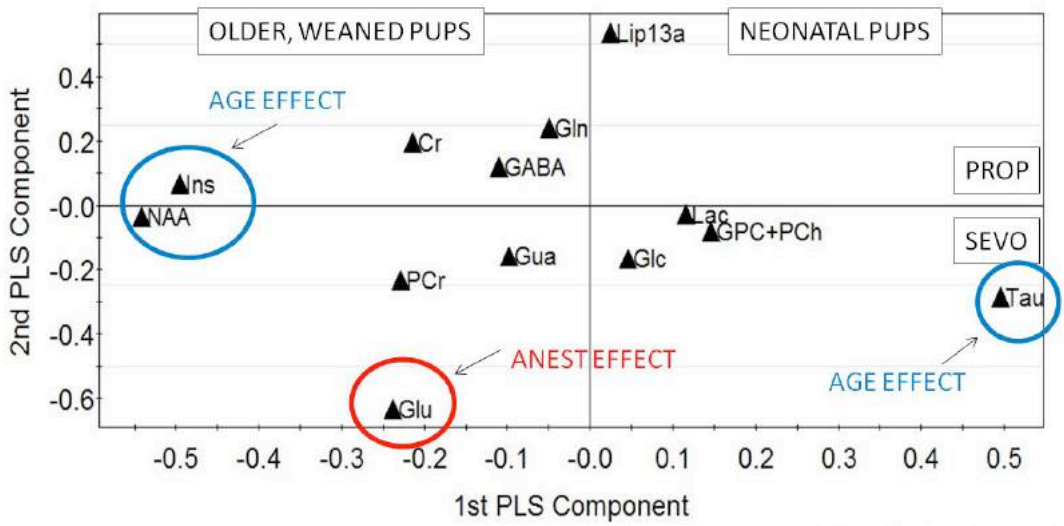
Following approval by the local IACUC, rats were divided into four groups based on age and anesthesia exposure: Neonatal Sevoflurane (n=11), Neonatal Propofol (n=10), Weaned Sevoflurane (n=8), and Weaned Propofol (n=9). All animals were monitored for respiratory rate, heart rate, temperature, and O2 sats while breathing 60% O2. The sevoflurane groups received 1 MAC Sevoflurane, while the propofol groups received 1 MAC equivalent doses. Total anesthesia duration for all animals was 6 hours; 1HMRS was performed in the hippocampus and thalamic regions using a 9.4T MRI.

Age and body weights were matched across groups. Metabolite milli-molar values attained via LCModel were compared across all four groups using two-way ANOVA analysis. Multiple metabolites differed by animal age; however, glutamate [Glu] was the only one that differed by type of anesthesia with $p < 0.0001$ for both brain regions. Post-hoc analysis revealed that glutamate was significantly higher in the weaned group; however, for the neonatal animals, there was no significant difference in glutamate between the two anesthetics. PLS-DA analysis showed a clear separation between the four groups with a Q2 value >0.3 for both regions, and confirmed our ANOVA results, see Fig. 1 (PLS-DA Loading Plot for Hippocampus).

Although [Glu] trended to increase in the neonatal brain with sevoflurane, the baseline [Glu] was lower compared to the young animals, which is probably related to brain maturity. Glutamate is the primary excitatory neurotransmitter in the brain and is also an essential intermediary in energy metabolism. Clearly from the point of view that [Glu] is representing metabolism, lower [Glu] in neonatal brain signifies lower metabolism and/or neuronal activity in agreement with neurophysiological data. The significance of the metabolic profiles in relation to potential neurotoxicity is currently being investigated.

(1) Makaryus R, Lee H, et al. The metabolomic profile during isoflurane anesthesia differs from propofol anesthesia in the live rodent brain. J Cereb Blood Flow Metab. Jan 26 2011

Fig. 1 – PLS-DA Loading Plot for Hippocampus



Anesthetic Toxicity #7 (77)

Junior Faculty Award

Switching Microglia to a Neuroprotective Phenotype: A Novel Way to Improve Neuronal Survival After Cardiac Arrest

Ines P. Koerner, M.D., Ph.D.; Jianming Wang, M.D.; Tetsuhiro Fujiyoshi, M.D., Ph.D.; Jonathan D. Raybuck, Ph.D.; K. Matthew Lattal, Ph.D.
Oregon Health & Science University

Background: While the introduction of therapeutic hypothermia has improved survival after cardiac arrest (CA) and cardiopulmonary resuscitation (CPR), many survivors are disabled by severe loss of memory and executive cognitive function. No specific treatment is available to reduce neuronal death and improve functional outcome. The brain's inflammatory response to ischemia can exacerbate injury and provides a potential treatment target that remains understudied. While activated microglia, the brain's resident immune cells, are thought to contribute to injury after ischemic stroke, little is known about their role after global ischemia during CA/CPR. We hypothesized that microglia are activated by CA/CPR and contribute to neuronal loss and functional deficit. We used a well-characterized mouse model to determine whether pharmacologic inhibition of the pro-inflammatory enzyme soluble epoxide hydrolase (sEH) after CA/CPR alters microglial activation and neuronal death in the ischemia-sensitive hippocampus.

Methods: Male adult C57Bl/6 mice underwent 8 minutes of CA followed by CPR. The sEH inhibitor 4-phenylchalcone oxide (4-PCO; 5 mg/kg ip) or vehicle were administered at 5 minutes after CA/CPR and repeated daily. Trace fear conditioning was used to test memory 10 days after CA/CPR. Microglial activation was assessed by immunostaining for the activation marker Mac-2 at 1, 3, and 10 days after CA/CPR. Surviving CA1 hippocampal neurons were counted at 3 or 10 days. Microglia where isolated from brains 1 or 3 days after CA/CPR using magnetic beads (Miltenyi Inc.). Expression of inflammatory cytokines in isolated microglia and in hippocampal tissue was measured by quantitative RT-PCR.

Results: Delayed death of CA1 neurons was evident as early as 3 days after CA/CPR and continued to day 10. Context, but not cued, freezing after trace fear conditioning was severely compromised 10 days after CA/CPR (42±8% after CA/CPR vs 72±5% in sham-operated animals), indicating loss of hippocampus-dependent memory acquisition. Activated (Mac-2 positive) microglia appeared in the hippocampus as early as 1 day after CA/CPR, before significant neuronal death was present, and persisted at 10 days. Concurrently, expression of pro-inflammatory tumor necrosis factor (TNF)-α and interleukin (IL)-1β increased. 4-PCO significantly increased hippocampal expression of anti-inflammatory IL-10 (2-fold vs. vehicle), while TNF- α and IL-1 β expression was unchanged. Analysis of isolated microglia confirmed that microglia were the main source of increased IL-10. Subsequent death of CA1 neurons was significantly reduced after 4-PCO (34 ± 4%) vs vehicle (52 ± 7%), whereas the number of Mac-2 positive microglia was unchanged.

Conclusions: Post-CPR treatment with 4-PCO selectively induced expression of anti-inflammatory and neuroprotective IL-10 in hippocampal microglia and reduced subsequent neuronal death without affecting microglial numbers. This suggests that sEH inhibition can alter the transcription profile in activated microglia to protect neurons and maintain function. IL-10 may be a signature gene of this beneficial microglial phenotype. Switching microglial gene expression towards a neuroprotective phenotype is a promising new therapeutic approach for ischemic brain injury.

Poster Presentation Abstracts

Cardiac

Cardiac #1 (60)

The Resistin Family of Molecules is Associated With Molecular and Physiological Evidence of Heart Failure

Steve Gibson, M.D., Ph.D.; Irina Kolosova, Ph.D.; Kazuyo Kegan, Ph.D.; Chunling Fan, Ph.D.; Roger A. Johns, M.D.
Johns Hopkins University School of Medicine

Cardiac #2 (36)

Resident Travel Award

Identification and Characterization of a Novel Compound That Protects Cardiac Tissue From hERG-Related, Drug-Induced Arrhythmias

Amanda N. Lorinc, M.D.; Franck Potet, Ph.D.; Raghav Venkataraman, M.S.; Veniamin Sidorov, Ph.D.; Franz Baudenbacher, Ph.D.; Sabina Kupershmidt, Ph.D.
Vanderbilt University

Cardiac #3 (62)

Combined Effect of Radiation and Hyperoxia on Cardiovascular Function

Viachaslau Barodka; Dan Berkowitz, M.D.; Dan Nyhan, M.D.; Sung Mee Jung, M.D.; Maggie Kuo, MA; Gautam Sikka, M.D.
The Johns Hopkins Medical Institution

Cardiac #4 (67)

Anesthetic Induction With Etomidate, Rather Than Propofol, is Associated With Increased Cardiovascular Morbidity After Non-cardiac Surgery

Ryu Komatsu, M.D.[1]; Jing You, M.S.[2]; Edward J. Mascha, Ph.D.[2]; Daniel I. Sessler, M.D.[3]; David L. Brown, M.D.[1]; Alparslan Turan, M.D.[3]
Anesthesiology Institute[1], Departments of Quantitative Health Sciences and Outcomes Research[2], Department of Outcomes Research, Cleveland Clinic

Cardiac #5 (70)

Hypobaric Oxygenation Promotes Reabsorption of Gaseous Microemboli During Cardiopulmonary Bypass in Swine

Keith E. Gipson, Ph.D., M.D.; Jeffrey B. Gross, M.D.
Department of Anesthesiology, University of Connecticut

Cardiac #6 (25)

The Complications of Uncomplicated Acute Type B Aortic Dissection: Refining the Penn Classification to Improve Patient Outcome

John G. Augoustides, M.D.; Prakash A. Patel, M.D.; Edward Y. Woo, M.D.; Wilson Y. Szeto, M.D.; Ron M. Fairman, M.D.; Joseph E. Bavaria, M.D.
University of Pennsylvania

Cardiac #7 (75)

Postoperative QT-Interval Prolongation in Patients Undergoing Non-Cardiac Surgery Under General Anesthesia

Peter Nagele, M.D., M.Sc.; Swatilika Pal, M.B.B.S., M.S.; Frank Brown, B.S.; Jane Blood, B.S., RN; Joshua Johnston, M.D.
Washington University School of Medicine

Cardiac #8 (79)

Low Levels of High-Density Lipoproteins are Associated With Acute Kidney Injury following Open/ Endovascular Revascularization for Chronic Limb Ischemia

Nader D. Nader, M.D., Ph.D.; Pradeep Arora, M.B.B.S.; Hasan H. Dosluoglu, M.D., FACS
SUNY-Buffalo

Cardiac #9 (49)

Role of Endothelial CSE/H2S in the Pathogenesis of Hypertension

Gautam Sikka, M.D.; Jochen Steppan, M.D.; Matthew S. Vandiver, B.S.; Lakshmi Santhanam, Ph.D.; Daniel Nyhan, M.B.B.CH.; Dan E. Berkowitz, M.B.B.CH.
Johns Hopkins University

Cardiac #10 (19)

Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 1 Diabetes Hyperglycemia in Mice

Robert E. Shangraw, M.D., Ph.D.; Sari A. Jouihan, M.S.; Wenri Zhang, Ph.D.; Nabil J. Alkayed, M.D., Ph.D.
Oregon Health & Science University

Cardiac #11 (85)

Ischemic Injury to Glomerular Endothelium: Potential Mechanism of Hyperglycemic Protection

Katie J. Schenning, M.D., M.P.H.; Michael P. Hutchens, M.D., M.A.
Department of Anesthesiology and Perioperative Medicine, Oregon Health and Science University - Portland, Oregon

Cardiac #12 (64)

Obesity Predicts Acute Kidney Injury Following Cardiac Surgery: Role of Oxidative Stress

Frederic T. Billings, M.D., M.Sc.; Mias Pretorius, M.D., M.Sc.; John Byrne, M.D.; Talat A. Ikizler, M.D.; Nancy J. Brown, M.D.
Vanderbilt University

Cardiac #13 (89)

Intraoperative Anaphylactic Reactions: A Retrospective Registry Analysis

Brian D. Hesler, M.D.; Edward Mascha, Ph.D.; Daniel Sessler, M.D.; John Tetzlaff, M.D.; Cameron Egan, B.S.; Leif Saager, M.D.
Department of Anesthesia, Cleveland Clinic - Cleveland, Ohio

Cardiac #1 (60)

The Resistin Family of Molecules is Associated With Molecular and Physiological Evidence of Heart Failure

Steve Gibson, M.D., Ph.D.; Irina Kolosova, Ph.D.; Kazuyo Kegan, Ph.D.; Chunling Fan, Ph.D.; Roger A. Johns, M.D.
Johns Hopkins University School of Medicine

Despite many advancements in medical therapy and surgical treatment of ischemic and valvular cardiomyopathy, heart failure has a five-year mortality of about 45-60. New avenues for treatment may present from recent evidence is defining heart disease at least in part as an inflammatory process. The Type 2 helper T cells (Th2) pathway of humoral immunity and its have been found increased in both cardiac fibrosis and dilated cardiomyopathy and are a prognostic indicator of disease severity. Alteration of the balance between Th2 cytokines therefore may provide another avenue for therapy of heart failure.

Recent evidence shows that the resistin family of molecules may be involved in the progression of cardiac disease states, including heart failure. This family of proteins is characterized by a similar structure of 10 equally spaced cysteine residues near the C-terminus. This family includes resistin-like molecule RELMalpha (also HIMF, hypoxia-induced mitogenic factor) and RELMbeta. HIMF has been found to activate the Phosphatidylinositol 3-kinases (PI3K)/Akt pathway. Furthermore, work from our laboratory and others has demonstrated RFM proteins as amplifiers of Th2 response.

Much evidence implicates the resistin family in cardiopulmonary pathology. HIMF expression increases greatly in the setting of hypoxia and is involved in the development on PAH by both chronic hypoxia and Th2-mediated inflammation etiologies and can reproduce much of the vascular and physiological characteristics of PAH after exogenous administration. The RFMs, especially resistin, have also been implicated in heart failure. Serum resistin levels correlate with both decompensation frequency and mortality in multiple studies. HIMF knockdown experiments retarded progression of PAH to right heart hypertrophy. This evidence indicates that the RFMs may participate in novel pathways of heart failure and provide alternative targets of therapy via a Type 2 helper T cell-associated mechanism.

We assessed the effects of a chronic hypoxia model of right heart failure on the expression level of proteins. Rats were either maintained in an environment of fractional inspired oxygen concentration of 10% for either 4 or 15 days. We found that expression levels of both HIMF and resistin were increased in the right ventricles of hypoxia-maintained rats. We additionally investigated whether HIMF could induce the PI3K/Akt pathway of cell growth and cardiac hypertrophy. Neonatal rat cardiomyocytes isolated into tissue culture showed a transient increase in Akt phosphorylation after HIMF protein administration, indicating activation of the PI3K/Akt pathway.

To assay for a physiological effect of the resistin family of molecules on cardiac development, we injected an adeno-associated virus construct containing HIMF into the tail veins of mice. At 8 weeks after injection, echocardiography demonstrated several parameters of worsening cardiac function, including decreased fractional shortening and increased interventricular septal thickness and relative wall thickness ($p < 0.05$). Hemodynamic studies showed increased left ventricle end systolic pressure ($p < 0.007$) and increased relaxation time ($p < 0.03$).

These early studies implicate the RFMs in the molecular pathways of heart, with additional studies planned to further the role of RFMS in the progression of heart failure in additional models, including a pharmacologically induced mouse model of pulmonary artery hypertension.

Cardiac #2 (36)

Resident Travel Award

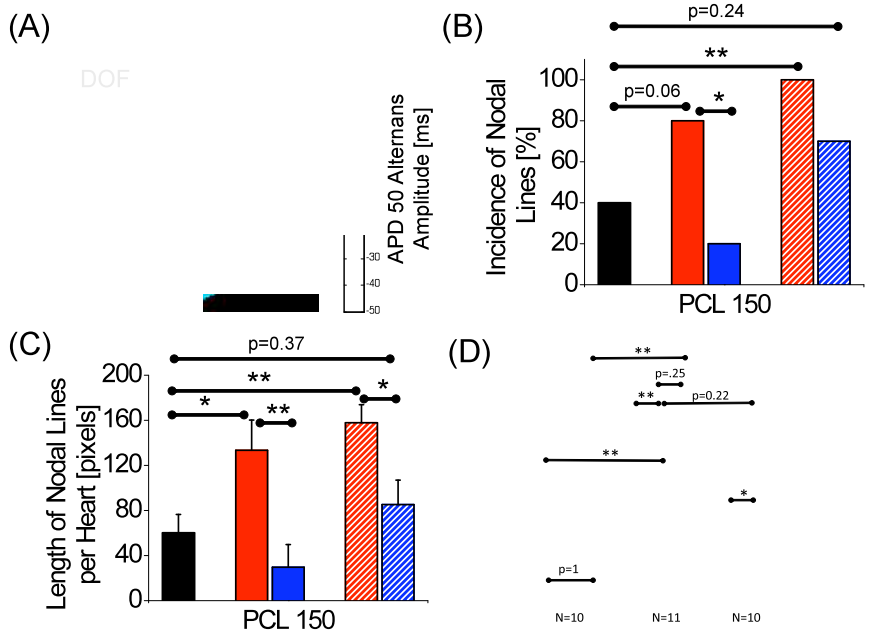
Identification and Characterization of a Novel Compound That Protects Cardiac Tissue From hERG-Related, Drug-Induced Arrhythmias

Amanda N. Lorinc, M.D.; Franck Potet, Ph.D.; Raghav Venkataraman, M.S.; Veniamin Sidorov, Ph.D.; Franz Baudenbacher, Ph.D.; Sabina Kupershmidt, Ph.D.
Vanderbilt University

Sudden cardiac death due to ventricular arrhythmias is a global health issue and accounts for 10-20% of adult deaths in the US alone. Ion channel modulation is a major target for cardiovascular therapeutics. The hERG-encoded K+ current, IKr, is essential for cardiac repolarization but also a source of cardiotoxicity because unintended hERG inhibition by diverse pharmaceuticals can cause arrhythmia and sudden cardiac death. Inhibition of IKr, either through class III antiarrhythmic drugs or through unintended block by agents prescribed for non-cardiac conditions, including over-the-counter drugs, can lead to acquired long QT syndrome (LQTS). Arrhythmias associated with the acquired LQTS present a serious clinical problem that has led to the withdrawal of several otherwise successful drugs from the market. In response, the FDA issued guidelines that require evaluation of novel chemical entities for their potential to induce QT prolongation early in drug development. It has been estimated that 50-70% of all lead compounds are eliminated at early stages due to hERG related safety issues thereby limiting the number of drugs that enter the development pipeline. For these reasons, development of a small molecule that could be co-administered to decrease the risk of arrhythmias in response to hERG inhibitors would improve public health, patient care, and greatly facilitate the drug discovery process.

We hypothesized that IKr reduction in response to a known inhibitor could be prevented by a small molecule. We identified and characterized a small compound, VU0405601, ("601") that reduces the sensitivity of hERG to the prototypical inhibitor, dofetilide and other known blockers. In isolated, Langendorff-perfused rabbit hearts, 601 reduced the incidence of dofetilide-enhanced arrhythmias. In addition to arrhythmia incidence, additional information regarding the mechanism of dofetilide-induced ventricular arrhythmias was obtained using voltage sensitive dyes and a CCD camera. In regards to arrhythmia mechanism, we found that prolongation of the action potential duration (a surrogate for QT measurement) does not correlate to arrhythmia incidence, 601 does not affect the magnitude or incidence of alternans, nor does it protect against dofetilide-mediated nodal line formation. However, 601 decreases the nodal line length and alternans gradient. Calcium handling and conduction block appear to have a role in arrhythmia formation which are currently under investigation along with the effect of 601 on droperidol-induced arrhythmia.

Figure 1



Cardiac #3 (62)

Combined Effect of Radiation and Hyperoxia on Cardiovascular Function

Viachaslau Barodka; Dan Berkowitz, M.D.; Dan Nyhan, M.D.; Sung Mee Jung, M.D.; Maggie Kuo, MA; Gautam Sikka, M.D.
The Johns Hopkins Medical Institution

Introduction: Spaceflight missions entail upto 24 hours of extravehicular activities per week. Astronauts are exposed to 100% oxygen during EVA activities in the space environment. The tissue response to hyperoxia in the space environment is influenced by exposure to radiation, mostly in the form of Galactic Cosmic Radiation. There are no obvious sequelae evident shortly after the EVA, however it is unknown if prolonged and repeated EVAs cause later tissue damage. Previously we have demonstrated that radiation induces and oxidative stress in the vessel which leads to impaired endothelial function and vascular stiffness. The question arises as to whether hyperoxia represents and added or synergistic risk with radiation for vascular endothelial oxidative stress and dysfunction.

Methods and Results: In order to test this we developed an animal model incorporating 4 groups of mice: one that was exposed to a hyperoxic environment, one that was exposed to radiation and one that was exposed to hyperoxia in addition to radiation. One group without hyperoxia or radiation served as a control group. Hyperoxia treatment was done by exposing mice to >95% oxygen for 8 hours 3 times during one week in a special chambers. Chambers have been designed and used by NASA to study hyperoxia/ hypoxia in animal model. Radiation treatment was done by exposing mice to 1 Grey gamma radiation at rate of 100 rad/minute. Mice were exposed for a period of 2 weeks. At the end of the 2 weeks period, terminal endpoints were determined 1) In vivo integrated cardiovascular function was measured using non-invasive Doppler to measure pulse wave velocity (PWV) 2) Ex-vivo endothelial function by measuring endothelial dependent vasodilation of aortic rings. Compare to unexposed animals PWV were increased both after exposure to hyperoxia and to radiation. Combined exposure to both hyperoxia and radiation resulted in additive effect and resulted in worse cardiovascular function as evidenced by maximum increase in PWV. In ex-vivo experiments of endothelial function we did not find any difference between control and exposed to radiation and hyperoxia groups.

Conclusion: Our data confirm that both hyperoxia and radiation adversely affect cardiovascular function and provides evidence that their negative effects are additive in nature.

Future Studies: The current results in animal model provide sufficient evidence to justify future studies in astronauts.

References

Soucy K G et al. J Appl Physiol 2010;108:1250-1258

Cardiac #4 (67)

Anesthetic Induction With Etomidate, Rather Than Propofol, is Associated With Increased Cardiovascular Morbidity After Non-cardiac Surgery

Ryu Komatsu, M.D.[1]; Jing You, M.S.[2]; Edward J. Mascha, Ph.D.[2]; Daniel I. Sessler, M.D.[3]; David L. Brown, M.D.[1]; Alparslan Turan, M.D.[3]
Anesthesiology Institute[1], Departments of Quantitative Health Sciences and Outcomes Research[2], Department of Outcomes Research, Cleveland Clinic

Introduction: Etomidate is occasionally used to induce anesthesia in critically ill patients because of its favorable hemodynamic profile. However, the drug causes prolonged adrenal impairment which blunts release of cortisol that normally accompanies surgical tissue injury [1]. Cortisol augments the vascular effects of endogenous epinephrine and norepinephrine, thus maintaining blood pressure [2]. Therefore, etomidate use may provoke postoperative hemodynamic instability. We tested the hypothesis that anesthetic induction with etomidate is associated with post-operative cardiovascular morbidity.

Methods: With IRB approval and informed consent waiver, we evaluated the electronic records of 31,148 ASA physical status 3-4 patients who had non-cardiac surgery at the Cleveland Clinic. Among these, anesthesia was induced with etomidate in 2,616 patients whereas 28,532 were given propofol. Two thousand one hundred forty-five patients given etomidate were propensity-score matched with 5,211 patients given propofol using preoperative and intraoperative confounding factors including age, gender, race, body mass index, hypothalamic/pituitary/adrenal disorder, cancer, cardiovascular/cerebrovascular disease, pulmonary disease, diabetes mellitus, ASA physical status, elective vs emergency surgery, intraoperative steroid use, use of regional anesthesia technique, and number of intraoperative opioid bolus doses. The groups were compared on post-operative cardiovascular morbidity (Table) and intraoperative vasopressor requirement using logistic regression; the significance criterion was 0.025 (Bonferroni correction). Finally, we summarized the differences in intraoperative hemodynamics between the etomidate and propofol patients using the standardized difference.

Results: Patients given etomidate had significantly greater odds of having cardiovascular morbidity (odds ratio [OR], 1.54; 97.5% CI, 1.22-1.94; $P < 0.001$). However, intraoperative vasopressor requirement (OR, 0.98; 97.5% CI, 0.86-1.12; $P = 0.72$) did not differ between the agents. The etomidate and propofol groups were descriptively similar on systolic blood pressure during closing to end of the case, and on diastolic blood pressure during induction to intubation (absolute standardized difference (STD) < 0.10). The propofol patients were more likely to have a lower systolic blood pressure during induction to intubation and during intubation to incision than the etomidate patients. Although slight differences in blood pressure between etomidate and propofol patients during other intraoperative periods were observed (absolute STD> 0.10), none of the differences were clinically important.

Discussion: Etomidate was associated with a substantially increased risk for cardiovascular morbidity. Clinicians should use etomidate judiciously, considering that improved hemodynamic stability at induction may be accompanied by substantially worse longer-term outcomes.

References:
[1] Fragen RJ, Weiss HW, Molteni A. The effect of propofol on adrenocortical steroidogenesis: a comparative study with etomidate and thiopental. Anesthesiology 1987;66:839-42
[2] Grunfeld JP, Eloy L. Glucocorticoids modulate vascular reactivity in the rat. Hypertension 1987;10:608-18

Table. Descriptions of in hospital cardiovascular morbidities

Morbidity	ICD-9	Description
Cardiac	458.2	**Iatrogenic hypotension**
	458.21	**Hypotension of hemodialysis** Intra-dialytic hypotension
	458.29	**Other iatrogenic hypotension** Postoperative hypotension
	997.1	Cardiac: arrest during or resulting from a procedure insufficiency during or resulting from a procedure Cardiorespiratory failure during or resulting from a procedure Heart failure during or resulting from a procedure *Excludes:* *the listed conditions as long-term effects of cardiac surgery or due to the presence of cardiac prosthetic device (429.4)*
	997.2	**Peripheral vascular complications** Phlebitis or thrombophlebitis during or resulting from a procedure *Excludes:* *the listed conditions due to:* *implant or catheter device (996.62)* *infusion, perfusion, or transfusion (999.2)* *complications affecting blood vessels (997.71-997.79)*
	998.0	**Postoperative shock** Collapse NOS during or resulting from a surgical procedure Shock (endotoxic) (hypovolemic) (septic) during or resulting from a surgical procedure *Excludes:* *shock:* *anaphylactic due to serum (999.4)* *anesthetic (995.4)* *electric (994.8)* *following abortion (639.5)* *obstetric (669.1)* *traumatic (958.4)*

ICD-9=International Classification of Diseases, ninth revision

Cardiac #5 (70)

Hypobaric Oxygenation Promotes Reabsorption of Gaseous Microemboli During Cardiopulmonary Bypass in Swine

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Introduction: Neurocognitive deficits following cardiac surgery remain prevalent and likely result in part from gaseous microemboli (GME)(1). Despite the use of microporous membrane oxygenators and the optimization of arterial line filters, numerous GME are still present in arterial blood during cardiopulmonary bypass (CPB)(2). Here, we promote reabsorption of GME by reducing the partial pressure of dissolved gases in blood to subatmospheric levels.

Methods: Hypobaric oxygenation was achieved using a sealed membrane microporous oxygenator with 100% O2 sweep gas delivered through a flowmeter to the sweep gas inlet. A vacuum regulator attached to the sweep gas outlet applied variable subatmospheric pressures to the gas phase to achieve physiologic PaO2. PaCO2 was controlled by varying the sweep gas flow rate at the flowmeter. Overpressurization of the gas phase was prevented by a positive pressure relief valve. In this manner blood was oxygenated in vitro in CPB circuits containing human blood and a simulated patient as well as in vivo in eleven 40 kg swine undergoing CPB. Gas exchange was monitored using arterial and venous blood gases and oximetry. Number and size of GME were recorded using Doppler sensors on the arterial line. Data presented are mean ± SEM.

Results: Gas exchange: In vitro application of subatmospheric sweep gas pressures (1.0, 0.75, 0.5 ATA) in the absence of nitrogen produced an expected linear decrease in PaO2 values (589, 346, 261 mmHg) while PaCO2 (35, 30, 29 mmHg) was maintained. In vivo, hypobaric oxygenation (0.66 ATA) was used to achieve stable physiologic blood gases (pH=7.43 PCO2=43 mmHg PO2= 187 mmHg) when compared to standard oxygenation practice using O2/Air (FiO2 = 68%) sweep gas mixture (pH=7.31 PCO2=57 mmHg PO2= 196 mmHg). Gas exchange was stable over 4 h of CPB, with no apparent adverse consequences in the CPB circuit or end-organ tissues of the swine.

Microemboli: Reduction of dissolved gases enabled reabsorption of GME in blood. In vitro, hypobaric oxygenation strongly reduced GME from both continuous and bolus sources. Hypobaric oxygenation combined with arterial filtration gave the best results. In vivo, entrainment of air in the venous return provided a continuous source of GME. Compared to GME observed during normobaric conditions, hypobaric oxygenation reduced the volume of GME leaving the venous reservoir, leaving the arterial filter, and arriving at the patient to 47 ± 10%, 6.4 ± 3.2%, and 0.03 ± 0.01% of control, respectively. These data confirm that GME are reabsorbed throughout the CPB circuit during hypobaric oxygenation.

Conclusions: Hypobaric oxygenation safely met the metabolic needs of large animals over 4 h CPB runs. Reduction of dissolved gases in blood greatly reduced GME loads by promoting active reabsorption of GME throughout the CPB circuit. This strategy represents a promising adjunct to arterial filtration as we seek to improve cognitive outcomes following cardiac surgery.

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Cardiac #6 (25)

The Complications of Uncomplicated Acute Type B Aortic Dissection: Refining the Penn Classification to Improve Patient Outcome

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University of Pennsylvania

Introduction: Acute type B aortic dissection (ATBAD) involves the descending thoracic aorta,beginning with an intimal tear distal to the left subclavian artery and presenting within 2 weeks of onset.

The management of ATBAD depends on clinical presentation, traditionally classified as uncomplicated or complicated. Although uncomplicated ATBAD is typically managed medically, there are still patients at excessive risk for serious aortic complications that may be preventable by endovascular intervention. In an effort to address this quality gap, we have recently derived the University of Pennsylvania (Penn) classification of ATBAD. In this classification, uncomplicated ATBAD presentations are classified as Class A, since they are characterized by an Absence of malperfusion or aortic rupture. The purpose of this study was to identify the risk factors in Penn Class A ATBAD that predict for downstream aortic complications, including mortality.

Methods: An English language literature search was conducted utilizing PubMed for all relevant studies since 2000, utilizing standard search terms. The identified risk factors were considered in three categories: medical therapy, aortic anatomy, and dissection extent (DeBakey IIIA - ATBAD limited to the descending thoracic aorta; DeBakey IIIB - ATBAD involving both the descending thoracic and abdominal aorta) .

Results: Although 12 trials adequately described outcomes out to the long-term, there were only 2 high-quality trials that examined the details of medical therapy, suggesting that tight medical management significantly protected against downstream aortic risk, especially if therapy included beta-adrenergic and calcium channel blockade. There were 12 trials that assessed aortic anatomy to identify the following significant predictors for late aortic complications: aortic diameter > 40mm, patent or partially thrombosed false lumen,large false lumen, and ulcer-like projections. There were no trials identified that examined aortic complications as a function of dissection extent as defined by DeBakey.

Conclusions: Uncomplicated ATBAD presentations are a misnomer and should be more precisely defined as Penn Class A presentations. This study has identified three therapeutic opportunities in Penn Class A ATBAD. Firstly, further trials should define the optimal conduct of medical therapy, including drug therapy, follow-up, and contemporary survival. Secondly, adequately powered prospective randomized trials should evaluate whether endovascular intervention can reduce mortality in patients with high-risk anatomic factors on presentation. Thirdly, further trials should examine whether the extent of ATBAD on presentation determines downstream aortic complications. Penn Class A presentations represent a major therapeutic opportunity from both the medical and interventional perspectives.

Cardiac #7 (75)

Postoperative QT-Interval Prolongation in Patients Undergoing Non-Cardiac Surgery Under General Anesthesia

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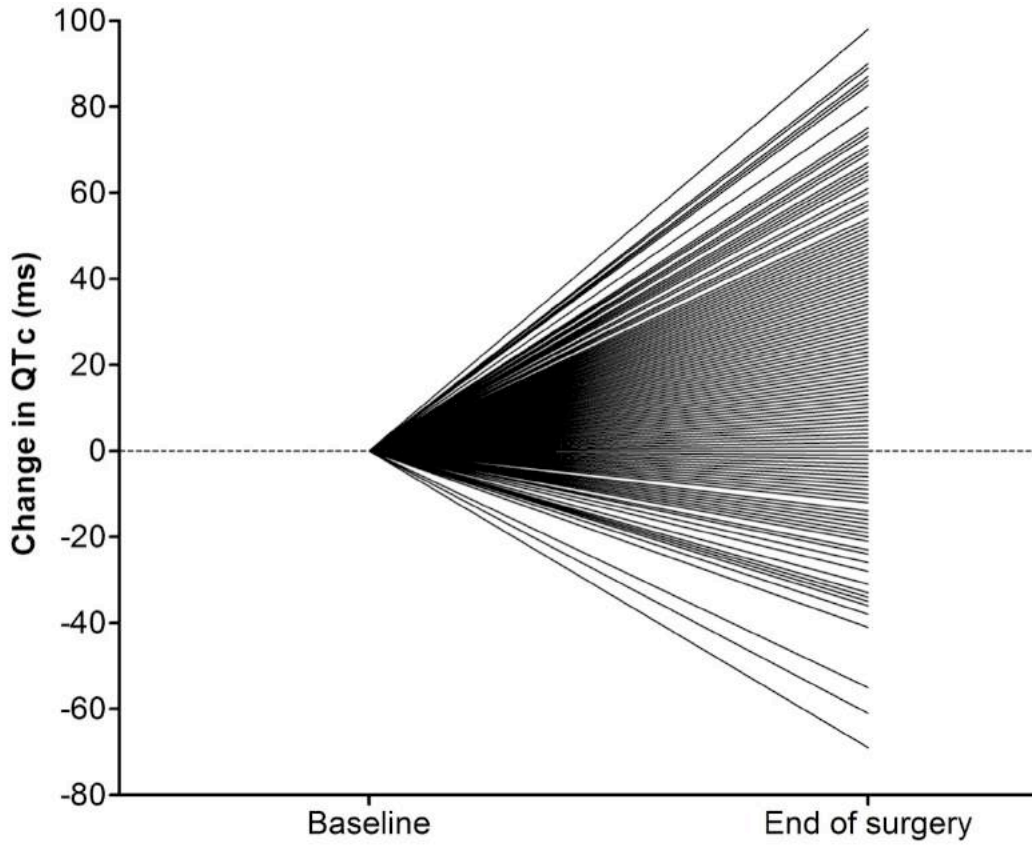
Background: Abnormal cardiac repolarization, indicated by a prolongation of the QT-interval, increases the risk for torsade de pointes, a potentially life-threatening arrhythmia. Many perioperatively administered drugs and conditions such as hypothermia prolong the QT-interval. Despite several reports of perioperative torsade de pointes, systematic evidence regarding perioperative QT-interval prolongation is limited.

Methods: Serial postoperative 12-lead ECGs were obtained from 469 adult patients with known or suspected atherosclerotic disease undergoing major non-cardiac surgery under general anesthesia. Heart-rate corrected (Fridericia's formula) QT-interval duration was the primary outcome. Preoperative QTc duration was compared to postoperative. All perioperatively administered drugs were recorded. EM.P.H.asis was placed on absolute QTc prolongation >500ms and relative increases of 30 and 60ms.

Results: At the end of surgery, 80% of the patients (345/429) experienced a significant QTc interval prolongation (ΔQTc +23 ± 26ms, 95% CI 20-25ms). Approximately 51% (219/429) had a QTc >440 ms, and 4% (16/429) a QTc >500ms. In 39% (166/429), the ΔQTc was >30ms, in 8% (34/429) >60ms, and in 0.5% (2/429) >100ms. No significant changes in ΔQTc occurred at subsequent time points. Several drugs had a large effect on ΔQTc: cefoxitin: +11ms; unasyn +14ms; zosyn +8ms; ciprofloxacin +7ms; ephedrine (+8ms) and metoclopramide (+8ms); hydromorphone -6ms. Postoperative body temperature had a weak negative correlation with ΔQTc (r= -0.15, p=0.02); serum magnesium, potassium and calcium concentrations were not correlated. One patient developed torsade de pointes ΔQTc: 29ms (0.4% incidence rate).

Conclusions: The study shows that postoperative QTc-interval prolongation is common and most likely drug-induced. The exact cause and its relevance are, however, unclear. Nevertheless, an association between postoperative QTc-prolongation and risk for torsade de pointes is likely. Increased vigilance for postoperative QTc-prolongation is recommended.



Cardiac #8 (79)

Low Levels of High-Density Lipoproteins are Associated With Acute Kidney Injury following Open/ Endovascular Revascularization for Chronic Limb Ischemia

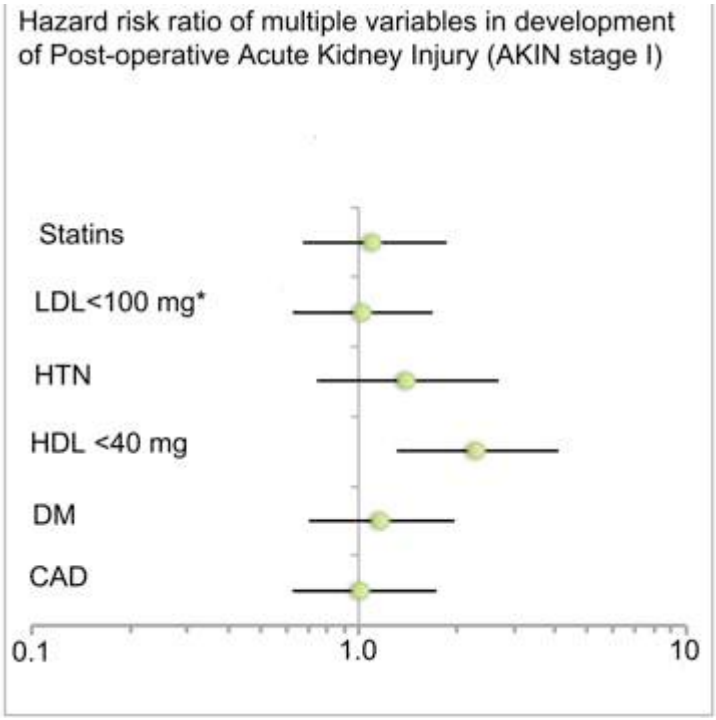
Nader D. Nader, M.D., Ph.D.; Pradeep Arora, M.B.B.S.; Hasan H. Dosluoglu, M.D., FACS
SUNY-Buffalo

Objective: To examine the association of high-density lipoproteins (HDL) and perioperative acute kidney injury (AKI) in patients undergoing revascularization of lower extremities.

Study Design: Cohort Study
Setting: Veterans Administration Medical Center, Inpatients
Subjects: 684 patients who underwent vascular intervention/surgery for symptomatic chronic limb ischemia at the between 01/2001-12/2009.
Predictors/Intervention: Serum Creatinine, HDL levels
Main Outcome Measures: Acute kidney injury as defined by Acute Kidney Injury Network (AKIN), mortality

Results: 684 patients (32% open, 68% endovascular/hybrid) were included in final analysis. 85 patients developed post-operative AKI. The patients who developed AKI were more likely to have diabetes mellitus, HDL <40, LDL/HDL >4.9, and preexisting CKD. Multivariate analysis using logistic as well as propensity score revealed that low HDL level (HR=2.4 [1.4 - 4.2]) and underlying CKD were independent factors associated with AKI (P<0.001).

Conclusions: AKI is common (12.4%) following revascularization for chronic limb ischemia. A low concentration of HDL is associated with increased odds of AKI after revascularization of the lower extremities. Strategies for increasing the HDL level in patients with high risk of postoperative AKI should be investigated.



Cardiac #9 (49)

Role of Endothelial CSE/H2S in the Pathogenesis of Hypertension

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Johns Hopkins University

One in every three Americans is affected by HTN (hypertension). HTN increases the risk for cardiac disease and stroke. Endogenous H2S (hydrogen sulfide), which plays a prominent role in a multitude of pathologies like inflammation/sepsis, hypertension, peripheral and cerebro-vascular disease and coronary artery disease, is now well characterized as a physiologic vasodilator. H2S is predominantly produced by CSE (cystathionin-γ-lyase) in the vascular endothelium. It caters to relaxation, primarily, through sulfhydration (a novel post-translational modification)[2] of IK, SK and KATP channels, resulting in vascular smooth muscle cell hyperpolarization. This effect is independent of the NO (Nitric Oxide) / cGMP/PKG axis. In 2003 Tang et. al studied H2S in spontaneously hypertensive rats (SHRs) and demonstrated a loss of CSE/H2S in HTN and a decrease in blood pressure (BP) on substitution of H2S.

Objective: To elicit if loss of endogenous H2S contributes to the pathogenesis of hypertension.

Methods and Results: Tail cuffs were used to measure BP in SHRs and control Wistar Kyoto rats (WKYs) starting at 4 weeks (w) of age until the time SHRs became hypertensive.

Infusion of intravenous glybenclamide (20mg/Kg) a KATP channel blocker, revealed a significant increase in systolic BP (SBP) in 4w old SHR (ΔSBP= 43.16 $\pm$24.24%, n=5) and 4w WKY (ΔSBP= 89.97 $\pm$41.40%, n=4), while little change was demonstrated in hypertensive 90w SHR (ΔSBP= 24.07 $\pm$21.99%, n=4), as measured invasively via aortic catheterization.

In a separate set of experiments, aortic rings isolated from age matched SHRs (n=5) and WKYs (n=5), were mounted on a DMT myograph, optimally stretched, prepared in physiologic buffer at 37ºC, and constricted with phenylephrine (1μM), for assessment of endothelial function. Acetylcholine (ACH) dependent maximum relaxation after treatment with L-Name (eNOS inhibitor) was modestly attenuated in aortas of 4w WKY (92.79 $\pm$2.64 to 83.26 $\pm$3.35%), 4w SHR (83.50 $\pm$4.47 to 59.48 $\pm$8.75%) and 90w old WKYs (71.39 $\pm$15.06 to 15.77 $\pm$5.16%). Contrary to that, this response was completely blocked in 90w SHRs (35.32 $\pm$5.16 to 0.24 $\pm$3.17%). Treatment with propargylglycine (CSE blocker) did not affect ACH mediated maximum relaxation in 90w SHR (35.32 $\pm$5.16 to 29.40 $\pm$5.86%), but it significantly attenuated the responses in 4w WKYs (92.79 $\pm$2.64 to 56.30 $\pm$4.55), 4w SHRs (83.50 $\pm$4.47 to 71.63 $\pm$12.25) and 90w SHRs (71.39 $\pm$15.06 to 8.13 $\pm$4.61%). Strikingly, rings from normotensive 16w SHR had a complete L-Name sensitive attenuation of endothelial relaxation (63.25 $\pm$5.15 to 2.74 $\pm$1.75%).

Progress and Conclusion: There appears to be a NO independent component of endothelial relaxation in normotensive blood vessels, which is sensitive to CSE inhibitors and blockage of KATP channels. This NO independent component of relaxation is absent in hypertensive and pre-hypertensive vessels; hence implying that loss of the CSE/H2S/KATP axis could be a primary mechanism preceding HTN. This ongoing project aims to measure CSE activity and sulfhydration of Kir 6.1-Cysteine 43 and GAPDH in normotensive/pre and post hypertensive blood vessels from different animal models of HTN to elicit if the CSE/H2S/KATP axis is a potential new target for the treatment of hypertension.

Cardiac #10 (19)

Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 1 Diabetes Hyperglycemia in Mice

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Oregon Health & Science University

Hyperglycemia worsens stroke, yet rigorous glycemic control in outpatient diabetic populations does not improve either the incidence or outcome from stroke (1). Failure of tight glucose control to improve neurologic outcome was also reported in critically-ill hyperglycemic patients (2). Attenuating hyperglycemia once a stroke has initiated has not improved neurologic outcome, and may be counterproductive (3). An alternative approach is to interfere with downstream molecular mediator(s) triggered by hyperglycemia but ultimately acting independent of prevailing glycemia. Soluble epoxide hydrolase (sEH), a product of the gene EPHX2, is abundant in brain and a potential mediator of ischemic injury via its removal of neuroprotective epoxyeicosatrienoic acids (EETs) (4,5). We tested the hypothesis that hyperglycemia exacerbates cerebral injury, at least in part, by up-regulating EPHX2 mRNA expression and increasing brain sEH activity in mice. Type 1 diabetes mellitus (T1D) was produced by STZ 50 mg/kg/day i.p, x 5 days in male C57/BL6 mice. At 4 wks, T1D and control mice were subjected to 45-min middle cerebral artery occlusion (MCAO) with or without sEH blockade by trans-4- [4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (t-AUCB)(6). The t-AUCB regimen was 1 mg/kg i.p. x final 6 days before MCAO. Study measures were plasma glucose concentration, EPHX2 mRNA expression, cerebral blood flow, and brain infarct size at 24 hrs. Hyperglycemic T1D mice exhibited 1.8-fold up-regulation of EXPH2 expression, and sustained brain diffuse regional infarct size 47-77% larger than in controls. Pretreatment with t-AUCB improved infarct size in both groups, and eliminated the difference between T1D and control infarct size, without altering glycemic status in either group. We conclude that T1D hyperglycemia upregulates EXPH2 mRNA expression coding for sEH, stimulates sEH production and worsens stroke, an effect obviated by sEH blockade. It remains to be determined whether similar findings occur in the more common Type 2 diabetes setting.

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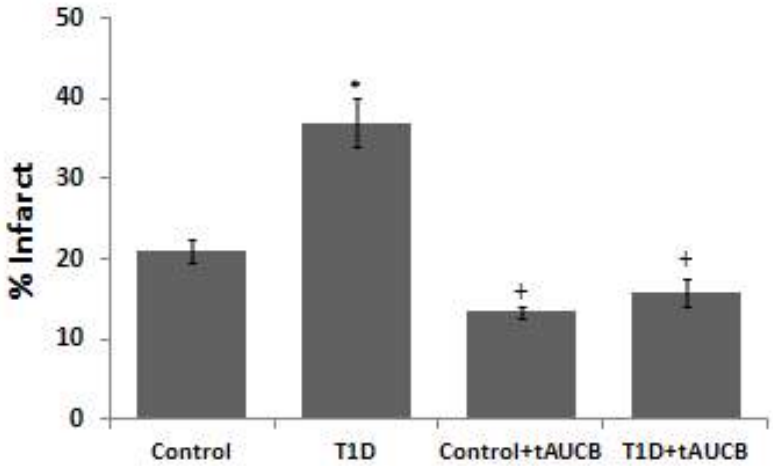

Fig 5. MCAO-induced hemispheric brain infarct size in T1D and control mice, with or without sEH blockade by t-AUCB (n=5/group). T1D mice received STZ 50 mg/kg i.p. q d x 5 days starting at day zero, and controls received vehicle only, and mice were exposed to MCAO at 4 wks. Brains were harvested at day 1 post-MCAO, and infarct size measured by TTC staining as described in methods. Left panel shows the results in the absence of t-AUCB. Right panel shows pretreatment with t-AUCB 1 mg/kg i.p. q d x 6b days immediately before MCAO testing. Asterisk (*) indicates difference from matched controls, and cross (✞) indicates difference from no t-AUCB, at $P<0.05$.

Cardiac #11 (85)

Ischemic Injury to Glomerular Endothelium: Potential Mechanism of Hyperglycemic Protection

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Introduction: Acute kidney injury (AKI) is a common perioperative complication that leads to high mortality. Unfortunately, there are no effective therapies. The most common cause of perioperative AKI is ischemia-reperfusion injury (IRI). Glomerular endothelium is a critical part of the glomerular filtration barrier, and ischemic injury to this barrier leads to increased microvascular permeability. Interestingly, animal investigations have shown that acutely, hyperglycemia (HG) protects against IRI in cardiomyocytes and retinal cells.(1,2) We hypothesize that HG at the time of ischemia protects the function of glomerular endothelial cells (gENC) via activation of a protective cellular signaling pathway, the sphingosine kinase-1/sphingosine-1-phosphate (SK1/S1P) pathway.

Methods: gENC were cultured on transwells in osmotically controlled, normoglycemic (5.5 mM glucose+20 mM mannitol) or HG conditions (25.5 mM glucose). After 7 days, gENC were subjected to a model of IRI: 8h of oxygen-glucose deprivation (OGD) and 12h of reoxygenation/glucose repletion(RGR). Transendothelial electrical resistance (TEER) and permeability to macromolecules (Fluorescein isothiocyanate conjugated to 70 kD Ficoll) were used as measures of gENC monolayer integrity, and were assessed prior to OGD (baseline value) and after 12h of RGR. Following OGD/RGR, total RNA was extracted from both control and HG gENC and real-time, quantitative PCR was performed to quantify sphingosine kinase-1 mRNA levels. Levels were normalized to RPL32, a reference gene. Statistical analysis was performed using 2-tailed Student's t-test.

Results: At baseline (prior to OGD), normoglycemic gENC had higher TEER (decreased permeability) compared to HG gENC (24±1Ω; $p<0.05$ n=3 experiments, 3 replicates/group). Following OGD/RGR, HG gENC were more resistant to OGD than control gENC as evidenced by higher TEER (Fig. 5, 85±4% of baseline in HG gENC; 70±2% baseline in control gENC; $p<0.05$, n=1 experiment, 3 replicates/group) and decreased Ficoll flux (p=0.16).(Figure) Using real-time quantitative PCR we found that sphingosine kinase-1 was increased relative to RPL32 following OGD/RGR in HG gENC when compared to control gENC.

Conclusions: These data suggest while chronic HG is detrimental to the integrity of gENC monolayers at baseline, acute HG protects against OGD-induced injury. Our data suggest that HG upregulates sphingosine kinase-1 in ischemic gENCs. Elucidating the mechanism of HG-induced protection could provide a focus for the development of protective therapies for AKI that do not expose patients to the potential adverse effects of HG.

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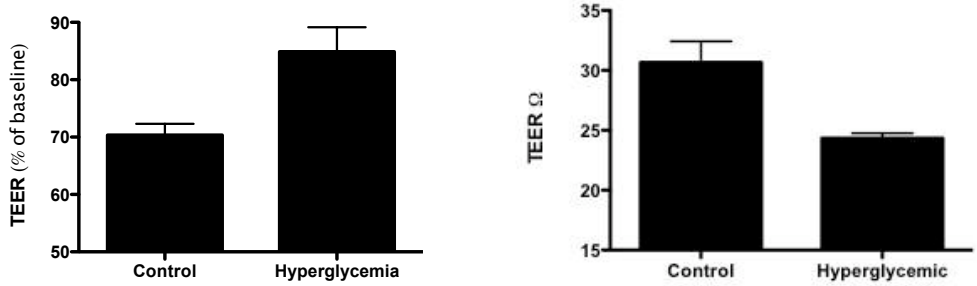
Funded by NIH grants DK090754-01A1 (MH) and T32GM082770 (JK)

Left: Effects of HG on *normoxic* gENC TEER following 7d of culture. Control (NG) gENC had higher TEER (31±2Ω) compared to HG gENC (24±1Ω) $p<0.05$ Right: Effects of HG on gENC monolayers following OGD/RGR. (TEER following OGD/RGR as percent of baseline)



Cardiac #12 (64)

Obesity Predicts Acute Kidney Injury Following Cardiac Surgery: Role of Oxidative Stress

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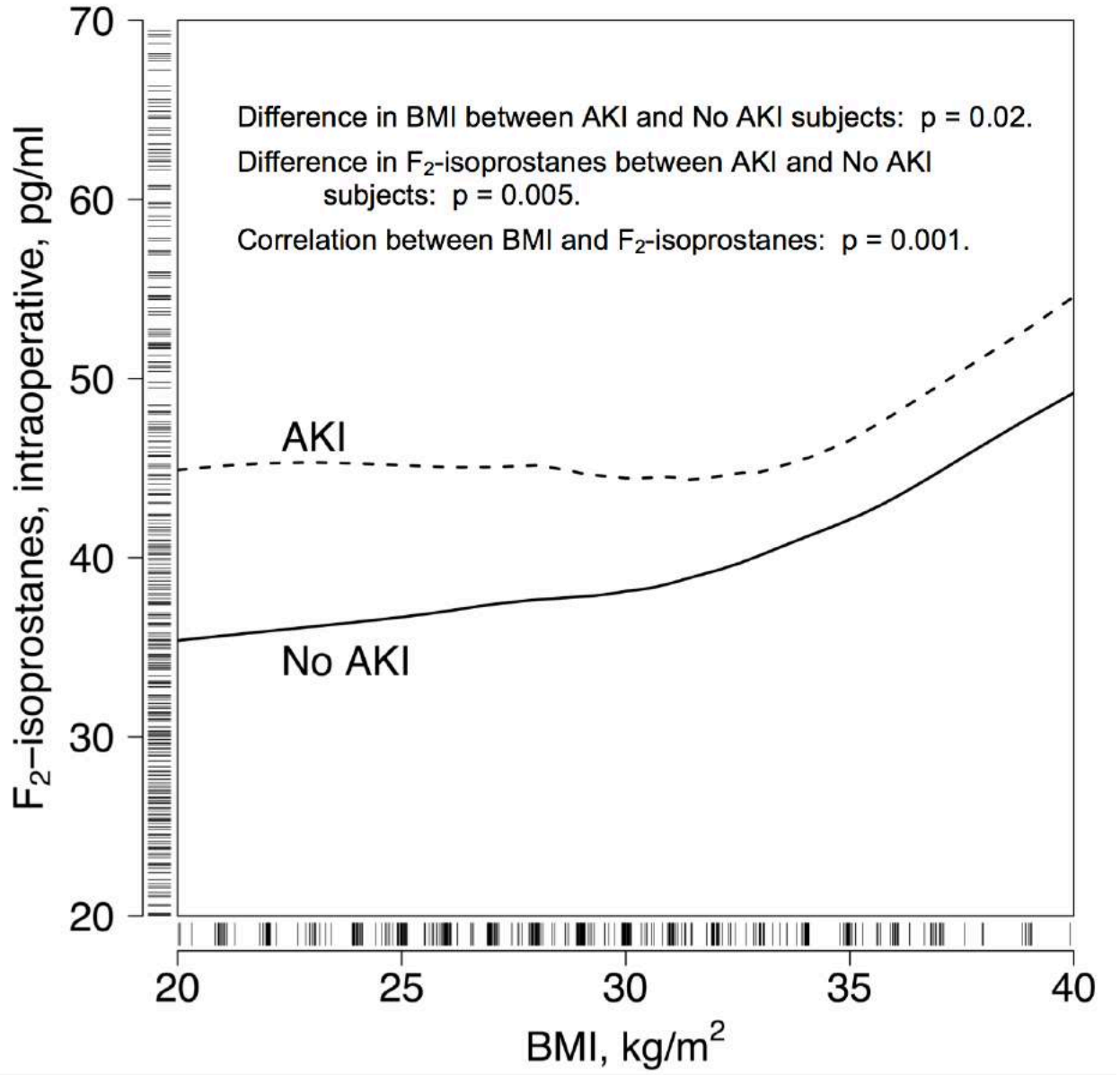
Vanderbilt University

Background: The prevalence of obesity in cardiac surgery patients has increased. Obesity increases oxidative stress, endothelial dysfunction, and inflammation, but the effect of obesity on postoperative acute kidney injury (AKI) is not known.

Methods and Results: We examined the relationship between body mass index (BMI) and AKI, defined using AKIN consensus criteria for AKI diagnosis (at least a 0.3 mg/dl or 50% increase in serum creatinine within 72 hours of surgery), in 445 cardiac surgery patients. We further examined whether oxidative stress (F2-isoprostanes), inflammation (interleukin-6), or anti-fibrinolysis (plasminogen activator inhibitor (PAI)-1) contribute to any relationship between BMI and AKI.

One hundred and twelve subjects (25.2%) developed AKI, and these subjects stayed in the hospital longer, were more likely to develop postoperative atrial fibrillation or pneumonia, and had an increased risk of 30-day death. Adjusted for preoperative and intraoperative risk factors for postoperative AKI, BMI independently predicted postoperative AKI (28.7% increases in the odds of AKI per 5 kg/m2 increases in BMI, 95% CI: 5.9-56.4, P=0.01). Baseline F2-isoprostane (23.4% higher odds of AKI per 50% increase in biomarker concentrations, P=0.04), intraoperative F2-isoprostane (38.1% higher, P=0.003), and intraoperative PAI-1 (18.1% higher, P=0.04) concentrations also independently predicted AKI. A trend was observed between intraoperative interleukin-6 concentrations and increased odds of AKI (7.3% higher, P=0.07), but baseline interleukin-6 and baseline PAI-1 concentrations had no association with AKI. BMI no longer predicted AKI after adjusting for the effect of F2-isoprostanes, suggesting that obesity affects AKI via the effects of obesity on oxidative stress. Adjustment for interleukin-6 or PAI-1 concentrations did not affect the association between BMI and AKI. Further, deconstruction of the obesity-kidney injury relationship into direct effects (independent of oxidative stress, inflammation, or anti-fibrinolysis candidate pathways) and indirect effects (effect of BMI on AKI via each candidate pathway) indicated that F2-isoprostanes but not interleukin-6 or PAI-1 partially mediate the relationship between obesity and AKI (P=0.03 for baseline oxidative stress and P<0.001 for intraoperative oxidative stress mediation).

Conclusions: Obesity independently predicts AKI following cardiac surgery. Oxidative stress may partially mediate the effect of obesity on AKI.


Difference in BMI between AKI and No AKI subjects: p = 0.02.
Difference in F2-isoprostanes between AKI and No AKI subjects: p = 0.005.
Correlation between BMI and F2-isoprostanes: p = 0.001.
AKI
No AKI
F2–isoprostanes, intraoperative, pg/ml
70
60
50
40
30
20
20
25
30
35
40
BMI, kg/m2

Cardiac #13 (89)

Intraoperative Anaphylactic Reactions: A Retrospective Registry Analysis

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Department of Anesthesia, Cleveland Clinic - Cleveland, Ohio

Background: The reported incidence of life-threatening hypersensitivity reactions, is 1:3,000 to 1:110,000 during anesthesia worldwide[1]; two-thirds of which are attributed to muscle relaxants[2]. A recent investigation in the US specifically investigating causative agents noted the incidence rate for referral to the allergist for perioperative anaphylactic reaction to be 1:34,000[3]. Our primary goal was to systematically determine the incidence and severity of allergic events during anesthesia in a large US population, and secondary to determine the association with possible causative agents.

Methods: With IRB approval, we identified adult patients undergoing non-cardiac surgery between 2005 and 2011 from the Cleveland Clinic Perioperative Health Documentation System (PH.D.S). The database was queried using five independent search strategies:

1)cardiovascular collapse (systolic BP<50 mmHg);
2)administration of epinephrine or diphenhydramine;
3)Allergy laboratory tests (tryptase, histamine, IgE);
4)physician comments suggestive of reaction (allergy, rash, edema...);
5)ICD-9 codes for allergic reactions.

Candidates identified via above search strategies were evaluated by a clinical adjudication committee. Each member reached an independent conclusion to the presence of a true allergic reaction. Given the variable presentation of allergic reactions[4] the severity of the allergic reaction was graded 1-5 (low, moderate, severe, arrest, and death).

Results: In our preliminary results we identified 1,899 unique candidates out of 110,618 patients queried. 59 adjudicated cases of anaphylactic reactions were confirmed, 51 of whom received muscle relaxants. The overall incidence of anaphylactic reactions was 5.3:10,000 [95% CI: 4.1, 6.9] and 1.2:10,000 [95% CI: 0.6, 2.1] in severity grade 3+ cases. Among patients exposed to muscle relaxants, the estimated incidence was 6.1:10,000 [95% CI: 4.6, 8.1] and 1.3:10,000 [95% CI: 0.6, 2.2] in severity grade 3+ cases. Compared to patients not receiving muscle relaxants, the relative risk for an anaphylactic reaction in patients given muscle relaxants was 2.1 [0.98, 4.4, P=0.051]. Similar results were observed when restricted to grade 3+cases. Women were twice as likely to experience an allergic reaction as men.

Conclusions: Our preliminary analysis shows an incidence of 5.3:10.000 patients and 1.2:10,000 when in grade 3+ reactions which is consistent with previous reports.

The administration of muscle relaxants is associated with a twofold increase in risk to develop anaphylaxis.
This study does not purport the causative agent for the anaphylactic reaction, it elucidates the incidence in a US population. With increased awareness of possible allergic reactions in the operating room, the discussion of causative agent from barbiturates to muscle relaxants to antibiotics may be addressed more clearly[5].

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Poster Presentation Abstracts

Education

Education #1 (10)

Basic Needs Assessment of Kenyans Primary Survey of Airway and Breathing in Mbagathi Hospital
Maureen McCunn, M.D.; Adam M. Thaler, D.O.; Hillary Dunlevy, M.D.; Meghan O'Brien, B.A.; Jennifer Cohn, M.D.; Rebecca Speck, M.P.H
University of Pennsylvania

Education #2 (38)

Basic Needs Assessment of Kenyan Healthcare Providers' Training and Confidence in Assessment of Arterial Hypotension at Mbagathi Hospital, Nairobi
Meghan T. O'Brien, B.A.; Adam Thaler, D.O.; Hillary Dunlevy, M.D.; Jennifer Cohn, M.D.; Rebecca Speck, M.P.H.; Maureen McCunn, M.D.
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Education #3 (78)

Bringing Perioperative Care to Honduras
Andrew M. Perez, M.D.; Benjamin Israelow; Rachel Schwartz; Carrie Bigelow; Aren Gottlieb, M.D.; Ram Roth, M.D.
Mount Sinai Medical Center

Education #4 (66)

The Use of High-Fidelity Simulation to Assess and Improve the Interpersonal Skills of the Practicing Anesthesiologist
Andrew D. Schwartz, M.D.; Samuel DeMaria, M.D.; Adam I. Levine, M.D.; Alan J. Sim, M.D.
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Education #5 (58)

Evidence-Based Red Blood Cell Transfusion Education Needs to Target All Levels of Health Care Providers
Thomas M. Chalifoux, M.D.; Jonathan H. Waters, M.D.
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Education #6 (39)

The Next Horizon in Determining Competence of Anesthesiology Residents: Embracing the Accreditation Council for Graduate Medical Education (ACGME) Milestones Project With Anesthesia Information Management Systems (AIMS)
Deborah A. Schwengel, M.D.; Lynette Mark, M.D.
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Education #7 (24)

"Feedback Wednesday": A Method to Improve Feedback to Residents and Sustain the Gains
Stephanie B. Jones, M.D.; Sharon Muret-Wagstaff, Ph.D., M.P.A.; Lauren J. Fisher, D.O.; John D. Mitchell, M.D.
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Education #8 (35)

Can Scholarly Activity Points during Residency Predict the Research Productivity of an Anesthesiologist?
Trent D. Emerick, M.D.; David G. Metro, M.D.; Rita M. Patel, M.D.; Tetsuro Sakai, M.D., Ph.D.
University of Pittsburgh Medical Center

Education #9 (17)

Resident Scholarly Activity: A Comparison Study Using a Rank-to-Match Population
Tetsuro Sakai, M.D., Ph.D.; Yan Xu, Ph.D.; David G. Metro, M.D.; Trent D. Emerick, M.D.; Rita M. Patel, M.D.
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Education #1 (10)

Basic Needs Assessment of Kenyans Primary Survey of Airway and Breathing in Mbagathi Hospital

Maureen McCunn, M.D.; Adam M. Thaler, D.O.; Hillary Dunlevy, M.D.; Meghan O'Brien, B.A.; Jennifer Cohn, M.D.; Rebecca Speck, M.P.H.
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Objective: To determine if health care providers possess the training and confidence necessary to meet basic airway and breathing needs for patient resuscitation at Mbagathi District Hospital, Kenya.

Background: Mbagathi District Hospital (M.D.H), Nairobi, is a 300 bed government district-level health care facility serving over 1 million Kenyans. Basic infrastructure, equipment, and supplies are lacking and staff training is highly variable. M.D.H has had an affiliation with the University of Pennsylvania for the past 4 years. Our hypothesis is that a cursory needs assessment of healthcare providers at M.D.H will inform the development of an education curriculum for training in basic “ABC’s”.

Methods: IRB approval from both the University of Pennsylvania and Mbagathi District Hospital was obtained. A Self Assessment of Clinical Skills was administered to medical and clinical officers, interns, and nurses asking them about their training and their level of comfort in addressing airway and breathing needs of patients.

Results: Of 20 respondents, 80% have been taught how, but 22% felt less than confident in their ability to create a patent airway. 100% felt they would benefit from additional training. 71% surveyed had been taught how to use an Ambu bag but only half (52%) felt confident in their ability to use an Ambu bag for oxygen delivery. In performing a breathing assessment, 62% use chest rise, 57% use the respiratory rate, 24% use a stethoscope, 10% use hand over mouth, and 5% use a pulse oximeter. Nearly two-thirds (62%) of respondents had not been trained to use a pulse oximeter. Of those who had been trained, 85% felt very confident in their ability to use a pulse oximeter. 100% of respondents felt they would benefit from additional training in pulse oximetry.

Conclusions: Airway and breathing assessments are vital to providers’ ability to treat patients in respiratory distress or in need of acute resuscitation. Despite some training, there is a lack of confidence in providers’ recognition of airway and breathing needs, and there is a lack of education in assessing the basic “ABC’s” in Mbagathi Hospital. All respondents indicated that they want additional help and assistance in their training. This presents an opportunity to develop curricula to meet these educational needs.

Education #2 (38)

Basic Needs Assessment of Kenyan Healthcare Providers' Training and Confidence in Assessment of Arterial Hypotension at Mbagathi Hospital, Nairobi

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Objective: To perform a knowledge and confidence-level evaluation of health providers' ability to assess systemic arterial hypotension in patients at Mbagathi District Hospital (M.D.H), Nairobi, Kenya.

Background: M.D.H is a 300-bed government first-level health care facility serving over 1 million Kenyans but basic infrastructure, equipment, and supplies are lacking and staff training is highly variable. We sought to determine if medical officers and nurses are confident and competent in assessing patients with arterial hypotension.

Methods: IRB approval from University of Pennsylvania and M.D.H was obtained. A subjective survey was developed and a needs assessment was performed to assess M.D.H healthcare providers' knowledge and confidence in recognizing patients in need of basic "ABC" resuscitation. Healthcare providers who work in the emergency room or hospital wards were eligible and participants included nurses, clinical officers, clinical officer interns, and a medical officer intern. We performed a descriptive analysis of results pertinent to measuring noninvasive arterial blood pressure (NBP) and recognition and assessment of systemic hypotension.

Results: 21 participants responded to questions on a Likert scale regarding training and confidence in measuring NBP and assessing hypotension, specifically, understanding the use of a sphygmomanometer, pulse palpation, capillary refill, jugular venous distension (JVD) and pulsus paradoxus (PP). Of those responding, all had been taught to measure NBP with a sphygmomanometer and were confident or very confident in their ability to do so. 85% measured NBP more than once per week. All had been taught to assess capillary refill, 95.2% to assess for palpable pulses, 63.2% to assess JVD, and 45% to assess PP. While pulses were assessed more than once per week by 66.7%, only 26.3% used any of the other skills more than once per week. Confidence was greatest for assessing palpable pulses and capillary refill, 85.7% and 81%, respectively, reporting confident or very confident. Participants were less confident assessing JVD and PP with only 36.8% and 10.5%, respectively, reporting confident or very confident. 85% desired additional training in measuring blood pressure while all desired additional training in the other circulatory monitoring skills. While 90% reported that they had been taught to treat hypotension and 76% had experience treating hypotension, only 62% felt confident in their ability to treat hypotension. 95% desired additional training in hypotension management.

Conclusions: Ability to assess and treat systemic arterial hypotension are basic skills vital to patient care. All of the health care providers surveyed at M.D.H had been taught to take a blood pressure and assess capillary refill and were confident in doing so, but fewer had been taught additional clinical pressure assessment skills such as evaluating for palpable pulses, JVD or PP. Moreover, confidence levels performing these skills did not match the number taught. These results reflect a self-perceived need for more education and evidence that many participants had not had adequate opportunity to use these skills or had not been taught all of the basic skills needed to meet their responsibilities for this aspect of patient care

Education #3 (78)

Bringing Perioperative Care to Honduras

Andrew M. Perez, M.D.; Benjamin Israelow; Rachel Schwartz; Carrie Bigelow; Aren Gottlieb, M.D.; Ram Roth, M.D.
Mount Sinai Medical Center

Introduction: Honduras is a nation of 7.6 million people, and it is the second poorest country in Central America with a GDP per capita of $4,100. Central and district governments run hospitals and clinics open to all Hondurans, but access is limited, economically stratified, and coverage is poor in rural areas. Life expectancy at birth in Honduras is 70 years and infant mortality is 23 deaths per 1,000 live births, compared to 78 and 7 in the United States. With a physician/population ratio of 57/100,000, there is a need for health care supplementation with continuous international medical brigades.

Program: Medical Students Making Impacts (MSMI) was founded by medical students at the Mount Sinai School of Medicine in 2001, in collaboration with the executive board of the charity organization Hope for a Healthier Humanity. The goal is to educate medical professionals and expose future physicians to healthcare in developing countries through immersive experiences. The MSMI team typically includes 4-6 surgeons, 3 anesthesiologists and 10-15 medical students. The hospital is a fully equipped and staffed facility that supports international surgical service groups, with 3-4 ORs and a 30-bed preoperative/recovery ward is available for patient care.

Implementation: MSMI procures donations and coordinates the transport of medical supplies for the annual week long mission, including surgical supplies, anesthesia supplies, antibiotics, and inhalational agents. Narcotics and benzodiazepines are provided by the hospital pharmacy. Students and physicians are organized into teams of general surgery, gynecologic surgery, and anesthesiology.

Patients are pre-screened by local doctors and arrive at the hospital with relevant laboratory data. Sixty-three patients were screened and 52 were scheduled for surgery in 2011 (Fig). Local operating room staff and ward nurses at the hospital coordinated peri-operative patient care. The procedures were performed under general, spinal, and regional anesthesia.

Results:
1. Local physicians have the opportunity to see and learn new techniques.
2. Students become fully integrated into patient care and management, assisting and observing all aspects of perioperative care and providing them with an invaluable experience not obtained in New York.
3. A pre-mission curriculum provides medical students and with the knowledge and skills needed to successfully execute an international surgical mission with the hope of continued participation throughout their entire medical careers.
4. The early exposure provides insight into other health care systems with the goal of international collaboration and improvement.
5. With the decreased availability of ancillary equipment for tests, students appreciate physical examination in addition to history. Going

Forward: We propose utilizing or establishing a website where international mission work can be promoted, coordinated, and implemented effectively. Additionally, the website may collect information for future research and for future governmental or non-governmental support.

Education #4 (66)

The Use of High-Fidelity Simulation to Assess and Improve the Interpersonal Skills of the Practicing Anesthesiologist

Andrew D. Schwartz, M.D.; Samuel DeMaria, M.D.; Adam I. Levine, M.D.; Alan J. Sim, M.D.
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Introduction: High Fidelity Simulation (HFS) is increasingly being incorporated into post-graduate medical education training programs. Simulation is recognized as an effective teaching tool for the six core competencies but its use as an assessment tool is still evolving. The Mount Sinai School of Medicine has been contacted in the past to evaluate and remediate anesthesiologists deemed incompetent. It is clear that clinical competency alone is not the measure of overall competency. Indeed, competence involves the interplay between the individual and their practice environment. Also, competency can change throughout a physician's career and evidence suggests an increased need for managerial skills competence with career progression. Herein, we report the use of HFS for evaluation, education and practice recommendation construction for a board certified anesthesiologist reported by his department chairman to have difficulties with interpersonal interactions.

Methods: An American Board of Anesthesiology (ABA) certified and full professor of anesthesiology in current practice was referred to our group for evaluation and possible remediation secondary to "challenging interpersonal skills", poor teamwork skills and an inability to manage others effectively.

A two-day simulation-based assessment program was developed intended to evaluate the six core competencies with specific focus on interpersonal skills. A discussion occurred between faculty in between simulation sessions and allowed for the tailoring of the simulation environment and case content to address current findings in a real-time fashion. A one-on-one debriefing session with the center director followed day one. Improvement suggestions were made at this time. An in depth debriefing also followed simulations on day two. Practice recommendations were again made at that time.

Results: We were able to demonstrate specific behavioral traits and identify situations where these traits rendered clinical care and interpersonal experiences problematic. These findings were consistent with the practice challenges described in the referral letter. The participant appeared rigid and inflexible in the environment. These traits made interaction with simulated senior residents, who were perceived to usurp the participant's authority, confrontational and condescending. Specifically, during one encounter, when the participant appeared to feel threatened by the resident, he demanded the resident "take a seat and sit down!" We were also able to identify situations where the participant proved to be a competent clinician and one that could be a tremendous resource in the care of critically ill patients and the supervision and education of junior residents. With feedback, we witnessed improvement with the participant's interpersonal skill set. Based on this program we recommended the participant be assigned to work with junior residents and be assessed regularly and asked to focus on the skills learned in the simulated environment.

Conclusions: HFS is a useful way of assessing and improving poor interpersonal skills even for fully credentialed and practicing anesthesiologists. We were able to use HFS simulation to replicate interpersonal practice challenges and effect improvement in the participant's managerial skill set after direct feedback. We will follow the participant's progress to determine whether lasting improvements are appreciated.

Education #5 (58)

Evidence-Based Red Blood Cell Transfusion Education Needs to Target All Levels of Health Care Providers

Thomas M. Chalifoux, M.D.; Jonathan H. Waters, M.D.
University of Pittsburgh

Introduction: Clinical provider order entry (also referred to as computerized physician order entry or CPOE), coupled with a computerized clinical decision support (CDS) system has been shown to improve the practice of blood transfusion therapy.[1] Most education efforts target physicians. In an effort to foster evidenced-based transfusion practices at the University of Pittsburgh Medical Center's CPOE when an order for (RBCT) is entered, an automatic CDS prompt alerts the practitioner if the patient's hemoglobin (Hb) > 8.5 mg/dL, well above the medical center's recommended hemoglobin level for transfusion, 7.5 mg/dL. The provider then has the option to continue to place the order or to cancel it. RBCT orders can be entered by physicians, physician extenders (CRNP, PA-C, CRNA), or by nurses in consultation with a physician or physician extender.

Objective: To stratify the level of health care provider entering RBCT orders in a single health care system.

Method: Data regarding RBCT at 8 hospitals over a 3-month period were analyzed. We analyzed all the RBCT orders for which the Hb level exceeded the recommended transfusion threshold. Of those transfusion orders that generated alerts, the percentage of alerts that were ignored was calculated. The level of provider who entered the order into the CPOE system was determined.

Results: 2870 total alerts were generated. Only 333 (11.6%) of the alerts were heeded. RBCT orders that prompted alerts were entered by various levels of health care provider: Nurses 917 (32.0%), physician extenders 676 (23.6%) and physicians (44.4%).

Conclusions: A high percentage of the CDS alerts were not heeded. Physicians enter less than one-half of the orders for RBCT in our health system. Future educational efforts to use evidence-based transfusion practices should target not only physicians, but physician extenders and nurses as well.

Reference:
Adams ES, et al. Computerized physician order entry with decision support decreases blood transfusion in children. Pediatrics 2011; 127:e1112-e1119

Education #6 (39)

The Next Horizon in Determining Competence of Anesthesiology Residents: Embracing the Accreditation Council for Graduate Medical Education (ACGME) Milestones Project With Anesthesia Information Management Systems (AIMS)

Deborah A. Schwengel, M.D.; Lynette Mark, M.D.
Johns Hopkins University

Background: In 2010 the ACGME announced the milestones project, which mandates an outcomes approach to medical education. Programs will be obligated to prove trainee competence at specified intervals of training. Definitions of competence for specified intervals of training are being developed at the national level, but once defined, methods of assessment will need to be chosen or developed to document competence in trainees. Evaluation tools differ in design and compliance; grade inflation, halo effects and poor inter-rater reliability are common problems. Multiple choice and oral board examinations, with direct observation and evaluation of residents, are the gold-standards for determining competence in anesthesiology. Some programs, including ours, have incorporated simulation and standardized patients to provide a well-defined, consistent process for determining clinical competence. Clinical teachers cannot be fair judges of trainees because they are invested in success of the trainees; safety for the patient is their first priority. With the nationwide transformation to AIMS, our speciality can readily incorporate these modalities into an outcomes evaluation for clinical competency. Among validated methods in other specialties are the chart-stimulated recall (CSR), and the mini-CEX (Clinical Evaluation Exercise). Currently orthopedic surgery uses a case-based evaluation process in their certification process. We hypothesize that a model of competency evaluation can be innovatively created in anesthesiology training by blending CSR and mini-CEX evaluation tools and using AIMS to access patient information and outcomes data.

Methods and Process of Proposal:
1. Define resident capabilities at specified training periods.
2. Create grading tool a priori for each case presentation on the ACGME core competencies and skills of preoperative assessment and risk evaluation, anesthetic plan and outcomes discussion.
3. Create a trained cohort of anesthesiologist evaluators via a newly created training program
4. Use model for:
• declaring competence for the milestones project
• determine needs for remediation or recommendation of probation
• preparation for examinations for the Board certification process in Anesthesiology or preparation for maintenance of certification
5. Use AIMS to have resident “defend” and present for competencies:
• choose cases for defense
• all cases would be cases previously done by the resident
• resident chooses defined # cases
• adjudication group chooses within those cases
6. Variables of case selection will focus on developmental level of resident:
• such as topic relevant to basic written examination in CA1 year
• appropriate ASA class
• subspecialties
• complications
7. Benefits - ensure that residents keep case log current.
8. Evaluation mock-up:
• Case 1 – 10 minutes with 5 minute debrief/transition
• Case 2 – 10 minutes with 5 minute debrief/transition
• Case 3 – 10 minutes with 5 minute debrief/transition
• Final 15 minute debriefing

Summary: This is a pilot milestones project, in development, to create a validated method of assessing competency in anesthesiology. Our goal is to study the method and establish the evidence base for this type of evaluative process.

Education #7 (24)

"Feedback Wednesday": A Method to Improve Feedback to Residents and Sustain the Gains

Stephanie B. Jones, M.D.; Sharon Muret-Wagstaff, Ph.D., M.P.A.; Lauren J. Fisher, D.O.; John D. Mitchell, M.D.
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Purpose: Few faculty have been taught how to give useful formative feedback to residents [1]. This may hamper resident training because effective feedback is essential to improving resident performance and preparing trainees for independent practice [2]. The purpose of this study was to assess whether a faculty development intervention increased the frequency and usefulness of feedback to residents.

Method: In Spring 2010, five 45-minute collaborative faculty workshops were completed over a 90-day period. Two approaches to feedback were taught in a crossover design. Half of the faculty received training first in a MiniCEX standardized evaluation format while the other half were taught facilitated debriefing; the two groups crossed over at the mid-point of the study period. Wednesday was targeted as a specific feedback day. Faculty received email reminders to provide feedback, while residents were asked to complete a web-based reflective feedback form. A Feedback Wednesday notice was begun and continues to be posted to our intranet homepage each week. Faculty and residents were surveyed electronically pre (2009) and post (2010, 2011) intervention. The study was exempted by the BIDMC IRB.

Results: Survey response rates in 2009, 2010, and 2011 respectively were 67%, 77%, and 91% for residents and 30%, 53%, and 62% for faculty. Combined frequencies for "always" and "frequently" (from a 5-point scale) and "agree" responses were calculated. Sixteen percent of residents rated feedback sufficient in 2009, compared with 30.2% and 30.6% in 2010 and 2011. Perceived usefulness of feedback also increased slightly, from 42.1% in 2009 to 47.6% and 57.1% in 2010 and 2011. Resident level of comfort receiving face to face feedback has remained relatively steady over the 3 years (86.8, 79.1, 87.8%). In contrast, the percentage of attendings that are comfortable giving face to face feedback increased at a statistically significant rate ($p \leq 0.05$) from 42.1% in 2009 to 60% and 77.8% in 2010 and 2011 (fig 1). The percentage of attendings reporting that feedback to residents is sufficient also improved following the workshop interventions, increasing significantly from 10.5% in 2009 to 40 and 42.9% in 2010 and 2011 (fig 1). When attendings were asked if they had changed the frequency,content, or way they gave feedback to the residents following the intervention, 79.4% agreed in 2010, and 69.8% agreed in 2011.

Conclusions: We have demonstrated improvement and sustained gains in faculty perceived sufficiency of feedback to residents. Faculty comfort delivering feedback has continued to improve over the intervention period. We continue to seek ways for residents to use this feedback in active reflection and goal-setting. This intervention format could be broadly applied to other academic programs to improve the feedback given to trainees.

References:

1. Rosenblatt MA, Schartel SA. J Clin Anesth, 1999. 11:519-27.
2. Ende J. JAMA, 1983. 250:77

Education #8 (35)

Can Scholarly Activity Points during Residency Predict the Research Productivity of an Anesthesiologist?

Trent D. Emerick, M.D.; David G. Metro, M.D.; Rita M. Patel, M.D.; Tetsuro Sakai, M.D., Ph.D.
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Introduction: The academic leadership of a department has a specific interest in identifying resident graduates with a promising career as future scientific contributors. A Scholarly Activity Point (SAP) system has been advocated as a system that can be used to quantify the value of scholarly productivity.

Hypothesis: SAPs accumulated during residency predict the future research productivity as an anesthesiologist.

Method: This IRB exempt study was conducted within a large academic anesthesiology residency program. Scholarly activity data during residency was obtained from the residency administration office from the Class of 1995 to the Class of 2010. Post-residency scholarly activity data was obtained for each graduate using publication data available through PubMed and through alumni grant information within the department. Intra-departmental presentations, creation of education modules, and publications which were not indexed in PubMed were not included in this analysis. Scholarly activity data was then converted into SAPs. The SAP system accounts for impact factor of manuscript publication, degree of authorship, awards obtained from conference presentations or research competitions, and type of scholarly activity completed (Table 1). The post-residency SAPs were annualized with the follow-up period. Data was also obtained on the completion of a fellowship and the eventual practice setting (academic or private practice) of each resident after completion of training or military obligations. The data was presented as mean±SD. Statistical analysis was performed with Spearman's correlation test. A p value of less than 0.05 was considered statistically significant. The analysis was also performed on the following subgroups: Classes of 1995-1999, 2000-2004, and 2005-2010.

Results: The total residents that graduated from this program between 1995 and 2010 were 194 with a mean class size of 12±4. The SAPs during residency per resident was 84.3±128.4. The percentage of residents per class without any SAPs during residency was 57±35% (96±5.3%, 59±22%, 23±20%, in the classes of 1995-1999, 2000-2004, 2005-2010, respectively). The annualized post-residency SAPs per resident graduate was 19.7±20.3. The percentage of graduates per class without any post-residency SAPs was 80±15% (72±15%, 79±16%, 88±10%, respectively). 49.0% (n=95) of resident graduates completed a fellowship. 39.2% (n=76) of resident graduates are in an academic faculty position. No significant correlation was found between SAPs during residency and the following outcomes: post-residency SAPs (p=0.93), completion of a fellowship (p=0.11), or choice of an academic faculty position (p=0.81). Subgroup analysis of the SAPs from the Classes of 1995-1999, 2000-2004, and 2005-2010 also did not show any significant correlation between any of the above outcome measures.

Conclusion: In the current definition, SAPs obtained during residency do not predict the future scholarly productivity as an anesthesiologist.

Education #9 (17)

Resident Scholarly Activity: A Comparison Study Using a Rank-to-Match Population

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Introduction: Scholarly activity is indispensable to the future growth of a specialty. While several programs report promoting scholarly activity, they have seldom reported the robust outcome of these initiatives. The aim of this study is to assess the impact of research training initiatives using a rank-to-match population as the control group.

Background: Since Academic Year (AY) 2006, initiatives to promote resident scholarly activity have been implemented in our department; for an ACGME approved research rotation, 1) faculty mentors are introduced to PGY3 residents in an annual lecture, 2) a Director of Research Rotation has been appointed, 3) letter of commitment from the faculty mentor is required, and 4) attendance at a weekly research rotation meeting is mandated. A research PBLD is provided annually to address residents' barriers to participating in research.

Methods: With IRB approval, the study group consisted of applicants who were matched to the anesthesiology program and started their residency in AY2005-AY2007. The control group participants were those on the residency ranking list during the same AYs who could have been matched with the program had they ranked the program high enough on their list (rank-to-match). The demographic features were compared between these groups, as well as the following main outcomes of residency scholarly activity: 1) percentage of residents who published peer reviewed manuscript(s); 2) quality of each publication assessed with Scholarly Activity Points (SAP), which is calculated as follows: SAP= 150 x (1 [original article], 0.75 [review article], or 0.5 [case report]) x (1 [first author] or 0.5 [other author]) x (Impact factor [IF] of the year of publication or 0.5 [if IF<0.5]); and 3) resident scholarly publication productivity calculated as the sum of the SAPs. Peer reviewed manuscripts were searched using PubMed. Statistical analysis was performed using Pearson's chi-squared test (or Fisher exact test) or Mann Whitney U-test. A p value less than 0.05 was considered statistically significant.

Results: Demographic features did not differ significantly between the study group (n=38) and the control group (n=220): male gender (25 [65.8%] vs. 142 [64.5%], p=0.89); US medical graduates (34 [89.5%] vs. 188 (85.5%], p=0.50); applicants with pre-residency publications (4 [10.5%] vs. 29 [13.2%], p=0.088). The percentage of residents who published peer reviewed manuscript(s) during residency was significantly higher in the study group (55.3% [21] vs. 13.2% [29], p<0.0001, Odds Ratio 8.14 with 95%CI of 3.85–17.21). The total number of publications was 28 (0.7 per resident) vs. 42 (0.2 per resident). As measured with SAP, the quality of each publication and the overall productivity of the residents with publications did not significantly differ between the groups (p=0.44, p=0.37, respectively); the median SAP of each publication was 184 (99–245 [inter quartile range]) vs. 146 (60–272), and the median SAP per residents with a publication was 206 (99–426) vs. 156 (60–411).

Conclusions: Implementing the structured initiatives increased the number of residents who published articles in peer reviewed journals.

Poster Presentation Abstracts

ICU

ICU #1 (18)

Effects of Continuous Positive Airway Pressure Ventilation on Upper Airway Patency During Induction of General Anesthesia: Nasal Mask vs. Full Face Mask

Yandong Jiang, M.D., Ph.D.; Jun Oto, M.D., Ph.D.; Qian Li, M.D., Ph.D.; William R. Kimball, M.D., Ph.D.; Jingping Wang, M.D., Ph.D.; Robert M. Kacmarek, Ph.D., RRT
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ICU #2 (12)

Effect of Methylnaltrexone on Laxation, Enteral Feeding and Residual Gastric Volume in Critical Care Patients

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ICU #1 (18)

Effects of Continuous Positive Airway Pressure Ventilation on Upper Airway Patency During Induction of General Anesthesia: Nasal Mask vs. Full Face Mask

Yandong Jiang, M.D., Ph.D.; Jun Oto, M.D., Ph.D.; Qian Li, M.D., Ph.D.; William R. Kimball, M.D., Ph.D.; Jingping Wang, M.D., Ph.D.; Robert M. Kacmarek, Ph.D., RRT
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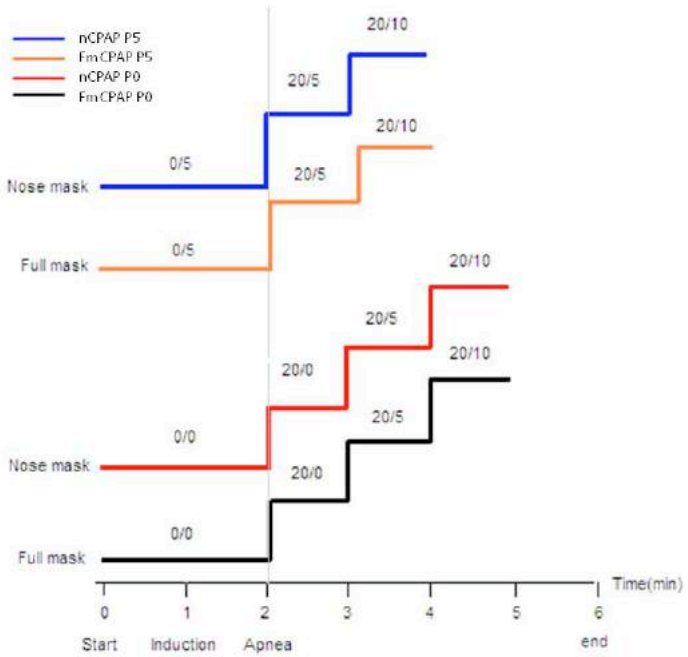
Background: Upper airway obstruction (UAO) is a common complication during induction of general anesthesia (GA). The mechanism of UAO during GA shares many similarities with that of obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) via nasal mask (nCPAP) is more effective maintaining airway patency than a full face mask (FmCPAP) in OSA patients. We hypothesized that nCPAP should be more effective in reducing UAO during induction of GA compared with FmCPAP. The aim of our study was to determine 1) if nCPAP during GA induction reduces the incidence and severity of UAO, and 2) if the application of PEEP prior to GA induction affects its efficacy.

Methods: Seventy-three adult patients requiring GA for elective surgery were randomly assigned into four groups: nCPAP P0, nCPAP P5, FmCPAP P0, and FmCPAP P5, where P0 and P5 represent positive end expiratory pressure (PEEP) 0 and 5 cmH2O applied prior to induction. Airway patency was assessed by measuring expired tidal volume (Vte) at given peak inspiratory pressure over PEEP (PIP/PEEP). Airway pressure profiles for each group are shown in Figure 1. Pre-oxygenation was done either via a nasal or full face mask. After induction, ventilation was initiated with the pressure support mode at a rate of 10 breath/min, fraction of inspired oxygen 1.0, and PIP/PEEP of 20/0, then 20/5 and finally 20/10 cmH2O each applied for 1 min. The patient's head was placed in the neutral position and no backward head tilt or jaw thrust was performed. At each pressure setting, 10 breaths were collected for determination of Vte and evaluation of the incidence and severity of UAO. Vte was calculated using a pneumotrace device.

Results: The rate of effective ventilation (Vte ≥ anatomical dead space) was higher in nCPAP compared with FmCPAP (86.6% vs.18.8%; $p < 0.001$). The median Vte in the group of nCPAP was larger than that of FmCPAP group (342 ml vs. 0 ml; $P < 0.001$). Application of PEEP prior to induction did not significantly affect the Vte in either approach (nCPAP pre- vs. post- GA induction; 433 ml vs. 341 ml, $p=0.21$) (FmCPAP pre- vs. post- GA induction; 0ml vs. 0ml, $p=0.09$).

Discussion: nCPAP used to treat OSA is nearly 100% effective as long as patient tolerates it. Under anesthesia, the tolerance should not be an issue due to deep sedation. Since UAO of OSA and under anesthesia share similarities, nCPAP should be highly effective during induction and potentially can achieve equivalent efficacy as it does for treating OSA. Our result confirmed this notion. Conclusion: nCPAP was more effective in maintaining upper airway patency during induction than FmCPAP. Application of PEEP prior to GA induction did not further reduce UAO.



Extra Files:

ICU #2 (12)

Effect of Methylnaltrexone on Laxation, Enteral Feeding and Residual Gastric Volume in Critical Care Patients

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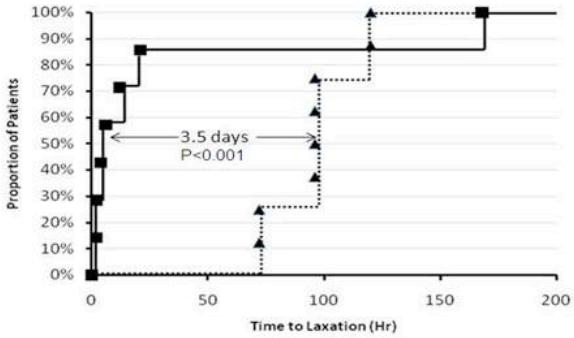
Introduction: Bowel dysfunction is a common problem in the critical care patient. Restoration of normal GI function is essential for establishing enteral feeding, protects against bacterial translocation leading to sepsis, alleviates GI discomfort due to constipation, and shortens ICU residence. The majority of critical care patients are sedated with opioids which contribute to GI stasis. Methylnaltrexone (MNTX), a quaternary ammonium compound that antagonizes peripheral opioid receptors but does not cross the blood-brain barrier, is approved for the treatment of opioid-induced constipation (OIC) in palliative care. Because several case reports suggested its utility in treating GI stasis in critically ill patients, we introduced MNTX, given subcutaneously, into our ICU. Following its introduction, we performed a retrospective chart review to assess its efficacy. The present study followed patients over a six-week period in our ICU that required rescue medication for GI stasis and compared standard rescue therapy with MNTX.

Methods: We performed a retrospective chart review of 88 non–surgical critical care patients, 15 of whom met the criteria of failure to defecate within 72 hr despite standard treatment with senna and sodium docusate. Eight of these patients received traditional rescue medication consisting of ½ sachet picolax plus 2 glycerin suppositories. Seven patients received MNTX (s.c. 0.15mg/kg). All patients continued on the existing senna/docusate. A separate clinician and the nursing staff recorded the responses to treatment. A responder was defined as laxation within 24hr. Additional measures included time to laxation following rescue medication, tolerance of nasogastric feed, sedation score and requirements.

Results: The two groups were well matched for age, APACHE II score and agitation score. Fentanyl dose was slightly greater in the MNTX group (178.6±85.9 vs g/hr, n.s.). The MNTX group was receiving twice the mean dose ofμ 150±75.6 norepinephrine (0.24±0.14 vs 0.11±0.08 mg/kg/min, p=0.04). Six of seven (85%) MNTX patients responded with laxation within 24hr versus 0/8 (0%) for standard therapy (p=0.001). The median time to laxation was 3.5 days faster in the patients treated with MNTX ($p < 0.001$) (Fig. 1). All MNTX patients, but only 50% of patients on standard therapy, progressed to enteral feeding. Of these, mean residual gastric volumes were 7.1±18.9 ml vs 216.3±235.7 ml (n.s.) in the MNTX and standard groups, respectively. Mortality was 2/7 for MNTX vs 4/8 for standard therapy.

Conclusions: Although this is a small retrospective study, the differences in outcome were nevertheless statistically and clinically significant in favor of MNTX. Not only does this MNTX rapidly produce laxation in critical care patients, it also shortens the progression time to enteral feeding and reduces residual gastric volumes. MNTX appears to relieve stasis in both the upper and lower GI tract of critical care patients.



Poster Presentation Abstracts

Management

Management #1 (50)

Difficult Airway Response Team (DART): Three Year Cumulative Data From a Large Academic Medical Center
Christina R. Miller, M.D.[1]; Alexander Hillel, M.D.[2]; Lauren Berkow, M.D.[1]; Kurt Herzer, M.Fc.[1]; Renee Cover, RN, B.S.N.[1]; Lynette Mark, M.D.[1]
Johns Hopkins School of Medicine[1]; Emory University[2]

Management #2 (41)

Extravasation of Intravenous Vesicants: Implementing a Comprehensive Systems-Based Safety Program
Lynette J. Mark, M.D.; Fay Horng, M.D.; Promise Ariyo, M.D.; Yanjun Xie; Matthew Li; Christine Lim
Johns Hopkins University

Management #3 (40)

Academic Partnership With a 501(c)(3) Organization to Advance Scientific Discovery and Improve Patient Outcomes
Lynette J. Mark, M.D.[1]; Philip Roman, M.D., M.P.H.[2]; Kurt Herzer, M.Sc.[1]; James Michelson, M.D.[3]; Andrew Wigglesworth[4]
Johns Hopkins University[1]; University of Maryland[2]; Unviersity of Vermont[3]; MedicAlert[4]

Management #4 (32)

Improving Operating Room Efficiency in the Labor and Delivery Suite: Evaluating Key Factors in Meeting Decision-to-Incision Goals for Urgent Cesarean Sections
Margaret G. Craig, M.D.
University of Texas Southwestern Medical Center

Management #5 (28)

Integration of Clinical and Academic Performance-Based Faculty Compensation Plans: The System and Its Impact on an Anesthesiology Department
Tetsuro Sakai, M.D., Ph.D.[1]; Mark E. Hudson, M.D., M.B.A.[1]; Peter J. Davis, M.D.[1,2]; John P. Williams, M.D.[1]
Department of Anesthesiology[1], Children's Hospital of Pittsburgh[2], University of Pittsburgh School of Medicine

Management #6 (16)

Changing the Captain of the Ship: Attending Handoffs in the Intensive Care Unit
Meghan B. Lane-Fall, M.D.; Maureen McCunn, M.D., MIPP; Rebecca Speck, M.P.H.; Charles Bosk, Ph.D.
University of Pennsylvania, Philadelphia, PA

Management #7 (51)

Association of Intraoperative Anesthesia Handovers with Postoperative Adverse Outcomes
Alparslan Turan, M.D.; Andrea Kurz, M.D.; Jing You, M.S.; Zeyd Ebrahim, M.D.; Daniel I. Sessler, M.D.; Leif Saager, M.D.
Cleveland Clinic

Management #8 (57)

The CQR Platform: A Novel Technology to Facilitate Longitudinal Data Collection and Evidence-Based Medicine
Roy C. Levitt, M.D.; Todor Mihajloski, M.S.; Richard McNeer, Ph.D., M.D.; Elizabeth A. Kelly, M.A.; Keith A. Candiotti, M.D.; David A. Lubarsky, M.D., M.B.A.
University of Miami Miller School of Medicine

Management #9 (27)

Leading Perioperative Change in an Era of Health Care Reform
Sharon Muret-Wagstaff, Ph.D.; Brett A. Simon, M.D., Ph.D.
Beth Israel Deaconess Medical Center / Harvard Medical School

Management #1 (50)

Difficult Airway Response Team (DART): Three Year Cumulative Data From a Large Academic Medical Center

Christina R. Miller, M.D.[1]; Alexander Hillel, M.D.[2]; Lauren Berkow, M.D.[1]; Kurt Herzer, M.Fc.[1]; Renee Cover, RN, B.S.N.[1]; Lynette Mark, M.D.[1]
Johns Hopkins School of Medicine[1]; Emory University[2]

Introduction: A difficult airway presents a challenge to medical providers and failure to control the airway can lead to major morbidity, mortality and litigation expenses. Between 2006 and 2008, several airway events at our institution prompted a root cause analysis and the formation of a strategy for improving complex airway management. The DART initiative, with operational, safety, and educational programs, was established in 2008 involving participants from four departments: Anesthesiology, Otolaryngology and Head and Neck Surgery (OHNS), Trauma Surgery, and the Emergency Department (ED). DART members from each discipline and a DART cart with standardized advanced airway equipment can be deployed hospital-wide within 10 minutes of an escalated code call ("DART call"). We have previously presented DART operations years 1 and 2. We now present additional data from DART year 3 and preliminary analysis of our 3 year cumulative experience.

Methods: Retrospective database review of all code and DART calls over 3 years.

Results: We report on 1,855 codes and 185 DARTs over 3 years. See table 1 for preliminary analysis of adult and pediatric DARTs, cases taken emergently to the OR for definitive management, and surgical airways. We note the increased use of the videolaryngoscopes for code and DART airway management, and report both successful and unsuccessful attempts at securing the airway with a Glidescope (Verathon Medical). There were no adult airway related adverse events or claims during this period.

Discussion: Our multidisciplinary DART initiative has been effective in improving the management of complex in-hospital airway emergencies. Although the videolaryngoscope is an important adjunct in airway management, there is a subset of patients who require more advanced tools for definitive airway management. Further analysis is needed to decide whether a videolaryngoscope should be included on our DART carts; currently it is available in the ORs, the ED and some ICUs. Over the 3 year period, the DART team chose to transport the patient safely to the OR for definitive airway management in about 20% of cases. In the OR, providers had the benefit of skilled nursing support, improved illumination and physical space, and additional surgical equipment. In institutions without a DART program and bedside equipment, a high level of care can be provided with the implementation of an emergency operating room protocol for difficult airways. Future directions for the DART program include in depth analysis of code and DART events and a cost-benefit analysis of the DART program.

Management #2 (41)

Extravasation of Intravenous Vesicants: Implementing a Comprehensive Systems-Based Safety Program

Lynette J. Mark, M.D.; Fay Horng, M.D.; Promise Ariyo, M.D.; Yanjun Xie; Matthew Li; Christine Lim
Johns Hopkins University

Introduction: Extravasation of an intravenous (IV) vesicant into the subcutaneous tissue may result in tissue necrosis. The Johns Hopkins Hospital has interdisciplinary protocols to manage extravasation. However, the operating room (OR) presents obstacles to identifying extravasation, including lack of visual or physical access to IV sites due to draping or positioning and anesthetized patients with altered pain responses. Analysis of patient safety net (PSN) reports institutionally revealed issues regarding provider recognition and treatment of extravasation. The devastating outcomes associated with extravasation prompted a systematic review and quality improvement of our processes.

Methods: A multidisciplinary group including physicians, nurses, and risk managers, identified key areas to improve current practice: safety, risk management, education, and information technology.1 CA2/CA3 residents were recruited as part of the systems-based practice designed in accordance with Accreditation Council for Graduate Medical Education (ACGME) competencies.2 They examined 2 years of PSN reports and risk management claims. Residents presented an educational program at anesthesiology Grand Rounds and as an online module, including photographs of extravasation that needed serial debridement, skin grafts, etc.; feedback indicated that photos were effective in re-enforcing the need for early identification and treatment. Pre- and post-education assessments evaluated provider knowledge of extravasation management and the effectiveness of educational interventions. Charts of vesicants, recommended dilutions and infusion rates, were posted in ORs and added to the resident handbook. Residents and hospital leadership evaluated other means of improving practice including alerts in electronic medical records and the Anesthesiology Information Management System (AIMS).

Results: This multi-modal assessment revealed several notable trends. First, the pre- and post-education assessments showed little improvement in provider knowledge of managing extravasation, suggesting inefficacy in the educational approach. Second, analysis of 226 PSN reports of extravasation showed the highest frequency of vesicants to be iodixanol, vancomycin, 20 mEq KCl, and lipids.

Conclusion: Perioperative extravasation due to IV vesicant administration is associated with significant morbidity. Review of current institutional practice identified opportunities to mitigate the risk of perioperative extravasation. The systems-based educational program will include clinical vignettes and photos instead of factual information only. Color laminated charts will be posted on OR drug dispensers, and pharmacy services will enhance labeling of vesicants. We will encourage provider reporting by creating data fields for OR assessment and treatment, and fields for hand-off communication in the AIMS system. Practices to enhance sustainability include ongoing PSN monitoring and incorporation into residents' education. These initiatives reflect a collaborative effort between anesthesia, surgery, nursing, and risk management to promote safety and deal with the issue of extravasation. Future research is needed to evaluate the impact of this approach on the frequency of these events.

Management #3 (40)

Academic Partnership With a 501(c)(3) Organization to Advance Scientific Discovery and Improve Patient Outcomes

Lynette J. Mark, M.D.[1]; Philip Roman, M.D., M.P.H.[2]; Kurt Herzer, M.Sc.[1]; James Michelson, M.D.[3]; Andrew Wigglesworth[4]
Johns Hopkins University[1]; University of Maryland[2]; Unviersity of Vermont[3]; MedicAlert[4]

Background: The MedicAlert Foundation, a 501(c)(3) organization with over 3 million members in 25 countries, is the only nonprofit emergency medical information service.1 It was endorsed by the American Society of Anesthesiologists (ASA) in 1979. In 1992, a multi-institutional academic collaboration, led by John Hopkins, was established with MedicAlert—the Anesthesia Advisory Council.2 The Council recognized the unique nature of the MedicAlert patient member registry–self reported, non-anonymous, and confidential (essentially, a "living database")—as a valuable research database to advance scientific discovery, improve outcomes, and disseminate critical patient information. The MedicAlert National Registry for Difficult Airway/Intubation (DA/I)3 was the first Council partnership initiative, in response to a national focus on closed claims airway events and the development of the ASA Practice Guidelines for the Difficult Airway. By 2009, MedicAlert identified over 11,000 members in the National Registry and requested that the Council rejuvenate and expand their academic collaboration.

Methods: In 2010, the MedicAlert Foundation and a multidisciplinary and multi-institution group convened at Johns Hopkins and agreed to a preliminary commitment and a systematic process of discovery. The MedicAlert Foundation generated a summary (sans patient identifiers) of its database's top 100 medical conditions, medications, allergies, and medical devices. More detailed information (total number, enrollment by year and by age group) for members with difficult airway/intubation (DA/I), latex allergy, and malignant hyperthermia (MH) was provided. Preliminary data revealed 11,459 DA/I patients, 33,069 latex allergy patients, and 11,931 MH patients.4 To test MedicAlert's ability to confidentially directly query members, research questions were solicited from airway expert Dr. Andy Ovassapian, MH expert Dr. Henry Rosenberg, and latex allergy expert Dr. Robert Brown and submitted to MedicAlert for member distribution. MedicAlert designed SurveyMonkeys for each condition and a one-attempt, email-only distribution was conducted (members can designate contact to be by phone, mail, or email).

Results: A Project Scope of Work was crafted between MedicAlert and Johns Hopkins. SurveyMonkey's 24-hour email responses included, in part: 713 difficult airway/intubation patients with 80 members reporting an episode of difficult airway management since enrolling; 284 MH patients with only 40 members reporting being members of Malignant Hyperthermia Association of the United States (MHAUS), and 2455 latex allergy patients with 681 members being healthcare workers. In 2011, the MedicAlert Foundation and The Johns Hopkins Office of Research Administration formalized a HIPAA-compliant data-sharing agreement and Project Scope of Work.

Conclusion: The academic partnership with this 501(c)(3) organization represents an opportunity to research the medical demographics of a large population and directly communicate (via MedicAlert) with members to allow researchers to build the database with additional information. While acknowledging limitations of self-repor

Management #4 (32)

Improving Operating Room Efficiency in the Labor and Delivery Suite: Evaluating Key Factors in Meeting Decision-to-Incision Goals for Urgent Cesarean Sections

Margaret G. Craig, M.D.
University of Texas Southwestern Medical Center

Introduction: There is consensus amongst obstetricians and obstetric anesthesiologists practicing in high-risk labor and delivery suites that hospitals should have the capability of beginning a cesarean section within 30 minutes of the decision to operate (1,2). In this prospective, observational trial, we examined 105 urgent cesarean sections in a busy academic teaching institution over a 6-week period to evaluate the factors causing delays in meeting that efficiency goal.

Methods: The data collected prospectively for all urgent cesarean sections from March 24, 2010 to May 9, 2010 included: times of obstetrician decision to perform urgent cesarean section, patient arrival to the operating room, time patient began sitting up for their neuraxial block placement, time of neuraxial block completion, time the nurse notified the surgeon that patient was ready for surgery, and the incision time.

Results: The median decision to incision time was 33 min (range 9-78 min). The median time for patient preparation for surgery and transport to the OR was 7 min (range 1-38 min). The median time from entering the OR to patient positioned for neuraxial block was 7 min (range 1-18 min). The median time for placement of anesthetic block was 7 minutes (range 1-19 min). The median time for the circulating OR nurse to call the surgeons stating that the patient was ready after completion of block was 2 min (range 0-18 min). The median time after the surgeons were called to the OR to surgical incision time was 10 min (range 1- 32 min).

Conclusions: The goal decision-to-incision time of thirty minutes or less was met in 32 cases (30% of the total). Our data reflected a similar outcome taken by the hospital each quarter in the year prior to our prospective observation, thus validating our data collection process. The time to place the neuraxial block in our setting was not a significant factor in the delay in meeting the goal decision-to-incision time for urgent cesarean section. The most significant delays occurred after completion of the neuraxial block (ie, time from calling the surgeon to incision = median time 12 min). Areas for focus to improve efficiency include positioning the patient for the neuraxial block while placing standard monitors and obtaining a fetal heart rate strip with the patient in the sitting position. In addition, having the surgeons begin surgical hand hygiene during the neuraxial block placement will augment efficiency in urgen cesarean sections.

References:

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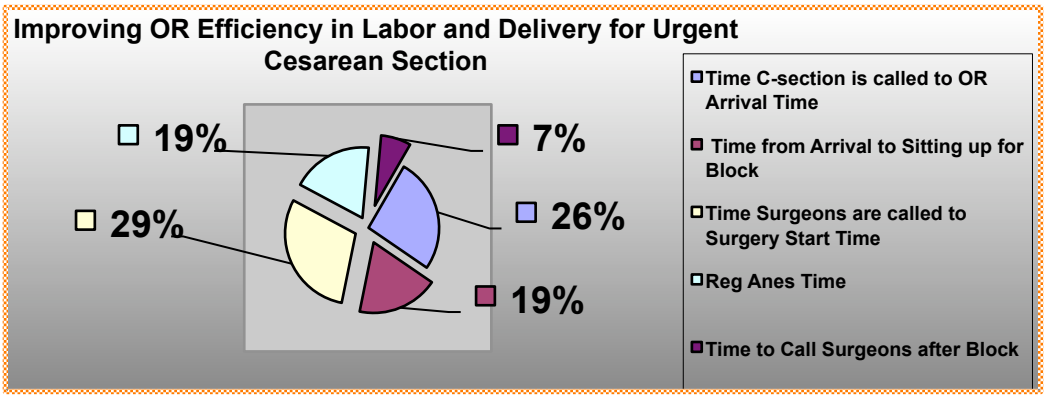
2. American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin 116: Management of Intrapartum Fetal Heart Rate Tracings. Obstetrics & Gynecology 2010; 116(5): 1232-1240.



Management #5 (28)

Integration of Clinical and Academic Performance-Based Faculty Compensation Plans: The System and Its Impact on an Anesthesiology Department

Tetsuro Sakai, M.D., Ph.D.[1]; Mark E. Hudson, M.D., M.B.A.[1]; Peter J. Davis, M.D.[1,2]; John P. Williams, M.D.[1]
Department of Anesthesiology[1], Children's Hospital of Pittsburgh[2], University of Pittsburgh School of Medicine

Introduction: The current economic environment makes it difficult for academic institutions to maintain academic and clinical activities. Productivity-based faculty compensation is reported to improve clinical productivity; however, the impact on academic productivity has not been fully described.

Method: An academic anesthesiology department has used a comprehensive clinical and academic performance-based faculty compensation program since fiscal year (FY) 2004. The non-performance based compensation portion of the salary (base salary), which accounts for approximately 70% of the total annual salary, is paid according to rank and years of service. The remainder of the salary (roughly 30% of the total annual salary) is performance based compensation. At the beginning of each FY, faculty must make a choice between clinical and academic career tracks. Academic faculty can devote up to 80% of their time to non-clinical activities. Payment for this non-clinical time is "salary at risk", which is earned through an academic merit matrix point system, in which each academic activity is weighted and specific merit matrix points are assigned. Unclaimed portions of the salary at risk are absorbed into the department budget at the conclusion of the FY.

In this retrospective administrative study (IRB exempt), the full time equivalent (FTE) of faculty members and their career tracks (clinical vs. academic) were described from FY2004 – FY2011 to analyze faculty retention and recruitment after implementation of the system. To evaluate academic productivity, the following data were analyzed: 1) the number of faculty members who successfully regained salary at risk, and 2) the annualized number of peer reviewed original research publications per academic FTE. The latter number was calculated by comparing FY2001 – 2003 and FY2006-2011 data. The data were described with mean ± 1 standard deviation. The Mann–Whitney U test was used for comparison. The level of significance was set at $p < 0.05$.

Results: After introduction of the compensation plan, total faculty FTE increased 149% from 125.1 (FY2004) to 186.8 (FY2011) to meet the clinical demand, while that of academic faculty was stable (17.8±2.3 FTE: 11.6±1.1% of the total FTE). All academic faculty successfully earned salary at risk in each FY (FY2004 – FY2011) through academic merit matrix points. The annualized number of peer reviewed original research publications per academic FTE increased from 0.31±0.18 (FY2001-2003) to 0.73±0.14 (FY2006-2011) ($p=0.024$) (Figure 1).

Conclusions: Integration of clinical and academic performance-based faculty compensation systems is feasible and efficacious in a large academic anesthesiology department.

Management #6 (16)

Changing the Captain of the Ship: Attending Handoffs in the Intensive Care Unit

Meghan B. Lane-Fall, M.D.; Maureen McCunn, M.D., MIPP; Rebecca Speck, M.P.H.; Charles Bosk, Ph.D.
University of Pennsylvania, Philadelphia, PA

Background: Handoffs, transfers of responsibility for patient care, are a prominent feature of hospital care (1). Most of the previous research on handoffs focuses on resident physician transitions (2), leaving unanswered the question of how attending-level handoffs influence patient care. The aim of our study is to improve understanding of this transition by eliciting themes relating to the features of attending handoffs in the intensive care unit (ICU).

Methods: This is a qualitative semi-structured interview study of intensivists at multiple United States academic medical centers. The recruitment strategy used is purposive snowball sampling, in which subjects are invited to participate and to suggest additional prospective subjects, thereby achieving breadth of specialty, experience, and geography. Recruitment will continue until thematic saturation (when each interview offers minimal additional information) is reached. The estimated number of subjects will be 30: 15 from the authors' institution and 15 from comparable academic medical centers. Grounded theory approach (3) is utilized for transcript analysis to elicit themes in three domains: the mechanics of handoffs, handoff norms and practices, and the impact of handoffs on patients and families. Interviews are digitally recorded via telephone, transcribed, and coded. NVivo qualitative analysis software is used for data management. Five pilot interviews (excluded from analysis) were conducted to develop the interview script.

Preliminary Results: One of three interview phases is complete, with 10 intensivists completing interviews. Subjects' attributes are described in Table 1. Responses related to the study's three domains were as follows: Handoff mechanics: Subjects rotate in and out of the ICU on a weekly (n=6) or bi-weekly (n=4) basis. All subjects conduct handoffs via telephone. Average handoff duration ranges from 15-90 minutes total for 8-24 patients. Handoff norms and practices: Subjects reported that vital handoff elements included clinical history, resuscitation preferences, and interactions with patients' families. Subjects valued concise handoffs (n=5). Most subjects would change some aspect of their current handoff practice (n=7). Typologies of handoff communication were identified: "The same people who are extremely compulsive and detail oriented, usually give the more complete and thorough sign-out." Handoffs' impact on patients/ families: Handoff was identified as potentially disruptive to patients and their families. Most subjects said that it was at least somewhat important to continue the therapeutic care plan when assuming care from another attending in order to minimize this disruption (n=7).

Conclusions: ICU attending handoffs exhibit features different from those previously described for other members of the care team. These unique interactions may have implications for quality and continuity of care in the ICU and merit future study.

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Management #7 (51)

Association of Intraoperative Anesthesia Handovers with Postoperative Adverse Outcomes

Alparslan Turan, M.D.; Andrea Kurz, M.D.; Jing You, M.S.; Zeyd Ebrahim, M.D.; Daniel I. Sessler, M.D.; Leif Saager, M.D.
Cleveland Clinic

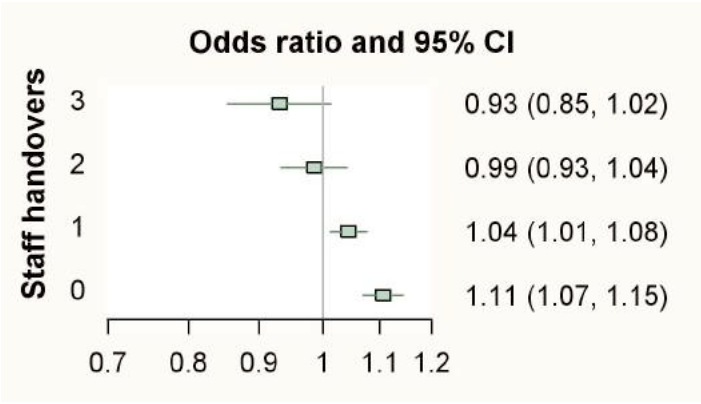
Introduction: Recent studies have evaluated patient-care handovers between paramedics and Emergency Department personal, shift handovers between critical care nurses, and handovers between housestaff for overnight and weekend coverage. However, intraoperative handovers between anesthesia providers have not been systematically explored. We therefore tested the hypothesis that the total number of intraoperative handovers between anesthesia providers during surgery is associated with increased postoperative complications.

Methods: We used data from 96,337 patients in the Cleveland Clinic Perioperative Health Documentation System registry. Our outcome was a collapsed composite (any versus one) of in-hospital mortality and 6 morbidities: serious cardiac, respiratory, gastrointestinal, urinary, bleeding, and infection. Total number of anesthesia handovers includes number of handovers between anesthesia staff and between non-staff including certified registered nurse anesthetist (CRNA), resident/fellow, and student registered nurse anesthetist (SRNA). We assessed the associations between the outcome and (1) total number of handovers, (2) number of staff and non-staff handovers, as well as (3) number of CRNA and resident/fellow handovers, each using a multivariable logistic regression.

Results: The observed incidence of the composite outcome was 13.5%. We found that increased number of anesthesia handovers was associated with increased odds of experiencing any major in-hospital morbidity / mortality (OR (95% CI): 1.05 (1.02-1.07) for a one unit increase in the total number of handovers; P < 0.001). Increased number of non-staff handovers was associated with worse outcome (OR (95% CI) of 1.07 (1.04, 1.10) for an increase of one handover; P < 0.001), while number of staff handovers was not associated with outcome (1.0 (0.96, 1.04), P = 0.99), each factor adjusted for the other. However, the association between the number of non-staff handovers and the outcome depended significantly on the number of staff handovers (staff-by-non-staff interaction: P = 0.001; Figure 1), and vice versa.For CRNAs, the odds of having the outcome increased as the number of handovers increased (odds ratio (95% CI) of 1.10 (1.05, 1.14); P < 0.001); however, no such association was observed for number resident/fellow handovers (1.02 (0.97, 1.07); P = 0.44). There was no interaction between number of CRNA handovers and staff handovers (P=0.13), but the odds ratio for resident/fellow handovers decreased from 1.07 to 0.83 as number of staff handovers increased from 0 to 3 (interaction P= 0.01). Furthermore, there was no significant interaction between CRNA and resident/fellow handovers on the outcome (P = 0.85).

Conclusions: More anesthesia handovers was associated with increased odds of having in-hospital morbidity/mortality. Overall, number staff handovers did not matter, while non-staff did. Interestingly, though, the relationship between staff handovers and outcome depended on the number of non-staff handovers, and vice-versa. Results might be affected by more handovers occurring among CRNAs compared with anesthesia staff or residents/fellows.

Figure 1. Odds ratios of having any in-hospital morbidities/mortality for a unit increase in the number of non-staff (including certified registered nurse anesthetist, resident / fellow, and student registered nurse anesthetist) handovers, at each level of staff handovers. There was a significant interaction effect between staff and non-staff handovers on the outcome (P = 0.001). We adjusted for age, gender, race, American Society of Anesthesiologist physical status, start time of surgery, duration of surgery, and principal diagnosis and procedure.



Management #8 (57)

The CQR Platform: A Novel Technology to Facilitate Longitudinal Data Collection and Evidence-Based Medicine

Roy C. Levitt, M.D.; Todor Mihajloski, M.S.; Richard McNeer, Ph.D., M.D.; Elizabeth A. Kelly, M.A.; Keith A. Candiotti, M.D.; David A. Lubarsky, M.D., M.B.A.
University of Miami Miller School of Medicine

Background: Longitudinal data collection in the clinical area is costly and complicated by the lack of patient-centric care and resource limitations. The collection of longitudinal data can improve patient care and the patient experience by facilitating quality assessments and continuous improvement, and treatment decisions based on comparing outcomes, assessing patient satisfaction, and supporting approved outcomes research. To facilitate longitudinal patient data collection in and outside the healthcare system, we have developed the CQR Platform (Clinical Quality and Research Platform) representing a wireless data collection tool (utilizing a touch screen application for tablets, smart phones, etc.). The CQR Platform is capable of high dimensional secure data collection on patients over time from any site (home, office, clinics, etc.). CQR data is collected in a proprietary secure database of self-reported and healthcare worker submitted patient data (via modules including validated questionnaires focused on pertinent clinical data) designed to communicate with electronic medical records. Our pilot data modules are focused on patient data collection in our pain treatment clinics.

Methods: The CQR Platform App provides a wireless tablet to collect medical history, medications, referring physicians, vital signs, responses to validated pain assessment questionnaires, as well as patient satisfaction data on each clinic visit. This information is updated by visit and stored on a secure server. The system is designed to facilitate the extraction of key clinical data for clinical assessment on each visit. Clinical data are submitted to the electronic medical record after each entry, where it may be reviewed by the treating healthcare provider(s). Over the course of time, patient outcomes can be assessed to obtain a high-level view of the cases being treated and develop quality reports comparing treatments, assessing performance, guiding future treatment selection, and to track and improve patient satisfaction across large numbers of patients. After ethics committee approval, clinical research may also be facilitated by extraction of longitudinal data where relevant.

Results: The CQR Platform is currently being launched in the Multidisciplinary Pain Clinics at the University of Miami Miller School of Medicine. A demonstration of the App and detailed description of the technology will be provided at the AUA session using a wireless tablet. We expect to report the progress of this technology toward reaching the outlined goals at the meeting.

Conclusions: The CQR Platform is a wireless touch screen supported electronic data collection tool that has the potential to facilitate convenient longitudinal patient data collection across the entire healthcare system (clinics, physician offices, etc.) and outside.

Management #9 (27)

Leading Perioperative Change in an Era of Health Care Reform

Sharon Muret-Wagstaff, Ph.D.; Brett A. Simon, M.D., Ph.D.
Beth Israel Deaconess Medical Center / Harvard Medical School

Background: The changing landscape of health care reform affords anesthesiologists new opportunities to lead transformative change in perioperative quality and safety, patient experience, and efficiency. However, new models are needed for today's anesthesiologists to develop effective leadership skills for tomorrow's healthcare environment. We sought to create and test a novel organizational platform to (1)support interdisciplinary learning, innovation, and improvement; and (2)foster critical leadership capability needed to sustain the model at individual, departmental, and institutional levels.

Methods: We launched Faculty Hour in 2010, an interdisciplinary partnership for performance excellence uniting Anesthesia, Surgery, Nursing, and others at a large teaching hospital. OR start time is moved 30 min. later each Tuesday to provide protected time, and a Steering Committee guides efforts along with Patient-Family Advisory Council input. Staff participate voluntarily at 6:45 AM in parallel 90-day chartered teams, cross-discipline division meetings, and faculty development sessions. Key elements include joint leadership by an anesthesiologist, surgeon, and nurse; leader prep sessions and toolkit; innovation discovery teams; data review; broad recognition; and short improvement cycles. In addition to immersion as team and session leaders, faculty devote a 90-day cycle each year to leadership skill seminars.

Results:
Individual: In the first 24 months, 153 individuals from anesthesia, surgery, nursing, and other groups served on chartered teams. Meanwhile, 11 cross-disciplinary divisions met quarterly, alternating with faculty development sessions (e.g., 74 anesthesiologists participated in clinical innovation workshops and leadership, scholarship, and education series). 40 of 74 (54%) Anesthesia faculty served in a leadership role.

Departmental: Organizational performance for the Anesthesia Dept. before and 12 months after introduction of Faculty Hour improved overall ($p<.0001$) with 9-38% point gains on Baldrige-based survey items (Fig. 1), e.g., improvements in % of faculty who reported they were encouraged and enabled to develop skills ($p=.05$) and to generate innovative ideas ($p=.0001$).

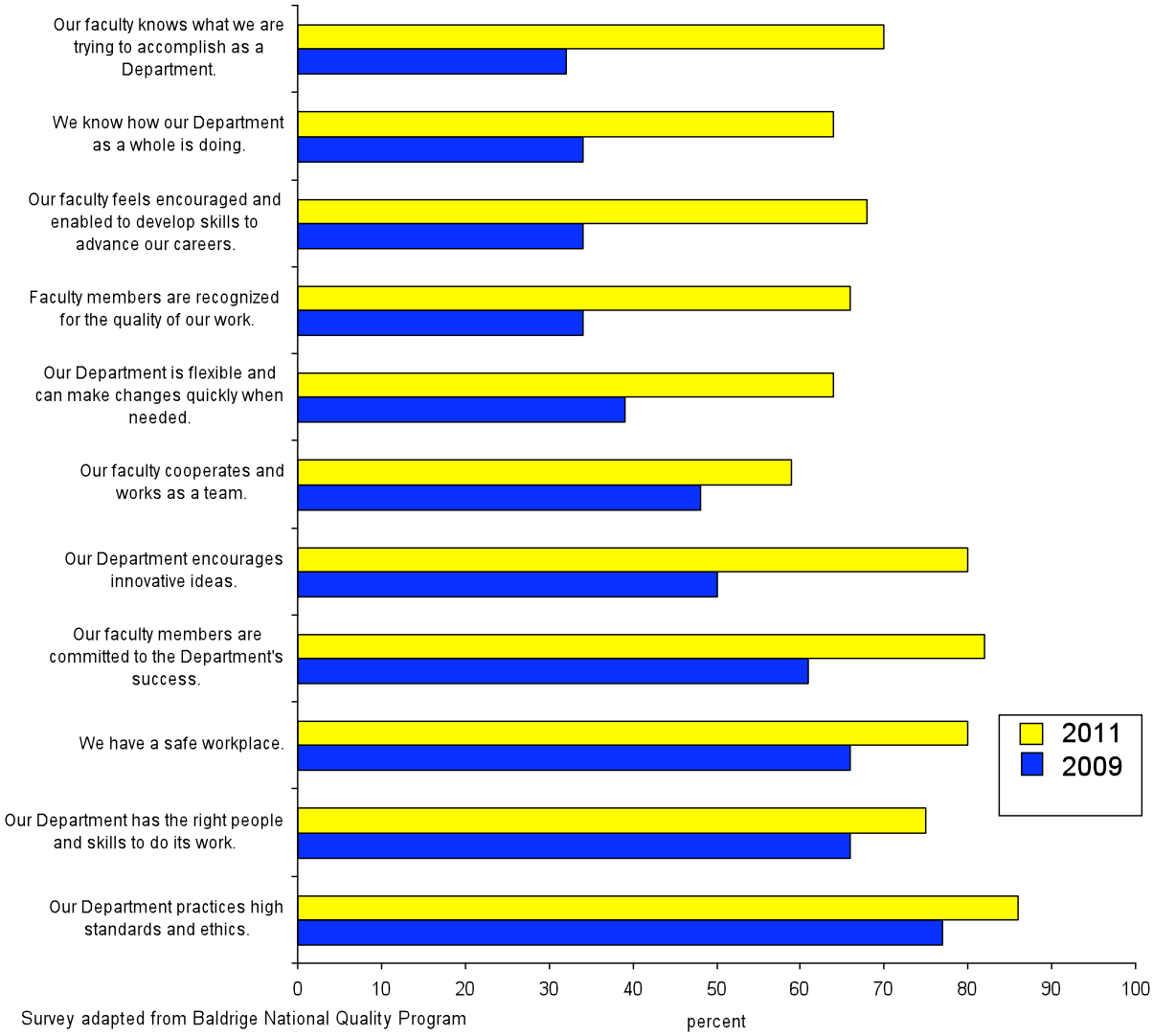
Institutional: Sample results from 15 chartered teams: Optimized OR layout to reduce surgical infection risk; improved patient flow with 1,200 annual miles saved in staff walking between sites; reduced instruments opened in robotics by 53%; launched monthly simulation-based OR team training; designed peer support program; created effective communication videos; implemented perioperative computerized physician order entry; improved communication with trauma patients and families. Importantly, on-time OR starts are best on Tuesdays.

Conclusions: We have instituted a replicable, sustainable platform for collaborative learning, innovation, and improvement in the OR environment. Anesthesiologists participate in leadership development and most have held new leadership roles. The Department shows striking evidence of change in organizational performance. Institutionally, early project results show improved efficiency and patient experience, and the Anesthesia Department is newly identified as an institutional leader in innovative care improvement.

Muret-Wagstaff S, Simon BA. Leading Perioperative Change in an Era of Health Care Reform. AUA 2012.

Figure 1. Organizational Performance, 2009 vs. 2011

Percent of Anesthesia faculty (RR 64%, N=44) who agree or strongly agree



Survey adapted from Baldrige National Quality Program

Poster Presentation Abstracts

Neuroscience

Neuroscience #1 (33)

The Effect of Intraoperative Infusion of Dexmedetomidine on Quality of Recovery After Major Spinal Surgery
Alex Bekker, M.D., Ph.D.[1]; Michael Haile, M.D., M.S.[2]; Richard Kline, Ph.D.[2]; Sorosch Didehvar, M.D.[2]; Beatriz Nistal-Nuno, M.D.[2]
UM.D.NJ-New Jersey Medical School[1]; NYU Medical Center[2]

Neuroscience #2 (73)

Statins and the Daily Risk of Delirium in Critically Ill Patients
Christopher G. Hughes, M.D.[1]; Alessandro Morandi, M.D.[2]; Ayumi K. Shintani, Ph.D., M.P.H.[1]; E. Wesley Ely, M.D., M.P.H.[1]; Pratik P. Pandharipande, M.D., M.S.C.I.[1]; Timothy D. Girard, M.D., M.S.C.I.[1]
Vanderbilt University School of Medicine[1]; Ancelle della Carità Brescia[2]

Neuroscience #3 (86)

Intraoperative Tight Glucose Control and Postoperative Delirium in Patients Undergoing Cardiac Surgery
Leif Saager, M.D.; Beverly Jong, M.D.; Jing You, M.S.; Andra Duncan, M.D.; Andrea Kurz, M.D.
Department of Outcomes Research, Cleveland Clinic

Neuroscience #4 (44)

Exercise and a Breaker of Advanced Glycation End Products Attenuate Age Related Vascular Stiffness and Decrease Tissue Transglutaminase Activity and Crosslinking
Dan E. Berkowtitz, M.D.; Jochen Steppan, M.D.; Gautam Sikka, M.D.; Lakshmi Santhanam, Ph.D.; Daniel Nyhan, M.D.
Johns Hopkins University

Neuroscience #5 (72)

The Geriatric Surgical Patient: Stress, Anesthetics, and Functional Outcomes
Stacie G. Deiner, M.D.; Charles V. Mobbs, Ph.D.; Jeffrey H. Silverstein, M.D.; Mary Sano, Ph.D.
The Mount Sinai School of Medicine

Neuroscience #6 (71)

Subclinical Systemic Inflammation in Obese Patients Prior to Total Knee Arthroplasty (TKA)
Syed Azim, M.D.; James Nicholson, M.D.; Ruth Reinsel, Ph.D.; Mario Rebecchi, Ph.D.; Helene Benveniste, M.D., Ph.D.
Anesthesiology and Orthopedic Surgery, Stony Brook University - Stony Brook, NY

Neuroscience #7 (80)

Prevalence and Risk Factors for Intraoperative Hypotension During Craniotomy for Traumatic Brain Injury
Deepak Sharma, M.B.B.S., M.D., D.M.; Michelle J. Brown, B.S.; Sakura Noda, B.A.; Randall M. Chesnut, M.D.; Monica S. Vavilala, M.D.
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Neuroscience #8 (69)

Tetracycline Derivatives Prevent Subarachnoid Hemorrhage From Intracranial Aneurysm Rupture
Tomoki Hashimoto, M.D.; Tomoki Hashimoto, M.D.
University of California, San Francisco

Neuroscience #9 (37)

Connectivity, rCBF & GABA Level Under Propofol Anesthesia (2 μg/mL) – MRI MRS Study in Volunteers
Ramachandran Ramani, M.B.B.S., M.D.; Maolin Qiu, Ph.D.; Margaret Rose, M.D.; Chang Helen, M.D.; Ruskin Keith, M.D.; Constable Todd Robert, Ph.D.
Yale University School of Medicine

Neuroscience #1 (33)

The Effect of Intraoperative Infusion of Dexmedetomidine on Quality of Recovery After Major Spinal Surgery

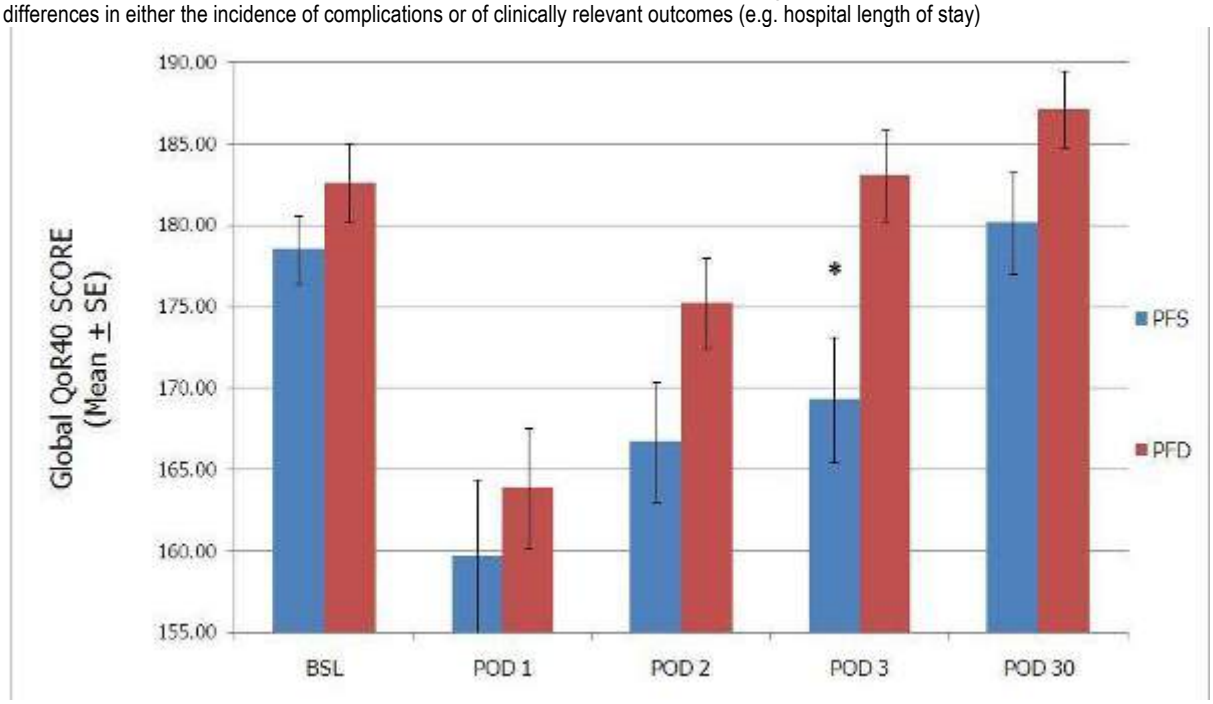
Alex Bekker, M.D., Ph.D.[1]; Michael Haile, M.D., M.S.[2]; Richard Kline, Ph.D.[2]; Sorosch Didehvar, M.D.[2]; Beatriz Nistal-Nuno, M.D.[2]
UM.D.NJ-New Jersey Medical School[1]; NYU Medical Center[2]

Background: Surgery induces a variety of metabolic, endocrine and immune changes collectively known as the "stress response", which often may lead to post-operative sickness behavior. Anesthetic management may modulate this physiological response thus affecting the postoperative course. We hypothesized that the intraoperative administration of dexmedetomidine (DEX), a sympatholytic agent, would reduce the stress response and improve the quality of recovery in patients undergoing major surgery.

Methods: We conducted a prospective randomized study of 54 patients undergoing multilevel spinal fusion. Anesthesia was maintained with either propofol/fentanyl/dexmedetomidine (PFD) or propofol/fentanyl/placebo-saline (PFS). The quality of recovery was assessed using a 40-item quality of recovery questionnaire (QoR40), a 9 questions fatigue scale (FFS), the MMSE and the digital span forward (DSF) and backward (DSB) tests. Cognitive tests were administered preoperatively, on postoperative days (POD) 1, 2, 3 and 30 (QoR40 and FSS only were administered on POD30 over the phone). Blood samples were collected at baseline, in the post-anesthesia care unit (PACU) and POD 1 and were analyzed for levels of cortisol, C-reactive , IL-1ra, IL-2, IL-6, IL-8,β, IL-1αproteins (CRP) as well as the cytokines IL-1 . Data was analyzed with SPSS software (version 18) usingαIL-10, and TNF multivariate and mixed model approach to test for the effect of surgery and drug group. Pairwise comparisons were assessed with t-test or rank tests after correcting for multiple comparisons. Resampling (bootstrap) techniques were used to confirm positive comparisons

Results: The global QoR40 scores showed a significant effect of time (F4, 114= 22.63, p < 0.001), and drug ((F1, 51= 4.368, p = 0.042) with average scores falling to lower values on POD 1 (163.63 + 2.47) and POD 2 (170.94 + 2.38) than on baseline (180.56 + 1.588, mean + SE, 2-tailed t-tests, p<0.001)(Figure 1). By POD 3, scores were significantly lower (-13.74 point difference, p=0.005) in the PFS group (169.3 + 3.87) than in the PFD group (183.04 + 2.76). All patients reported significantly higher levels of fatigue postoperatively, but intergroup difference in FSS was detected on POD3 only, with scores in the PFS group higher than in the PFD group (50.0 + 4.0 vs 36.3 + 4.9, p=0.035). No behavioral assessments were significantly different on POD 30. In both groups, plasma cortisol levels were highest in the PACU while CRP levels were elevated on POD 1. DEX significantly reduced levels of cortisol but not CRP. Levels of cytokines Il-6, Il-8, and Il-10 levels were significantly higher immediately after surgery and at POD 1. Plasma levels of other cytokines were not affected by surgery. DEX significantly reduced postoperative rise in IL-10, but not in IL-6 or IL-8.

Conclusions: DEX infusion during multilevel spinal fusions improved the quality of recovery and reduced fatigue in the early postoperative period. Moreover, it reduced plasma levels of cortisol and IL-10 in comparison to control group. Our sample size was not sufficient to detect differences in either the incidence of complications or of clinically relevant outcomes (e.g. hospital length of stay)



Neuroscience #2 (73)

Statins and the Daily Risk of Delirium in Critically Ill Patients

Christopher G. Hughes, M.D.[1]; Alessandro Morandi, M.D.[2]; Ayumi K. Shintani, Ph.D., M.P.H.[1]; E. Wesley Ely, M.D., M.P.H.[1]; Pratik P. Pandharipande, M.D., M.S.C.I.[1]; Timothy D. Girard, M.D., M.S.C.I.[1]
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Introduction: Delirium is highly prevalent in critical illness and independently associated with worse outcomes including cost, length of stay, cognitive impairment, and mortality.(1) One of the leading hypotheses of delirium pathogenesis during critical illness is neuroinflammation.(2) Statins carry important anti-inflammatory and other pleiotropic effects that might interrupt the neuroinflammatory cascade and reduce delirium risk.(3) Conversely, statin discontinuation leads to a pro-inflammatory state and is associated with worse neurological outcomes after cerebrovascular insult.(4) We sought to determine the effects of statin administration and discontinuation on delirium during critical illness.

Methods: After IRB approval, we conducted a multicenter, prospective cohort study of medical and surgical ICU patients in shock and/or respiratory failure. We classified positive statin exposure as pre-hospital use (according to physician admission notes) and/or in-ICU use (according to hospital medication administration records). During their ICU course, duration of statin use and duration of discontinuation of pre-hospital therapy were recorded. Delirium was assessed daily using the Confusion Assessment Method for the ICU.(5) Multivariable regression models with generalized estimating equations were used to analyze associations between statin exposure or discontinuation and daily risk of delirium after adjusting for age; pre-existing cognitive impairment;(6) severe sepsis; stroke risk;(7) APACHE II;(8) daily severity of illness,(9) mechanical ventilation, creatinine, and bilirubin; daily use of sedatives, steroids, and drotregcogin alfa; propensity score for statin use.(10)

Results: Among 819 patients studied, median age was 61years, and APACHE II was 27; 745 (91%) were mechanically ventilated, and 275 (34%) had severe sepsis. Of the 275 (34%) pre-hospital statin users, 109 had their statin held in the ICU; 237 (29%) patients overall were in-ICU statin users. In total, 606 (74%) patients had delirium during their ICU course. After adjusting for covariates, in-ICU statin use reduced the daily odds of delirium by 44% [Odds Ratio (OR) 0.66; 95% confidence interval (CI): 0.48-0.90], but pre-hospital statin use did not (OR 1.02; 95% CI: 0.77-1.36). Among pre-hospital users, however, each day a statin was held increased the daily odds of delirium by 6% (OR 1.06; 95% CI: 1.02-1.09).

Conclusions: Statin use in the ICU was independently associated with a reduction in delirium during critical illness, and discontinuation of previously used statins was associated with an increase in delirium. Further investigation is needed to confirm the neuroprotective effects of statins during critical illness.

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Neuroscience #3 (86)

Intraoperative Tight Glucose Control and Postoperative Delirium in Patients Undergoing Cardiac Surgery

Leif Saager, M.D.; Beverly Jong, M.D.; Jing You, M.S.; Andra Duncan, M.D.; Andrea Kurz, M.D.
Department of Outcomes Research, Cleveland Clinic

Background: Delirium is a serious, frequent postoperative complication and has been associated with prolonged critical care and hospitalization, long-term cognitive decline, and mortality.(1,2) The incidence of delirium ranges from 37% - 46% in the general surgical population,(3) increasing to 60 – 80% in ICU patients.(4) Cardiac surgery carries a higher risk of post-operative delirium, and has been reported in 11.5% - 52% of patients. The occurrence of hyperglycemia in surgical patients is associated with worse outcome, including increased risk of death, infectious complications, impaired wound healing, and additional post-operative morbidity.(5) Observational data suggests that glucose control with intensive insulin therapy during the peri-operative period may improve post-operative outcomes. We sought to test the hypothesis that tight blood glucose control using a hyperinsulinemic-normoglycemic clamp technique reduces the incidence of postoperative delirium measured by the Confusion Assessment Method (CAM).

Methods: With IRB approval, 198 adult patients undergoing cardiac surgery were consented and randomly assigned to intraoperative tight glucose control or standard therapy. Patients were screened for delirium twice daily for up to five days postoperatively. We considered a patient "delirious" if CAM testing was positive at any time. We assessed the association between both groups and postoperative delirium using a logistic regression. SAS software version 9.2 (SAS Institute, Cary, NC, USA) and R software version 2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Results: Demographics and baseline variables were well balanced between the groups (Figure 1). 41 out of 198 (21%) patients screened positive for delirium on at least one assessment. Patients who received tight glucose control had a higher probability to be diagnosed delirious as compared to those who received standard therapy (26/93 vs. 15/105; relative risk (RR), 95% CI: 1.96, 1.11-3.5; P = 0.02, univariably).

Discussion: Our overall incidence of postoperative delirium is on the lower end of previous findings in patients recovering from cardiac surgery, but similar to more recent reports. It seems possible that this represents increasing awareness of delirium and implementaition of guidelines. Tight intraoperative glucose control contributed to a statistically and clinically significant increase in postoperative delirium. A possible mismatch between increased cerebral energy demand during cardiac surgery and restriction of glucose supply might contribute to this surprising finding.

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Neuroscience #4 (44)

Exercise and a Breaker of Advanced Glycation End Products Attenuate Age Related Vascular Stiffness and Decrease Tissue Transglutaminase Activity and Crosslinking

Dan E. Berkowtitz, M.D.; Jochen Steppan, M.D.; Gautam Sikka, M.D.; Lakshmi Santhanam, Ph.D.; Daniel Nyhan, M.D.
Johns Hopkins University

Introduction: Cardiovascular disease is the leading cause of morbidity and mortality at an advanced age. Pathologically, aging is associated with increased vascular stiffness, which can be measured by pulse wave velocity (PWV) - an important index of vascular aging. Although both dynamic and structural changes have been described in aging, the underlying molecular mechanisms remain poorly understood. Tissue Transglutaminase (TG2), which forms crosslinks between extracellular matrix proteins, may contribute to this pathobiology. Another mechanism is the formation of advanced glycation end products (AGEs) resulting in irreversible non-enzymatic glycosylation of proteins. We hypothesized that aging associated changes in vascular stiffness as measured by PWV can be attenuated by exercise and breakdown of AGEs.

Methods: We determined age-dependent changes in vascular stiffness in male Fisher rats by measuring PWV using a dual blood pressure catheter in vivo over a wide range of blood pressures (BPs). The animals were stratified into three groups: young, middle aged, old. We determined the changes in in vascular stiffness following either exercise alone (4 weeks) or exercise plus ALT-711 injection (AGE breaker) in old animals. Furthermore we measured TG2 activity and crosslinking.

Results: Aging lead to an incremental increase in PWV that is more pronounced at higher BPs. According to PWV animals were categorized into three groups: young (3-4 month), middle aged (5-9 month) and old (above 9 month of age). Baseline BPs were identical, but PWV was significantly different at baseline and at higher BPs. Exercise alone failed to attenuate the increased PWV in old animals, but significantly decreased TG2 activity and crosslinking. The combination of an AGE breaker and exercise significantly reduces PWV and vascular stiffness.

Discussion: We demonstrated that PWV is lowest in young animals and then gradually increases as the vasculature stiffens. Interestingly, PWV in the different age groups converges at lower BPs suggesting that at lower pressures passive properties are less important. At higher BPs, the curves diverge suggesting that collagen becomes the major passive contributor, leading to stiffer vessels. A short period of exercise at an advanced age fails to attenuate vascular stiffness, despite decreased TG2 activity and increased TG2 crosslinking, suggesting that once vascular remodeling has occured exercise alone is insufficient to reverse this process. The additional treatment with an AGE-breaker, however, reduces vascular stiffness even in old animals. This novel finding has potential therapeutic implications for the aging population and further studies extending these results seem to be warranted.

Neuroscience #5 (72)

The Geriatric Surgical Patient: Stress, Anesthetics, and Functional Outcomes

Stacie G. Deiner, M.D.; Charles V. Mobbs, Ph.D.; Jeffrey H. Silverstein, M.D.; Mary Sano, Ph.D.
The Mount Sinai School of Medicine

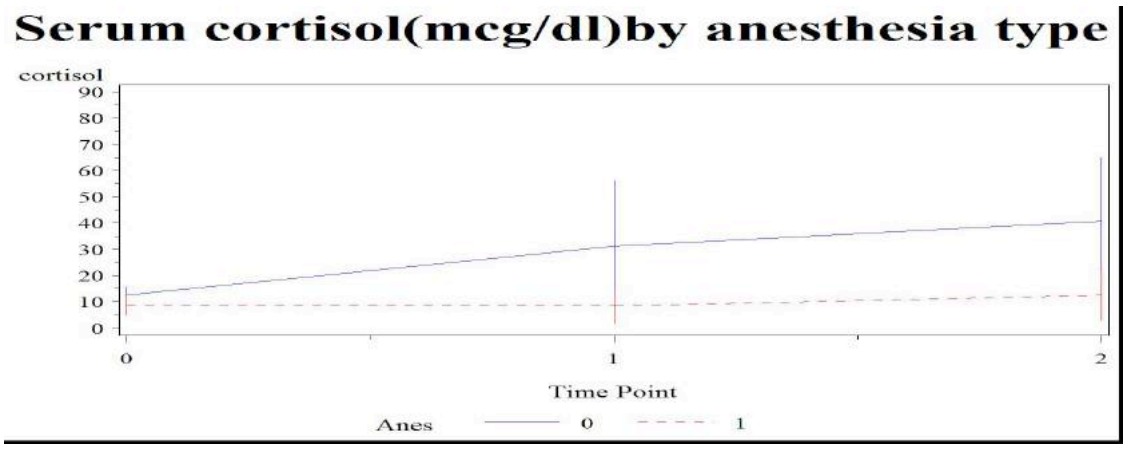
Background: Elderly surgical patients experience disproportionately high perioperative morbidity and mortality including postoperative cognitive dysfunction (POCD) and delirium even after adjustment for preoperative comorbidities and procedure type1. This results in longer hospital stays and greater median hospital cost 2. Human studies suggest TIVA suppresses stress response (cortisol). Animal studies suggest older animals have prolonged stress response and are prone to cognitive dysfunction3,4. In this study we examine two general anesthetics (GA): gas (GS-sevoflurane) vs. total intravenous anesthesia (TIVA) to clarify the association between the physiologic response to stress and cognition. Prior studies focused on regional vs. general anesthesia, NOT a comparison of different GA. Surprisingly little is known about the optimal conduct of a GA, especially in high risk older patients. Aims: 1) Determine the incidence of delirium and immediate POCD in patients who receive GS vs. TIVA Hypothesis: TIVA will be associated with a lower incidence of delirium. 2a) Compare the stress response (serum cortisol(C) and epinephrine (E)) in GS vs. TIVA

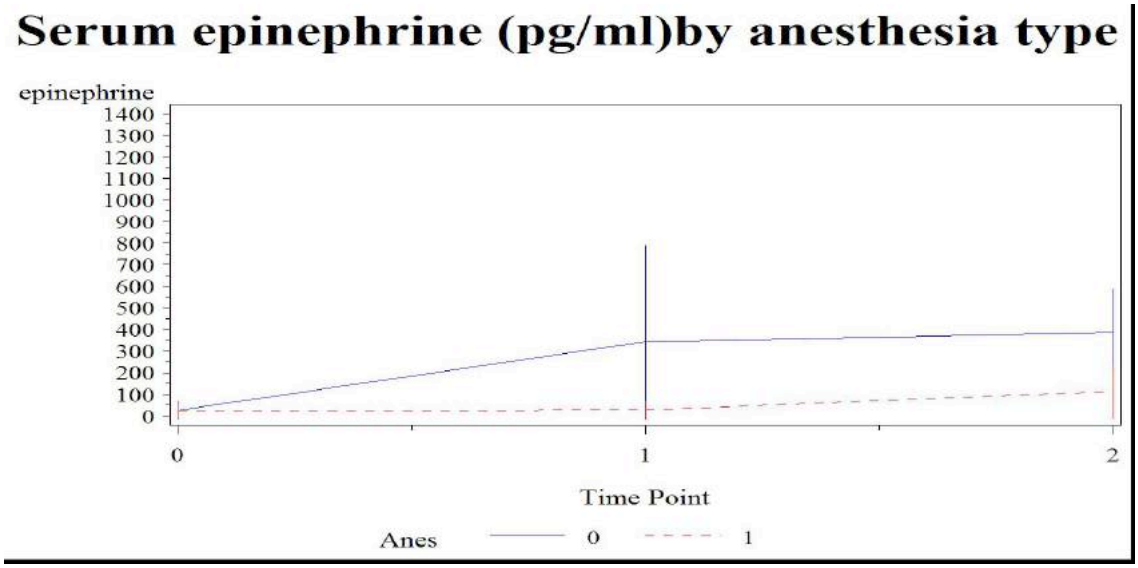
Methods: Patients received baseline cognitive testing and Mini Mental Status Exam (MMSE) and were assigned a standardized maintenance anesthetics. Arm #1: maintenance of anesthesia with sevoflurane and intravenous narcotic. Arm#2: propofol and intravenous narcotic. Postoperatively we administered daily CAM and MMSE. The full cognitive battery will be repeated at 3 and 6 months. Blood collection was performed to determine C and E levels 1) Prior to surgical start 2) Prior to extubation 3)2 hours after surgery.

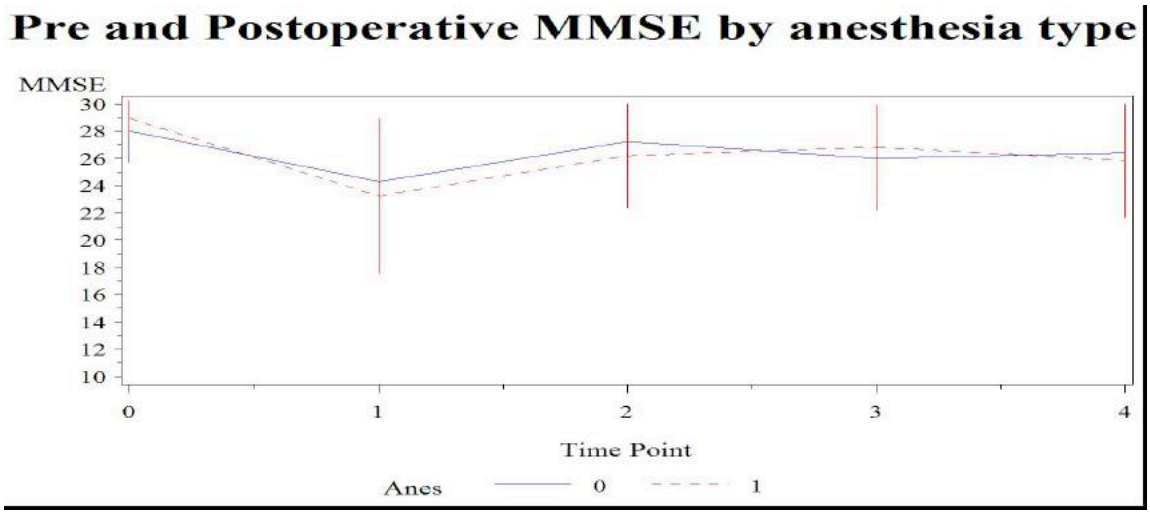
Results: Since September 2011, 24 patients consented and completed the in-hospital portion of the protocol. There was no significant difference between the TIVA and GS groups with respect to ASA status, surgical duration, estimated blood loss, and baseline MMSE (28.1 vs. 28.0, NS). The GS group was significantly older than the TIVA group 78.7 vs. 71.6 ($p<.0012$). MMSE was not different between the two groups at any time point (Fig1). Delirium was observed in 0/8 of GS patients and 5/16 TIVA patients. This trend was not statistically significant ($p =.13$). Peak C and E levels were higher in patients who receive GS (Fig 1).

Discussion: These preliminary results suggest that immediate cognitive recovery is similar between patients undergoing anesthesia with GS vs. TIVA. A greater proportion of patients who received TIVA suffered from postoperative delirium; despite that the TIVA group was significantly younger. While the result was not significant, we anticipate that this strong trend will continue to be evident as the study progresses. C and E levels confirmed results seen in non-age stratified populations. Patients will be reexamined with full cognitive battery at 3 and 6 months to allow us to use more sensitive tools to examine for persistent cognitive dysfunction. We will also analyze our blood samples for ApoE genotype. With this information, we plan to create a logistic model of predictors of delirium including anesthesia type, stress response, Apo E genotype, and procedure type. This will be the first model to look at the relationship between genetics, stress response, anesthesia and delirium.

Figure 1: The geriatric surgical patient: stress, anesthetics, and functional outcomes







Anes 0 (blue)= gas Anes(red)= total intravenous anesthesia

Neuroscience #6 (71)

Subclinical Systemic Inflammation in Obese Patients Prior to Total Knee Arthroplasty (TKA)

Syed Azim, M.D.; James Nicholson, M.D.; Ruth Reinsel, Ph.D.; Mario Rebecchi, Ph.D.; Helene Benveniste, M.D., Ph.D.
Anesthesiology and Orthopedic Surgery, Stony Brook University - Stony Brook, NY

Introduction: Thirty percent of adults are classified as obese with a body mass index (BMI) >30 [1]. High BMI is linked to development of osteoarthritis of the knee [2] and there is a hypothesized association between obesity, inflammation and pain in these patients [3]. Inflammation develops because fat tissue actively produces cytokines such as interleukin 6 (IL-6) and leptin. Leptin, an adipocyte-derived protein hormone also acts as a cytokine and can induce a heightened inflammatory state [4]. The average BMI of TKA patients is reported to be ≥30 and it is likely therefore that these patients present with subclinical inflammation prior to surgery. We conducted a prospective study to test the hypothesis that obese patients (BMI ≥ 30) are characterized by higher levels of IL-6, TNFα and leptin compared to patients with BMI<30 before TKA.

Methods: Our study protocol was approved by the IRB. We enrolled patients scheduled for elective unilateral TKA under spinal anesthesia. Blood samples and cerebrospinal fluid (CSF) were collected at the time of the spinal anesthesia. Quantikine HS immunoassay kits (R&D Systems, Inc, MN) were used to measure the levels of IL-6, TNFα and leptin in the samples according to the manufacturer's instructions.

Results: A total of 20 patients were recruited. Serum and CSF data from 19 patients were available for analysis. The mean BMI of obese versus non-obese patients was 26.9 ± 3.2 (N=5) and 34.8 ± 1.6 (N=14), respectively. The serum concentration of IL-6, [IL-6], was significantly higher in the obese patients compared to non-obese patients (Obese: 2.6 ± 1.3 vs. Non-obese: 1.1 ± 0.8, p=0.03); however there were no CSF [IL-6] group differences. No differences in [TNF-α] were observed between the two groups. The ratio between the concentration of leptin in CSF and serum was calculated and regression analysis demonstrated a negative correlation between [Leptin]CSF:[Leptin]serum and BMI (R2=0.40, p=0.003, Figure 1). Further, [Leptin] in CSF and serum were significantly higher in the obese patients; and the [Leptin]CSF:[Leptin]serum ratio was significantly lower in the obese compared to non-obese patients (p<0.01).

Conclusions: We demonstrated higher serum levels of IL-6 and leptin in addition to higher CSF levels of leptin in obese patients compared to non-obese patients indicating presence of subclinical inflammation prior to surgery. A heightened inflammatory state prior to surgery may adversely affect obese patient's post-operative recovery including pain status and warrants further investigation. We are in the process of following TKA patients' inflammatory state in parallel with pain and functional status post-surgery.

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Neuroscience #7 (80)

Prevalence and Risk Factors for Intraoperative Hypotension During Craniotomy for Traumatic Brain Injury

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Background: Hypotension after traumatic brain injury (TBI) is associated with poor outcomes. However, data on intraoperative hypotension (IH) are scarce and the effect of anesthetic agents on IH is unknown. We examined the prevalence and risk factors for IH, including the effect of anesthetic agents during emergent craniotomy for isolated TBI.

Methods: A retrospective cohort study of patients ≥ 18 years who underwent emergent craniotomy for TBI at Harborview Medical Center (level-1 trauma center) between October 2007 and January 2010. Demographic, clinical and radiographic characteristics, hemodynamic and anesthetic data were abstracted from medical and electronic anesthesia records. Hypotension was defined as systolic blood pressure (SBP) < 90 mmHg. Univariate analyses were performed to compare the clinical characteristics of patients with and without IH and multiple logistic regression analysis was used to determine independent risk factors for IH.

Results: Data abstracted from 113 eligible patients aged 48±19 years was analyzed. Intraoperative hypotension was common (n=73, 65%) but not affected by the choice of anesthetic agent. Independent risk factors for IH were multiple Computed Tomographic (CT) lesions (AOR 19.1 [95% CI: 2.08-175.99]; p=0.009), SDH (AOR 17.9 [95% CI: 2.97-108.10]; p=0.002), maximum CT lesion thickness (AOR 1.1 [95% CI: 1.01-1.13]; p=0.016), and anesthesia duration (AOR 1.1 [95% CI: 1.01-1.30]; p=0.009).

Conclusion: Intraoperative hypotension was common in adult patients with isolated TBI undergoing emergent craniotomy. The presence of multiple CT lesions, subdural hematoma, maximum thickness of CT lesion and longer duration of anesthesia increase the risk for IH.

Clinical Characteristics of Patients With and Without Intraoperative Hypotension (Systolic Blood Pressure < 90 mmHg)

	Intraoperative Hypotension (n= 73)	No Intraoperative Hypotension (n= 40)	p value
Glasgow coma scale score (n=111)	8 ± 4 (3-15)	9 ± 4 (3-15)	0.61
TBI severity			0.62
Mild (13-15)	21	12	
Moderate (9-12)	11	8	
Severe (≤8)	41	18	
Pupil asymmetry (n=40)	29 (40%)	11 (28%)	0.22
ED Hypotension (n=5)	3 (4%)	2 (5%)	1
ED Hypertension (SBP >140 mmHg) (n=93)	59 (81%)	34 (85%)	0.8
ED Tachycardia (heart rate > 100 bpm) (n=43)	27 (37%)	16 (40%)	0.46
ED Bradycardia (heart rate < 60 bpm) (n=37)	22 (30%)	15 (38%)	0.53
ED mannitol (n=58)	40 (55%)	18 (45%)	0.33
CT lesion thickness (mm) (n=88)	25 ± 21 (2-91)	19 ± 13 (2-56)	0.13
CT lesion type			0.02
Subdural hemorrhage (n=70)	50 (68%)	20 (50%)	
Extradural hemorrhage (n=19)	6 (8%)	13 (33%)	
Multiple hemorrhages (n=18)	13 (18%)	5 (13%)	
Intracerebral hemorrhage (n=5)	3 (4%)	2 (5%)	
CT midline shift >5mm	42 (58%)	21 (53%)	0.74
Anesthetic induction agent (n=110)			0.875
Propofol (n=64)	40 (55%)	24 (60%)	
Etomidate (n=4)	3 (4%)	1 (3%)	
Inhalational induction (through tracheal tube) (n=42)	27 (37%)	15 (38%)	
Maintenance Anesthetic agent (n=109)			0.37
Isoflurane (n=37)	22 (30%)	15 (38%)	
Sevoflurane (n=72)	49 (67%)	23 (58%)	
Fentanyl (n=89)	53 (73%)	36 (90%)	0.46
OR Baseline SBP (mm Hg)	129 ± 38 (60-270)	143 ± 28 (90-200)	0.05
OR Baseline Hypertension (SBP>140 mmHg) (n=55)	31 (42%)	24 (60%)	0.08
Intraoperative blood loss (mL) (n=112)	406 ± 346 (75-1800)	553 ± 630 (50-2500)	0.18
Intraoperative mannitol (n=45)	30 (41%)	15 (38%)	0.841
Intraoperative fluid balance (mL) (n=112)	2035 ± 1818 (-600-9150)	2410 ± 1678 (122-6300)	0.2
Anesthesia time (min)	228 ± 70 (128-437)	189 ± 60(93-317)	0.003
In-hospital mortality (n=18, 16%)	14 (19%)	4 (10%)	0.28

Neuroscience #8 (69)

Tetracycline Derivatives Prevent Subarachnoid Hemorrhage From Intracranial Aneurysm Rupture

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Background and Purpose: Pharmacological stabilization of aneurysms for the prevention of aneurysmal growth and rupture may be an attractive alternative approach to surgical or endovascular approaches in a subset of patients with intracranial aneurysms. Recently, we have developed a mouse model of intracranial aneurysm that recapitulates key features of intracranial aneurysms. In this model, subarachnoid hemorrhage from aneurysmal rupture causes neurological signs that can be easily detected by a simple neurological examination (Figure 1). Using this model, we tested whether tetracycline derivatives can prevent the rupture of intracranial aneurysms in mice.

Methods: Aneurysms were induced by a combination of hypertension and a single injection elastase into the cerebrospinal fluid in mice. Treatment with vehicles, minocycline, doxycycline, or SB-3CT was started one week after aneurysm induction. Aneurysmal rupture was detected by neurological symptoms and confirmed by presence of intracranial aneurysm with subarachnoid hemorrhage.

Results: Minocycline and doxycycline were able to reduce rupture rates (mice with ruptured aneurysms / mice with any aneurysms) (vehicle vs. doxycycline = 80 vs. 35%, $P < 0.05$; vehicle vs. minocycline = 73 vs. 24%, $P < 0.05$) without affecting the total incidence of aneurysms (Figure 2 and Figure 3). However, SB-3CT, a selective inhibitor against MMP-9 and MMP-2, was not able to reduce the rupture rate (62 vs. 55%, $P = 0.53$) (Figure 4).

Conclusions: It was feasible to use a mouse model of intracranial aneurysms to test pharmacological prevention of aneurysmal rupture. Tetracycline derivatives, doxycycline and minocycline, may be able to prevent aneurysmal rupture by blocking inflammation or matrix metalloproteinases.

Figure 1. Representative unruptured and ruptured intracranial aneurysms

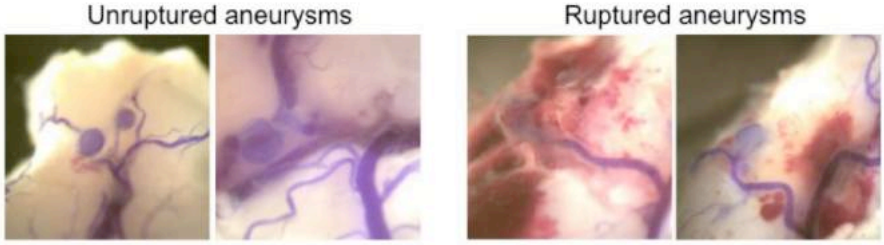


Figure 2. Protective effects of minocycline against aneurysmal rupture

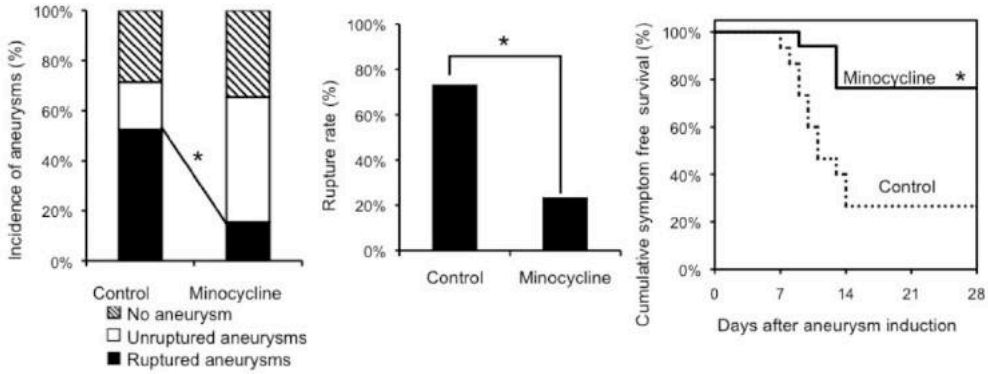


Figure 3. Protective effects of doxycycline against aneurysmal rupture

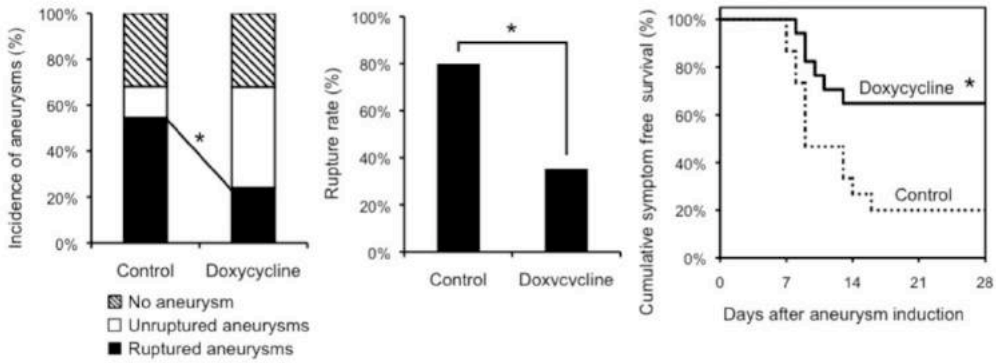
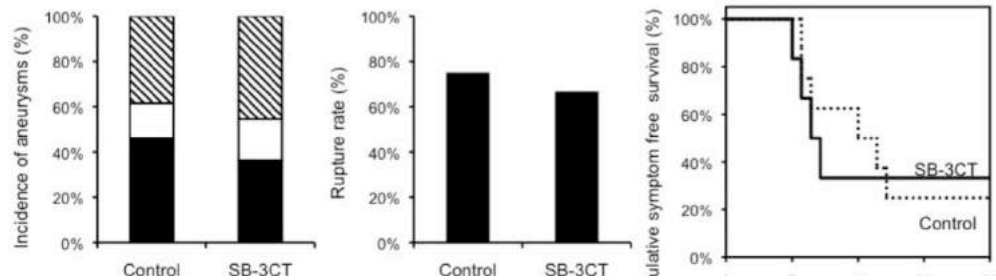


Figure 4. SB-3CT, a selective inhibitor for MMP-9 and MMP-2 did not prevent aneurysmal rupture.



Neuroscience #9 (37)

Connectivity, rCBF & GABA Level Under Propofol Anesthesia (2 μg/mL) – MRI MRS Study in Volunteers

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Introduction: Magnetic Resonance Imaging and Spectroscopy (MRI & MRS) are powerful imaging tools for measuring the subjective effects of anesthesia. Regional CBF (rCBF) measurement reflects the alteration in neuronal activity induced by anesthesia in specific regions of the brain, while functional connectivity (Fc) measures the internal organization of the brain in the resting state. It is also known that Propofol acts by augmenting GABA agonist activity at the synaptic level. In our previous studies with 0.5 MAC Sevoflurane we have demonstrated non-uniform change in rCBF with altered Fc in the higher order regions1. Our aim in this protocol was to study the effect of Propofol (0.5 MAC equivalent - 2 μg/mL plasma level) on rCBF, Fc and GABA level (thalamus). Our hypothesis was Propofol 2 μg/mL will:
1) Decrease the rCBF in the frontal cortex and thalamus
2) Decrease the Fc in the higher order regions
3) Increase the GABA level in the Thalamus

Methods: The study protocol was approved by the Yale University IRB. ASA 1 volunteers in the age group of 19 to 30 years were the subjects studied.

Anesthesia: Subjects fasted for 8 hours before the study. Anesthesia protocol included ASA monitors, 2 IV's (one for injecting Propofol and one for drawing blood sample for Propofol assay). Propofol was administered using a Stanpump (Marsch protocol) linked to a Harvard 22 syringe pump and the target plasma level was 2 μg/mL.

Imaging: Two cycles of imaging was carried out – awake and anesthesia. In each cycle the resting-state BOLD (blood oxygen level dependent contrast – qualitative measure of neuronal activity), rCBF (pulsed arterial spin labeling technique – PASL) and GABA, glutamate level (1H MR spectroscopy) was measured. GABA, glutamate was measured in the thalamus (30mm x 30mm x 30mm volume). Imaging was carried out in a 3 Tesla Siemens Trio.

Data Analysis: Data from all the subjects was co-registered in a common standard stereotactic skull image (Talairach). Connectivity (Fc) was measured by identifying the low frequency oscillations in the resting-state BOLD (< 0.08 Hz) and the intrinsic connectivity contrast (ICC) technique. rCBF data in the awake state and anesthesia was averaged across all subjects, change in rCBF (δ CBF) was calculated and a voxel based SPM map was generated. Voxels with significant change in rCBF with Propofol were identified using a Talairache atlas. The difference in GABA, glutamate level between the awake state and anesthesia was calculated.

Results: Clinically 30 / 32 subjects were sleeping (OAAS score ≤ 2 – no response to call) and no one remembered any of the events during the imaging.
1) rCBF decreased in most of the regions (frontal, parietal, occipital and temporal lobes and thalamus). In the anterior cingulate, insula and parahippocampal gyrus there was a modest rise in rCBF.
2) Connectivity (Fc) pattern was variable under Propofol. Fc did not change in the thalamus and posterior cingulate while in the cortex there were regions with increase as well as decrease in connectivity. In the anterior cingulate Fc increased while in the insula and pre frontal cortex Fc decreased.
3) There was a significant increase in GABA level in the thalamus with Propofol while glutamate change was not significant.
4) While the target Propofol level was 2 μg/mL actual level fell short in most subjects (up to 40% less)

Discussion: At 2 μg/mL plasma level there is a significant rise in GABA level in the thalamus, with decrease in rCBF in most regions including the thalamus. However Fc was not altered in the thalamus (as was observed with 0.5 MAC sevoflurane also) and in the posterior cingulate (locus for DMN - default mode connectivity).

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Poster Presentation Abstracts

Obstetrics

Obstetrics #1 (68) **The Effect of Perioperative Intravenous Lidocaine and Ketamine on Recovery After Hysterectomy**

Martin V. Grady, M.D.; Edward J. Mascha, Ph.D.; Daniel I. Sessler, M.D.; Andrea Kurz, M.D.
Cleveland Clinic

Obstetrics #2 (54) **Targeting Uterine Smooth Muscle TMEM16 Calcium Activated Chloride Channels to Suppress Oxytocin Induced Contractions and Calcium Handling**

George Gallos, M.D.; Hiromi Funayama, D.D.S., Ph.D.; Matthew Siviski, B.S.; Xiao W. Fu, Ph.D.; Richard M. Smiley, Ph.D., M.D.; Charles W. Emala, M.D.
Columbia University

Obstetrics #1 (68)

The Effect of Perioperative Intravenous Lidocaine and Ketamine on Recovery After Hysterectomy

Martin V. Grady, M.D.; Edward J. Mascha, Ph.D.; Daniel I. Sessler, M.D.; Andrea Kurz, M.D.
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Introduction: Previous work suggests perioperative intravenous ketamine infusion reduces postoperative pain and that perioperative intravenous lidocaine infusion reduces postoperative narcotic consumption, speeds recovery of intestinal function, improves postoperative fatigue, and shortens hospital stay. But whether perioperative intravenous lidocaine and/or ketamine infusion enhances acute functional recovery remains unknown. We therefore tested the primary hypothesis that perioperative intravenous lidocaine and/or ketamine infusion in patients undergoing open abdominal hysterectomy improves acute rehabilitation as measured by a six-minute walk distance (6-MWD) on postoperative day 2 (POD2).

Methods: With IRB approval, we enrolled patients between the ages of 18 and 75 years who were having elective laparotomy abdominal hysterectomy or uterine myomectomy surgery with general anesthesia. Patients were anesthetized with midazolam, propofol, fentanyl, rocuronium and sevoflurane in air/oxygen, followed by PCA morphine for postoperative analgesia. Patients were factorially randomized to one of four groups: 1) lidocaine and placebo; 2) placebo and ketamine; 3) placebo and placebo; and, 4) lidocaine and ketamine. Lidocaine was given as a bolus (1.5 mg/kg) just before skin incision, followed by an infusion of 2 mg/kg/h for the first 2 hours and then 1.2 mg/kg/h until 24 hours after surgery. Ketamine was given as a bolus (0.35 mg/kg) just before skin incision, followed by ketamine infusion of 0.2 mg/kg/h for the first 2 hours and then 0.12 mg/kg/h until 24 hours after surgery. The study was completely double blinded. The primary outcome was 6-MWD on POD2; secondary outcomes included pain scores, opioid consumption, PONV, and fatigue score.

Results: We conducted a pre-planned interim analysis after 64 patients were enrolled (half the planned number) assessing simultaneously the effect of lidocaine versus placebo and ketamine versus placebo and the interaction between lidocaine and ketamine on 6-MWD. The results for lidocaine crossed the pre-planned futility boundary; the results for ketamine did not cross either the futility or efficacy boundary, but trended towards harm. The Executive Committee thus stopped the trial. No interaction effect was observed between lidocaine and ketamine. There were no statistically significant differences in any of the secondary outcomes between the lidocaine and non-lidocaine groups, or between the ketamine and non-ketamine groups.

Discussion: Our results contrast with previous studies in which lidocaine and ketamine reportedly improved postoperative pain scores, opioid consumption, and fatigue scores. These results in hysterectomy surgery may differ because previous studies were in larger operations such as colon resection, radical prostatectomy, and thoracic surgery. Our results do not support the use of adjuvant lidocaine or ketamine in patients having open abdominal hysterectomy.

Table 2. Effects of IV Lidocaine and Ketamine interventions on primary outcome of 6-minute walk distance, in meters, on the second postoperative morning *

Factor	Mean ± SD (m)	Difference (97.5% CI) †	*P* value †
Lidocaine (N = 31)	205 ± 65 [a]	-0.16 (-41, 41)	0.99
Non-Lidocaine (N = 31)	202 ± 73 [a]		
Ketamine (N = 30)	195 ± 77 [b]	-18 (-58, 23)	0.32
Non-Ketamine (N = 32)	210 ± 61		

* Data are presented as means ± SD

† Analysis of covariance adjusted for baseline 6-minute walk distance; all 62 patients included in the model based on modified-intent-to-treat; interaction *P* value between the two intervention effects = 0.96; significant if $P < 0.003$ for efficacy and $P > 0.5311$ for futility; 97.5% confidence intervals adjusted for group sequential design (using confidence coefficient of 2.97) to maintain the overall alpha of 0.025 for each intervention and 0.05 for the trial.

[a and b] N = 1 and 2 missing data

Obstetrics #2 (54)

Targeting Uterine Smooth Muscle TMEM16 Calcium Activated Chloride Channels to Suppress Oxytocin Induced Contractions and Calcium Handling

George Gallos, M.D.; Hiromi Funayama, D.D.S., Ph.D.; Matthew Siviski, B.S.; Xiao W. Fu, Ph.D.; Richard M. Smiley, Ph.D., M.D.; Charles W. Emala, M.D.
Columbia University

Background: Pre-term labor is a major health challenge that is associated with high maternal and fetal morbidity. Since the pharmacologic armatarium for treating pre-term labor has limited efficacy, novel mechanisms capable of promoting uterine smooth muscle relaxation may be clinically valuable to suppress pre-term labor. Although previous work has suggested the importance of calcium activated chloride flux in the generation of uterine smooth muscle contraction, not until recently has the molecular identification of the receptor family been confirmed to be the TMEM16 family of proteins. We questioned whether the TMEM16 family of receptors was expressed in human uterine smooth muscle cells, and whether selective blockade of this receptor could attenuate oxytocin induced calcium release and result in functional inhibition of spontaneous (stretch-induced) uterine contractions.

Methods: Following IRB approval, samples of pregnant human myometrium were obtained during C-section and processed for mRNA isolation. Commercially obtained human cultured primary airway smooth muscle cells were also processed for mRNA in parallel, and subjected to RT-PCR analysis for TMEM A and B isoforms. Primary human airway smooth muscle cells were loaded with Fura-2 and the ability of pharmacologic blockade of the TMEM receptor (tannic acid) on subsequent oxytocin-induced calcium release was assessed. To assess the functional implications of TMEM16 blockade on uterine contractions, we performed organ bath experiments on excised murine uterine segments examining the effect of niflumic acid (100uM) on subsequent stretch-induced contraction frequency. Where appropriate data is presented as mean ± SEM; $p < 0.05$ in all cases was considered significant.

Results: RT-PCR demonstrates mRNA encoding TMEM16 A and B isoforms in primary human uterine smooth muscle cell cultures as well as from human uterine tissue obtained at C-section. Pretreatment with the TMEM16 A and B receptor blocker (tannic acid 100uM) attenuated oxytocin-(1uM) induced calcium release (0.097 +/- 0.02 RFU; n=15) compared to vehicle controls (0.521 +/- 0.03 RFU; n=5; $p<0.001$). Additionally, TMEM16 blockade during spontaneous uterine contractions demonstrated a decrease in subsequent contractile frequency (7 +/- 1.0 peaks/15min; n=2) compared to both untreated and vehicle treated controls (12.0 +/- 0.6 peaks/15min; n=4; and 11.5+/- 0.5 peaks/15min; n=2) respectively(Figure 1).

Conclusion: Messenger RNA encoding TMEM16 A and B is expressed in human pregnant tissue and non-pregnant human primary uterine smooth muscle cells. Blockade of TMEM16 A and B attenuates oxytocin-induced calcium release and suppresses spontaneous uterine contractions. Targeted blockade of endogenous TMEM16 receptors may represent a novel therapeutic option for patients in pre-term labor.

Poster Presentation Abstracts

Pain

Pain #1 (48)

Exploration of the Functional Connectivity Differences Between Pain and Resting States

James W. Ibinson, M.D., Ph.D.[1]; Shiv Dua, B.S.[2]; Fernando E. Boada, Ph.D.[1]; Gerald F. Gebhart, Ph.D.[1]
The University of Pittsburgh[1]; George Washington University[2]

Pain #2 (15)

Usefulness of the Opioid Risk Tool to Predict Aberrant Drug-Related Behavior in Patients Receiving Opioids for the Treatment of Chronic Pain

Dina Diskina; Michael A. Ashburn, M.D., M.P.H.; Lisa R. Witkin, M.D.; Shawn Fernandes; John Farrar, M.D., Ph.D.
Perelman School of Medicine, The University of Pennsylvania

Pain #3 (31)

Junior Faculty Award

An Engineered Water Soluble Variant of Human MU Receptor

Renyu Liu, M.D., Ph.D.; Jose M. Perez-Aguilar, Ph.D.[1]; Jin Xi, M.S.[2]; Xu Cui, M.D., Ph.D.[2]; Min Li, M.D.[2]; Jeffery G. Saven, Ph.D.[1]
Department of Chemistry[1]; Department of Anesthesiology and Critical Care[2]; University of Pennsylvania

Pain #4 (52)

Time Course and Potency of the Novel KCC2 Inhibitor D4

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Vanderbilt University Medical Center

Pain #5 (63)

Impact of Epineurium on Minimum Stimulation Threshold Current During Ultrasound-Guided Subgluteal Sciatic Nerve Block

Antoun Nader, M.D.; Yogen Asher, M.D.
Department of Anesthesiology, Northwestern University, Feinberg School of Medicine

Pain #1 (48)

Exploration of the Functional Connectivity Differences Between Pain and Resting States

James W. Ibinson, M.D., Ph.D.[1]; Shiv Dua, B.S.[2]; Fernando E. Boada, Ph.D.[1]; Gerald F. Gebhart, Ph.D.[1]
The University of Pittsburgh[1]; George Washington University[2]

Introduction: Functional magnetic resonance imaging (FMRI) investigations of pain have provided substantial insight into the workings of the human brain(1). An emerging technique is the use of "functional connectivity", which identifies areas of the brain that co-vary with each other as a surrogate marker for neuronal interconnections. Functional connectivity has shown that different patterns of connectivity can be seen is several disease states, including diabetic neuropathic pain(2) and temporomandibular disorder(3). These two studies, however, show opposite changes in connectivity between the anterior cingulate cortex (ACC) and the insula, an area involved in both the lateral and medial aspects of the pain matrix and thus well suited to serve as the seed area of choice in pain studies(4). Direct comparisons of functional connectivity during pain processing and at rest in normal volunteers have not been adequately explored, but may provide some insight in this controversy.

Materials and Methods: In an IRB approved study, transcutaneous electrical nerve stimulation to the right index finger was used on 15 healthy volunteers to create 2 different painful stimulations: a block design that repeated 30 seconds of painful stimulation with 30 seconds of rest 4 times (Pain 1), and a constant 2 minute stimulation (Pain 2). These sessions were separated by 4 minutes of rest. Additionally, a 4 minute rest period preceded any painful stimulation. Whole brain FMRI images were collected with a 3 T scanner. Using the contralateral insula as a seed region, the functional connectivity patterns were found (FSL software, www.fmrib.ox.ac.uk/fsl) and compared across pain tasks.

Results: Connectivity maps showing areas that covaried with the contralateral insula were generated for all three conditions and showed connections between the insula and most of the pain matrix. The parameter estimates of the connectivity were qualitatively larger with Pain 1 when compared to Pain 2, however, a statistical analysis failed to find any difference between the two. Comparisons of the resting state with the two pain states suggests that connectivity to the ACC may significantly increase during pain processing, but the result is not consistent with all subjects and needs to be further investigated.

Discussion: Researchers are hoping that by applying functional connectivity analysis to patients with chronic pain syndromes, we will be able to gain a better understanding of the brain's role in chronic pain. However, this technique is still new and differences in the connectivity patterns between the resting and painful states in normal volunteers has not been thoroughly investigated. This study suggests that the "connectivity" of a key pain area, the ACC, increases as a result of painful stimulation in normal subjects, although this finding is still preliminary and requires further investigation into its repeatability and dependence on subject factors.

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Pain #2 (15)

Usefulness of the Opioid Risk Tool to Predict Aberrant Drug-Related Behavior in Patients Receiving Opioids for the Treatment of Chronic Pain

Dina Diskina; Michael A. Ashburn, M.D., M.P.H.; Lisa R. Witkin, M.D.; Shawn Fernandes; John Farrar, M.D., Ph.D.
Perelman School of Medicine, The University of Pennsylvania

Objectives: The primary objective of this study was to determine if the Opioid Risk Tool (ORT) is predictive of aberrant drug-related behavior (ADRB) in patients receiving opioids for the treatment of chronic non-cancer pain, and if there was a difference between the patient self-administered or physician answered ORT based on the history and prior medical records.

Design: This is a descriptive study using a single-center retrospective review of prospectively collected data.

Setting: Academic tertiary care outpatient pain management clinic

Patients: One hundred and twenty five chronic pain patients who had been consented, received opioids as part of their therapy, and were followed for a minimum of 3 months with a minimum of 2 clinic visits were included in the study. Of these, a physician-completed ORT was available for 125 patients, and a patient-completed ORT was available on 87 patients.

Interventions: As part of an outcomes data collection program, all patients were requested to complete the ORT at the time of the initial visit. A member of the health care team also completed the ORT for each patient based on information from the patient and outside medical records available on the day of the initial visit. Data were collected about patient demographics, pain location and diagnosis, and specific medication therapy. The medical records available at the Pain Center were then reviewed and analyzed for evidence of ADRB following the institution of chronic opioid therapy, according to set criteria based on information obtained from periodic urine drug screens (UDS) and from physician notes.

Main Outcome Measure: The primary study outcome measure the presence of moderate to severe aberrant drug-related behavior associated with the administration of chronic opioids for the treatment of pain.

Results: Of the 125 patients included in this study, 87 completed an ORT at the time of the initial visit, and a physician-completed ORT based on data available at the time of the initial visit was completed for all 125 patients. Based on the physician-completed ORT, 106 (84.8%) were determined to be at low risk (score 0-3), 14 (11.2%) were medium risk (ORT score 4-7), and 5 (4%) were high risk (ORT score ≥ 8). There was good correlation between the patient-completed and physician-completed ORT (correlation coefficient = 0.61). During the observation period, patients received chronic opioids for an average of 7.8 months (range 2 – 17 months). Moderate to severe aberrant drug-related behavior was identified in 53 of 125 patients (42.1%). Based on the physician-completed ORT, 41 of 106 (38.7%) who were low risk had ADRB, 8 of 14 (57.1%) who were moderate risk had ADRB, and 4 of 5 (80% who were high risk had ADRB. The patient-completed ORT was not strongly predictive of moderate to severe ADRB (OR=1.03).

Conclusion: Neither the patient-completed or physician-completed ORT was predictive of moderate to severe aberrant drug-related behavior in patients receiving chronic opioid therapy for the treatment of pain in our pain center.

Pain #3 (31)

Junior Faculty Award

An Engineered Water Soluble Variant of Human MU Receptor

Renyu Liu, M.D., Ph.D.; Jose M. Perez-Aguilar, Ph.D.[1]; Jin Xi, M.S.[2]; Xu Cui, M.D., Ph.D.[2]; Min Li, M.D.[2]; Jeffery G. Saven, Ph.D.[1]
Department of Chemistry[1]; Department of Anesthesiology and Critical Care[2]; University of Pennsylvania

Background: Despite of addiction, lethal respiratory depression, and countless other side effects, the therapeutic use of opioids has soared worldwide(1). The μ opioid receptor (MUR) is the major target of opiates and is linked to most of the notorious side effects. Studying the structure function relationship (SFR) of the MUR is limited because it is an intrinsic membrane protein and lacks high resolution structural data. Here, we present a water soluble variant of human μ receptor (WSMUR) over-expressed in E-coli system as a potential novel tool for further SFR studies.

Methods: While water soluble variants of membrane proteins have been successfully engineered in our group using published structures as templates(2), no crystal structure of μ- receptor is available. A comparative (homology) model of the human mu-receptor (P35372) was built as an alternative starting point using the structure of β2-adrenergic receptor (2RH1)(3) and bovine rhodopsin (1U19)(4) since they belong to the Class A G-protein coupled receptor family. The WSMUR was then engineered by redesigning highly exposed hydrophobic residues on the surface of transmembrane domain with hydrophilic residues in a manner consistent with the model structure. The WSMUR model was then evaluated with molecular dynamic simulation in an aqueous environment and with a docking algorithm (Autodock). The protein was: expressed in an E. coli system and purified. WSMUR was characterized using electrophoresis, mass-spectrometry, dynamic light scattering, circular dichroism (CD), and a time resolved fluorescence based opioid binding assay.

Results: During a 200 ns (300 K) molecular dynamic simulation, WSMUR retained its initial structure similar to the (Figure 1A). Agonists and antagonists were docked into the model with the results in agreement with the published mutagenesis studies. The protein was successfully expressed in E-coli with high yield, purified and the sequence confirmed using mass-spectrometry. The solubility of the protein was more than 5 mg/ml in sodium phosphate buffer. The CD spectra indicated that WSMUR is predominantly alpha helical (Figure 1B: 47% alpha helical, 15% beta turn, and 24% random coil), which is consistent with the secondary structure of the native protein. The CD spectra are invariant over a wide range of pH (6~9). Dynamic light scattering studies indicated that WSMUR is predominantly a monomer (93% of the mass). The affinity of WSMUR with naltrexone is 53 ± 16 nM (mean ± SD) as indicated in figure 1C, which is close to that of its native protein (around 8nM).

Conclusions: A WSMUR was engineered, over-expressed, purified and characterized. Results so far find it to be consistent with existing structural and binding information. This provides a potential novel tool to further investigate the SFR for human MUR.

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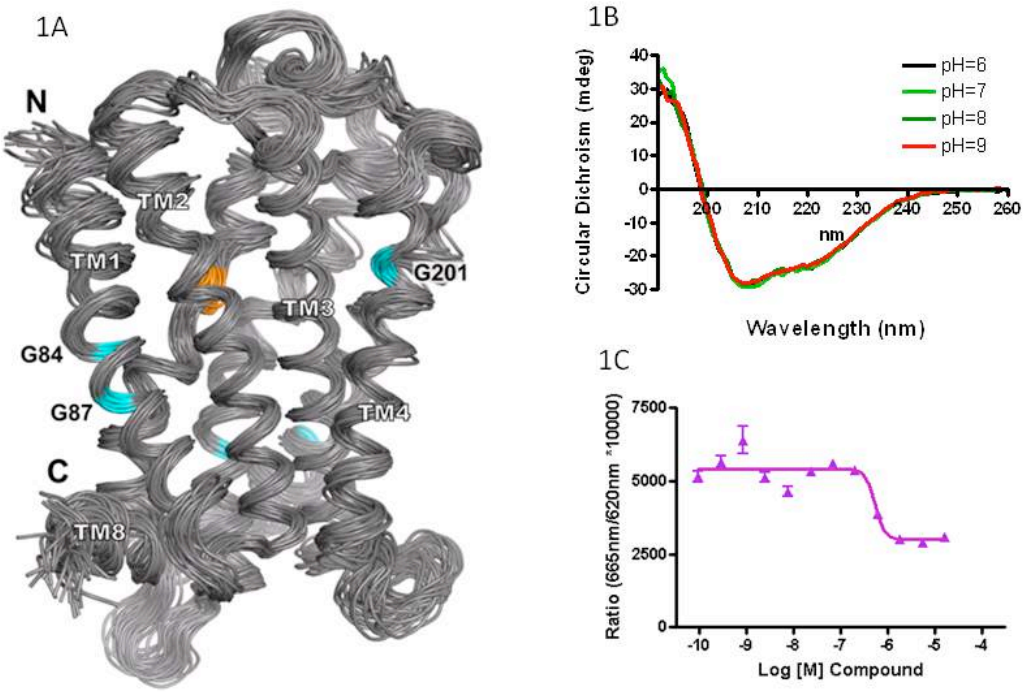

Figure 1 A presents a view of 50 superimposed structures of the engineered water soluble variant of human μ receptor (WSMUR) from the last 50 ns of 200 ns molecular dynamics simulation in an aqueous environment. The structures remain dominantly alpha helical and did not deviate significantly from their initial structure. Figure 1B demonstrates the secondary structure of the expressed and purified WSMUR which is dominantly alpha helical in the buffer (20 mM NaHPO4, pH 7.0). Figure 1C demonstrates the affinity of naltrexone to the WSMUR is 53 ± 16 nM .

Pain #4 (52)

Time Course and Potency of the Novel KCC2 Inhibitor D4

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Background: KCC2, a neuronal-specific K-Cl cotransporter, is involved in pain perception physiology through its effects on postsynaptic inhibition in spinal cord neurons. Several studies have demonstrated that decreased KCC2 expression in the spinal cord is associated with increased pain perception (1, 2). In this study, we injected a newly identified, highly potent and selective inhibitor of KCC2 (D4) intrathecally into a cohort of mice to measure its effect on heat-evoked nociceptive responses. These tests were performed with different concentrations of the test drug and at various time points to assess the drug's potency and duration, respectively.

Methods: Commercially available intrathecal catheters were modified and surgically placed into a cohort of 10 mice. After recovery from the procedure, the mice were injected with D4 using this catheter. Nociceptive measurements (hotplate assays at 55oC) were performed at 20, 50, 80, 110, 170, and 290 minutes after intrathecal injection of the test drug at a concentration of 20 μM and compared with vehicle controls. Next, to assess the potency of D4 in vivo, we diluted the compound to reach final concentrations of 10, 5, 2.5, and 1 μM. Again, latency to respond to a 55oC heat stimulus was measured 50 minutes after intrathecal injection of D4 at these concentrations.

Results: Two mice in the cohort were omitted because of postprocedure complications. There was a statistically significant decrease ($P < 0.05$) in withdrawal latency after D4 injection at the 50, 80, and 110 minute time points (Figure 1). The D4 effect was no longer observed after 3 and 6 hours. D4 significantly decreased withdrawal latency ($P < 0.01$) at concentrations ranging from 2.5 μM to 20 μM. There was no statistical difference at 1 μM.

Conclusions: Inhibition of KCC2 by D4 led to decreased heat-evoked withdrawal latency in mice as measured by hot plate assay at 55oC. D4 is a highly potent KCC2 inhibitor and produces its effect at concentrations as low as 2.5 μM after intrathecal injection. With the isolation of this novel KCC2 inhibitor, we now have the ability to verify the contribution of KCC2 to the nociceptive phenotype of certain genetically modified mice.

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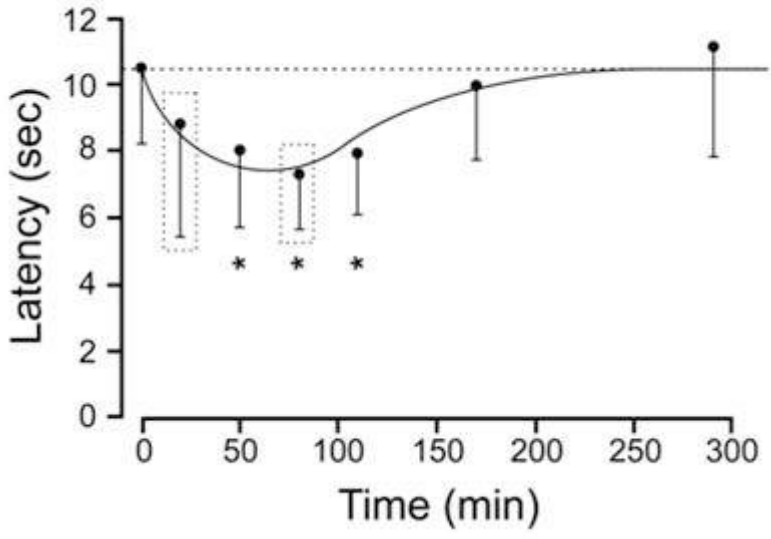

Pain #5 (63)

Impact of Epineurium on Minimum Stimulation Threshold Current During Ultrasound-Guided Subgluteal Sciatic Nerve Block

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Introduction: The minimum threshold current (MTC) that evokes a desired evoked motor response (EMR) is frequently sought for sciatic nerve localization. MTCs ranging from 0.14 to 0.46 mA have been reported in studies evaluating sciatic nerve analgesia.1-4 With the availability of echogenic needles it is possible to visualize the position of the needle tip relative to the epineurium. We evaluated the relation between the needle tip and MTC required to elicit an evoked motor response with the needle tip external and internal to the epineurium of the sciatic nerve.

Methods: After IRB approval, eighty-seven patients undergoing knee replacement were recruited to participate. A 21 g echogenic stimulating needle connected to the negative lead of the nerve was directed toward the sciatic nerve using a subgluteal approach. The needle tip was directed toward the medial component of the sciatic nerve under ultrasound visualization until indentation of the epineurium was visualized and the MTC recorded. The needle was then advanced into the sub-epineurium space, between the components of the sciatic nerve, and the MTC determined. To verify sub-epineurium injection, the spread of local anesthetic was observed. Patients were followed until the resolution of the block and were contacted by phone at 2 weeks and at one month to evaluate neurological symptoms. All patients were examined for neurological deficits at one month following surgery using a calibrated filament. Minimum current thresholds were compared using a paired t-test. Cumulative probabilities densities for extra and sub-epineurium minimal thresholds were calculated.

Results: The mean MTC for extra epineurium stimulation was 0.52 ± 0.16 mA (95% CI 0.48-0.55) compared to 0.20 ± 0.09 mA (95% CI 0.18-0.22) in the sub-epineurium. The mean difference from extra to sub-epineurium was 0.32 ± 17 mA (95% CI 0.28-0.35). The lower 5% interval of the MTC of the outside epineurium was between 0.22-0.24 mA. The upper 5% interval of the MTC of the inside epineurium was between 0.16-0.22. The highest mA recorded inside the epineurium was 0.44mA while the lowest mA achieved outside the epineurium was 0.18mA. All blocks produced motor and sensory anesthesia. One patient reported transient neurological symptoms beyond one month which resolved by 11 weeks.

Discussion: Traversing the epineurium of the sciatic nerve substantially decreased the MTC needed to obtain an EMR, suggesting that MTC <0.22 mA is likely associated with subepineural positioning. Subepineural injections may be preferred for sciatic nerve block to reduce onset time and increase block success. Similar to previous studies we did not observe an increased incidence of long-term clinical sequelae following subepineural injection.

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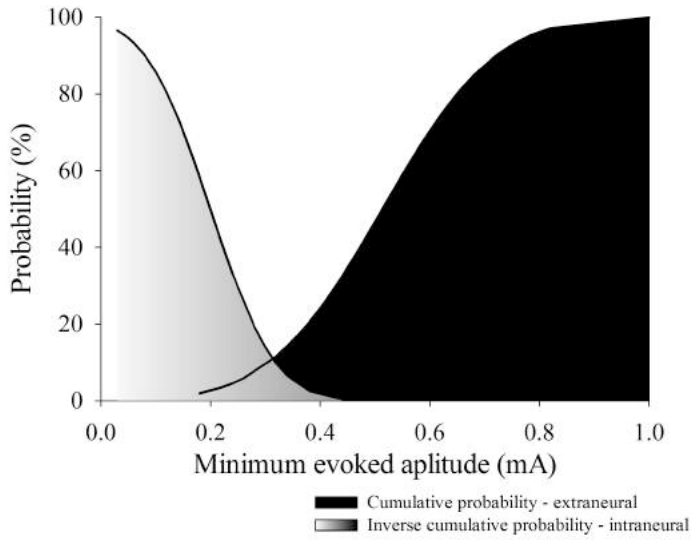

Poster Presentation Abstracts

Pediatrics

Pediatrics #1 (13) **Effect of High Body Mass Index on Early Post-Tonsillectomy Pain in Children**

Olubukola O. Nafiu, M.D.; Amy Shanks, M.S.; Theodore T. Tremper
University of Michigan, Ann Arbor, Michigan

Pediatrics #2 (76) **Hemodynamic Slow Waves Induced With PEEP Oscillation to Measure Cerebrovascular Reactivity**

Ken Brady, M.D.[1]; Kathleen Kibler, B.S.[1]; David Kaczka, M.D.[2]; Dean Andropoulos, M.D.[1]; Blaine Easley, M.D.[1]; Craig Rusin, Ph.D.[1]
Texas Children's Hospital, Baylor College of Medicine[1]; Harvard Medical School[2]

Pediatrics #3 (34) **Objective Measure of Caudal Block: A Neural Blockade Monitor in Children**

Jessica A. George, M.D.[1]; Wayne I. Sternberger, Ph.D.[1,2]; John Gearhart, M.D.[1,3]; Robert S. Greenberg, M.D.[1,4];
Johns Hopkins University[1], Applied Physics Laboratory[2], Pediatric Urology[3], Pediatric Anesthesiology[4]

Pediatrics #1 (13)

Effect of High Body Mass Index on Early Post-Tonsillectomy Pain in Children

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University of Michigan, Ann Arbor, Michigan

Introduction: Obesity is associated with several acute and chronic disorders in adults and children (1,2). An emerging body of evidence also indicates that obesity is associated with heightened postoperative pain experience in adults (3,4). Mechanisms underlying these differential pain experiences are still unclear. Tonsillectomy and adenoidectomy (T&A) are among the most commonly performed operations in children and it is often associated with moderate to severe postoperative pain. Risk factors for post-tonsillectomy pain (PTP) have not been comprehensively characterized and no study to date has assessed the possible role of obesity as a risk factor for PTP.

Objective: The purpose of this investigation was to determine whether there is an association between high body mass index (BMI) in children and the occurrence of early post-tonsillectomy pain (PTP). The hypothesis tested was that high body mass index (BMI) increases severity of early PTP.

Methods: Using a retrospective cohort study design, we extracted data on all children aged 3-17yr that underwent adeno-tonsillectomy (T&A) over a two-year period from our anesthesia clinical information system. Patients were classified into normal or high BMI groups using age and sex-specific BMI chart. Post-tonsillectomy pain scores were then compared between the groups. Clinically significant (moderate-severe) early PTP was defined as pain score ≥ 5 within the first 15min of admission to the post anesthesia care unit (PACU).

Results: Among 462 patients, 35.1% were overweight or obese. This group included a higher proportion of older children the majority of whom were female. The overall incidence of moderate to severe early PTP was 21%. All the patients received at least one or more intraoperative opioid (morphine 94.2% and fentanyl 21.9%). Compared to those in the normal BMI group, children with high BMI had significantly higher unadjusted odds of having moderate-severe early post-tonsillectomy pain (48.9% vs. 14.1%, OR = 7.01, 95% CI =3.9-12.8, $p<0.001$). Of note, total intraoperative morphine dose was higher in children with moderately severe PTP (3.3±2.4mg vs. 2.1±1.5mg; $p<0.001$). After controlling for several clinically relevant covariates, high BMI was the most consistent risk factor for moderate to severe PTP in this cohort of children (Fig 1).

Conclusion: These results indicate that overweight and obese children suffer a worse PTP experience than their lean peers. The mechanism(s) underlying this differential pain experience deserve further elucidation.

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Pediatrics #2 (76)

Hemodynamic Slow Waves Induced With PEEP Oscillation to Measure Cerebrovascular Reactivity

Ken Brady, M.D.[1]; Kathleen Kibler, B.S.[1]; David Kaczka, M.D.[2]; Dean Andropoulos, M.D.[1]; Blaine Easley, M.D.[1]; Craig Rusin, Ph.D.[1]
Texas Children's Hospital, Baylor College of Medicine[1]; Harvard Medical School[2]

Background: The Pressure Reactivity Index (PRx) is a correlation between arterial blood pressure (ABP) and intracranial pressure (ICP). PRx is useful to identify cerebral perfusion pressures (CPP) associated with cerebrovascular autoregulation, and favorable outcome after trauma. Precision of the PRx is rate limiting and due to variable spontaneous low frequency hemodynamic activity. We sought to improve PRx precision by causing a fixed-frequency ABP oscillation by varying positive end-expiratory pressure (PEEP). We hypothesized that PRx precision would improve with induced low-frequency ABP waves (iPRx), and that iPRx precision would be replicated by analysis of the phase angle difference between ABP and ICP at the input frequency ($\Delta\phi$AI).

Methods: Anesthetized neonatal swine (n=10) with ABP, ICP, and intracranial laser-Doppler monitors were ventilated with PEEP at 5 cmH2O, and then with PEEP that oscillated between 5 and 10 cmH2O over a 60-second period. The PRx was recorded as a moving correlation coefficient between ABP and ICP from spontaneous slow wave activity (0.05 – 0.003 Hz), during static PEEP. The iPRx was similarly recorded with oscillating PEEP. $\Delta\phi$AI was recorded as the phase angle difference between ABP and ICP at the PEEP oscillation input frequency. Precision measurements of the PRx, iPRx, and $\Delta\phi$AI were done as [standard deviation]/[range of possible values] (S.D./RPV). ABP was reduced by hemorrhage. Accuracy of the iPRx and $\Delta\phi$AI were assessed after averaging in 5mmHg bins of CPP and dichotomizing above and below the lower limit of autoregulation (LLA). LLA was determined using laser-Doppler scatter plots across CPP at the intersection of two best-fit lines.

Results: PEEP oscillation increased the precision of autoregulation monitoring. S.D./RPV for the PRx, iPRx and $\Delta\phi$AI were 0.16 (0.13 – 0.20), 0.10 (0.07 – 0.11), and 0.08 (0.07 – 0.15) respectively (median and IQR; p=0.0006). Values of iPRx above and below the LLA were -0.42 (-0.37 to -0.47) and 0.43 (0.34 to 0.52; Arbitrary Units, mean and 95% C.I.). Values of $\Delta\phi$AI above and below the LLA were 144° (139° to 150°) and 55° (46° to 64°). Receiver-operator characteristics (ROC) showed similar accuracy for both iPRx and $\Delta\phi$AI with area under ROC curve of 0.988 (95% C.I. 0.97-1.00) for both indices. An iPRx value of -0.04 was 95% sensitive and 95% specific for loss of autoregulation. A $\Delta\phi$AI of 116° was 95% sensitive and a $\Delta\phi$AI of 102° was 95% specific for loss of autoregulation.

Conclusion: Oscillating PEEP reduced noise in the PRx. $\Delta\phi$AI replicates the correlation analysis of PRx with similar precision and accuracy. Safe application of these findings in a clinical environment may yield faster, more accurate delineation of optimal CPP.

Figure 1: Accuracy of iPRx and $\Delta\varphi$AI. A) Using laser-Doppler defined lower limits of autoregulation (LLA), iPRx of -0.04 (dashed horizontal line) was 95% specific and 95% sensitive for delineating cerebral perfusion pressure (CPP) below the LLA. B), the area under receiver-operator characteristic curve (AUC) using the laser-Doppler derived LLA demarcation was 0.988 for the iPRx. C) $\Delta\varphi$AI of 115° was 95% sensitive for delineating CPP below LLA. $\Delta\varphi$AI of 103° was 95% specific for delineating CPP below LLA. D) $\Delta\varphi$AI monitoring yielded the same AUC as iPRx.

Pediatrics #3 (34)

Objective Measure of Caudal Block: A Neural Blockade Monitor in Children

Jessica A. George, M.D.[1]; Wayne I. Sternberger, Ph.D.[1,2]; John Gearhart, M.D.[1,3]; Robert S. Greenberg, M.D.[1,4];
Johns Hopkins University[1], Applied Physics Laboratory[2], Pediatric Urology[3], Pediatric Anesthesiology[4]

Background: Significant progress has been made in the use, efficacy, and safety of anesthesia. However, clinical tools are not currently available to specifically monitor or objectively evaluate the effectiveness of local anesthetic blocks in humans or animals. We evaluated a technology that has the ability to monitor the effects of local anesthetics on the patient and inform the clinician regarding patient condition from onset to termination of neural blockade.

The ability to collect and interpret data to characterize the effect of blocking agents would give the clinician an unparalleled means to limit toxicity, improve dosing regimens to better approximate analgesic need (both in location and quality), manage uncooperative patients (adult asleep), pediatric uncooperative (developmental or communication barrier), and better refine techniques (differential blockade) for patients. We present preliminary data and establish proof of principle using a new monitor that objectively measures the effect of caudal epidural block in children. We measure changes over time in surface electromyogram (EMG) associated with administration of local anesthetic in the caudal epidural space, compared to penile block, in children undergoing circumcision.

Methods: Nine children (6 months to 2 years of age) undergoing circumcision were studied using a prospective, randomized, open treatment observational study after parental consent of this IRB approved protocol. After general anesthetic induction (sevoflurane, LMA, and IV placement) subjects were randomly assigned to receive either caudal (bupivacaine 0.25% w/ 1:200K epinephrine, 1ml/kg) or penile block (bupivacaine 0.25%, 0.5ml/kg). Surface EMG was recorded at T6, T8, T10 [left & right], & L2 at baseline and after local anesthetic injection during the operative procedure. Post-operative analysis of EMG (normalized root mean squared averages, EMGRMS) was used to assess the changes seen between groups.

Results: All subjects had intra-operative courses consistent with effective block. Normalized decreases in EMGRMS (Figure 1) were seen at 5 minutes in all patients who received a caudal block in T6, T8, & T10 but not in the patient who received a penile block and demonstrated good sensitivity and specificity for discrimination of block type.

Discussion: Compared to baseline, recognizable decreases in non-stimulated EMGRMS were present in all subjects upon administration of local anesthetic in the caudal space at the thoracic and abdominal myotomal/dermatomal (T6-T10) levels. In contrast, increases in EMGRMS were noted in T6-T10 levels in all subjects who received penile block. This effect makes discriminating between caudal and penile block in these levels both sensitive and specific.

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Poster Presentation Abstracts

Pharmacology/Anesthetic Mechanisms

Pharmacology/Anesthetic Mechanisms #1 (65)

Model of the Cytochrome P450-Cytochrome b5 Complex From NMR and Mutagenesis Data

Lucy Waskell, M.D., Ph.D.; Shivani Ahuja, Ph.D.; Sangchoul Im, Ph.D.; Subramanian Vivekanandan, Ph.D.; Kazutoshi Yamamoto, Ph.D.; Ayyalusamy Ramamoorthy, Ph.D.
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Pharmacology/Anesthetic Mechanisms #2 (21)

GABA-A Receptor Facilitation Reduces Firing of Neuronal Assemblies in a Computational Cortical Model

Kingsley P. Storer, M.D., Ph.D.[1]; George N. Reeke, Ph.D.[2]
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Pharmacology/Anesthetic Mechanisms #3 (88)

Specific Hypersensitivity to Volatile Anesthetics in a Mouse Lacking Ndufs4, a Subunit of Mitochondrial Complex I

Margaret M. Sedensky, M.D.; Albert Quintana, Ph.D.; Richard D. Palmiter, Ph.D.; Phil G. Morgan, M.D.
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Pharmacology/Anesthetic Mechanisms #4 (43)

Optoanesthesia With Meta-Azipropofol in Xenopus Tadpoles

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Pharmacology/Anesthetic Mechanisms #5 (29)

Norepinephrine Blocks Isoflurane-Induced Activation of Firing in Putative Sleep-Promoting VLPO Neurons

Michael R. Chalifoux, M.D.; Hilary S. McCarren, B.S.; Jason T. Moore, B.S.; Sheryl G. Beck, Ph.D.; Max B. Kelz, M.D., Ph.D.
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Pharmacology/Anesthetic Mechanisms #6 (30)

Induction of General Anesthesia is Accompanied by Loss of Criticality in the Dynamics of the Brain

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Weill Cornell Medical College[1]; Columbia University[2]; The Rockefeller University[3]

Pharmacology/Anesthetic Mechanisms #1 (65)

Model of the Cytochrome P450-Cytochrome b5 Complex From NMR and Mutagenesis Data

Lucy Waskell, M.D., Ph.D.; Shivani Ahuja, Ph.D.; Sangchoul Im, Ph.D.; Subramanian Vivekanandan, Ph.D.; Kazutoshi Yamamoto, Ph.D.; Ayyalusamy Ramamoorthy, Ph.D.
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Introduction: The majority of drugs used by anesthesiologists are metabolized by 20 of the 57 different human liver cytochromes P450. This means that a mere 20 proteins are major determinants of the efficacy, duration of action, and toxicity of the drugs used in the ~ 25 million anesthetics administered in the United States per year. The cytochromes P450 are a superfamily of ~ 8000 mixed-function oxygenases that have been identified in all kingdoms of life, including animals, plants, eukaryotes, and bacteria. Cytochrome P450 cleaves the oxygen molecule, with the assistance of electrons provided by its two redox partners, and inserts an atom of oxygen into a hydrophobic substrate to enhance its water solubility and eventual secretion by the kidney. The two redox partners of cytochrome P450 are cytochrome b5 and cytochrome P450 reductase. When cytochrome b5 provides the electrons to cytochrome P450, product is formed 10-100 fold faster than when the reductase provides the electrons. Knowledge of the principles that govern the cytochrome P450-cytochrome b5 protein-protein interaction and mechanism of action will have a tremendous impact on our understanding of drug metabolism and our ability to harness this knowledge for the design and synthesis of safer, more effective drugs. An important first step toward understanding the molecular basis of the action of cytochrome b5 with and on cytochrome P450 is to determine the structure of the cytochrome P450-cytochrome b5 complex. A formidable technical challenge to achieving this goal is the fact that only the membrane-bound forms of these proteins interact. NMR methods have been developed to study the structure of the complex between cytochrome P450 and cytochrome b5 in membrane mimetic environments. The structural NMR studies in conjunction with mutagenesis experiments have enabled us to propose an electron transfer pathway between the two proteins.

Methods: The mutant proteins were generated using standard molecular biology techniques. E coli was used to express unlabeled and stable isotopically-labeled (7H, 15N, 13C) proteins. All proteins were purified to homogeneity prior to studying them.

Results and Discussion: The structure of the full-length, membrane-bound form of cytochrome b5 was determined using stable isotopically-labeled protein. Addition of low-spin and high-spin unlabeled full-length microsomal cytochrome P450 2B4 to cytochrome b5 allowed us to determine, using high resolution 900 MH2 NMR and paramagnetic relaxation enhancement experiments, which residues on cytochrome b5 were perturbed by the addition of cytochrome P450. This allowed us to deduce the binding site on cytochrome b5 for cytochrome P450. Using the NMR structure of cytochrome b5 and the crystal structure of cytochrome P450 2B4, we calculated (using the program HADDOCK) the structure of the complex between the two full-length cytochromes. Site-directed mutagenesis studies were in good agreement with the NMR-determined structure. The complex interface is dynamic, sampling similar but non-identical surfaces. The acidic, complex surface of cytochrome b5 binds to the concave, basic surface of cytochrome P450 2B4. Arginine 125 on cytochrome P450, which forms a salt bridge between the heme propionates of cytochrome P450 and cytochrome b5, is proposed to serve as the electron transfer pathway between the proteins.

Pharmacology/Anesthetic Mechanisms #2 (21)

GABA-A Receptor Facilitation Reduces Firing of Neuronal Assemblies in a Computational Cortical Model

Kingsley P. Storer, M.D., Ph.D.[1]; George N. Reeke, Ph.D.[2]
Weill Cornell Medical College[1]; The Rockefeller University[2]

Background: Our understanding of how general anesthetics act on individual cells and on global brain function has increased significantly over the last decade. What remains poorly understood is how anesthetics act at intermediate scales. Several major theories eM.P.H.asize the importance of neuronal groups in the phenomenon of consciousness. We have undertaken computer modeling to determine how GABA-A facilitating agents such as propofol may influence the dynamics of neuronal group formation.

Methods: A computer model of cortical neurons with connections modified by synaptic plasticity was examined. At baseline the model spontaneously formed neuronal collections. Direct effects of GABA-A facilitation and indirect effects on input drive were then examined to study their effects on this process.

Results: Facilitation of GABA-A and input drive reduction reduced the firing frequency of both inhibitory and excitatory neurons in a dose-dependent manner. The diminution in spiking rates led to dramatic reductions in the firing frequency of neuronal groups. Simulated EEG output from the model at baseline exhibits γ and θ rhythmicity. The direct and indirect GABA-A effects reduce the amplitude of these underlying rhythms and modestly slow the γ rhythm.

Conclusions: GABA-A facilitation both directly and indirectly inhibits the ability of neurons to form spontaneous interacting collections. A lack of group formation supports explanations of anesthetic induced loss of memory and consciousness arising from theories of neuronal group selection and transient neuronal assembly formation.

Figure Legend: Distribution of neuronal groups on the simulated cortical surface. Lines of the same color connect neurons that are firing as part of the same group. Five corresponding time points at 10000 ms apart are shown for (A) baseline and (B) combined GABA-A facilitation and input drive reduction. The simulated effects of propofol reduce the size and frequency of activated groups and prevent multiple groups from firing concurrently to form larger assemblies.

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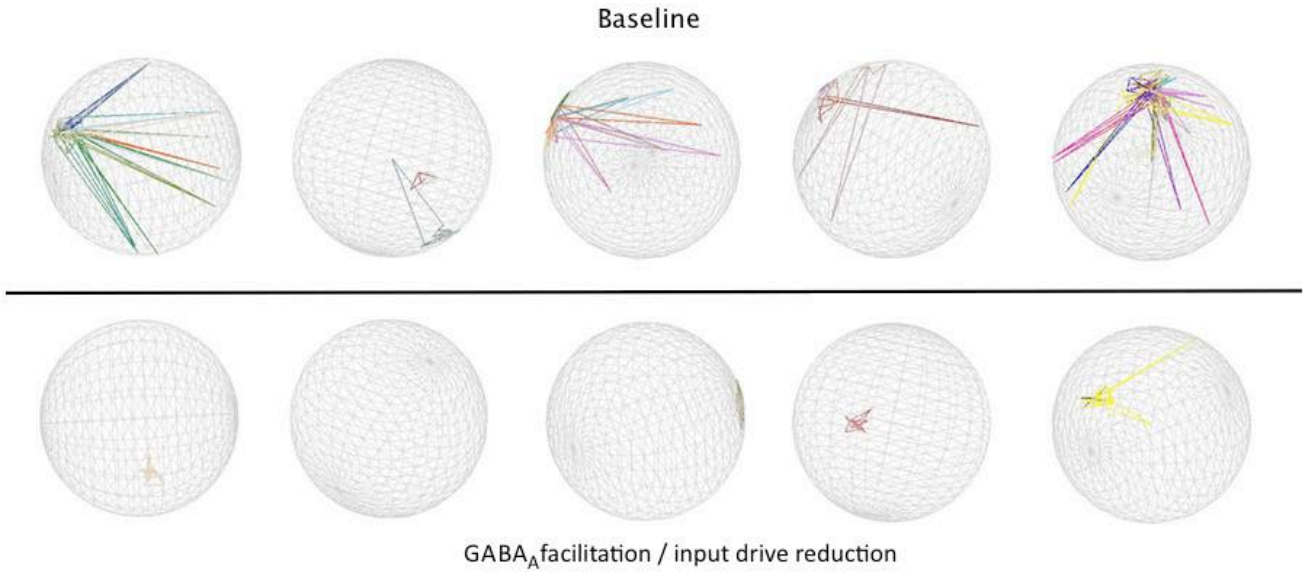

Pharmacology/Anesthetic Mechanisms #3 (88)

Specific Hypersensitivity to Volatile Anesthetics in a Mouse Lacking Ndufs4, a Subunit of Mitochondrial Complex I

Margaret M. Sedensky, M.D.; Albert Quintana, Ph.D.; Richard D. Palmiter, Ph.D.; Phil G. Morgan, M.D.
University of Washington

Introduction: The mechanism of action of volatile anesthetics (VAs) remains incompletely understood. In earlier studies, we found that defects specifically in complex I of the mitochondrial electron transport chain altered sensitivity to VAs in the nematode C. elegans (1,2). We previously reported hypersensitivity to isoflurane in a mouse carrying a knockout (KO) mutation in a subunit of mitochondrial complex I (Ndufs4) (3,4). A role for mitochondrial function underlying VA action was corroborated by studies showing that children with mitochondrial dysfunction in complex I are also sensitive to sevoflurane, using BIS recordings as an endpoint (3). We have now extended our studies of the Ndufs4 KO mouse to include sensitivities to halothane, propofol and ketamine using the righting reflex as an endpoint. We find strikingly specific responses by the Ndufs4 KO mouse to these anesthetics indicating that the effects of mitochondrial mutations do not cause a nonspecific depression of the CNS.

Methods: Young (P23-27) Ndufs4 KO mice were compared to age-matched, wild-type littermates at an age before any severe CNS phenotype is apparent. Genotypes were confirmed by PCR for all mice. Mice were anesthetized with incremental doses of isoflurane or halothane in a closed chamber. Anesthetic concentrations were determined by gas chromatography. Lack of response to a non-crushing tail clamp stimulus was the anesthetic endpoint. The EC50 was determined as described by Sonner (4). Studies of propofol and ketamine were done by peritoneal injection and tested for loss of righting reflex (LORR). All mice were either studied under a warming lamp such that ambient temperature was maintained at 36oC or on a warming blanket to maintain body temperature.

Results: Ndufs4-KO mice were very hypersensitive to isoflurane and halothane, with an EC50s of 0.44+.07(SD)% and 0.52 +.11(SD)%, respectively. Wild-type, control mice had an EC50 of 1.23+.13% and 1.28+.07%, similar to previously published reports for this strain of mouse (4). Ndufs4 KO mice were mildly hypersensitive to propofol (ED50 37 + 5 mg/kg KO; ED50 67 + 5 mg/kg WT). Surprisingly, Ndufs4 KO mice were resistant to ketamine (ED50 105 + 7 mg/kg KO; ED50 66 + 6 mg/kg WT).

Discussion: The mice with mitochondrial dysfunction have a change in VA sensitivity that is the largest reported to date for a mammal. The differences in the sensitivities to anesthetics indicate that these responses are not the result of nonspecific defects in CNS function in the KO animal. These data reinforce the concept that mitochondrial complex I contributes specifically to VA sensitivity. We are now studying cell specific Ndufs4 KO animals to identify the mechanism underlying these changes.

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Pharmacology/Anesthetic Mechanisms #4 (43)

Optoanesthesia With Meta-Azipropofol in Xenopus Tadpoles

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General anesthetics are among the most promiscuous drugs used, and the molecular binding partners that contribute to hypnosis, amnesia, and analgesia remain unproven. The identification of anesthetic targets is hindered by low affinity interactions (μM KD values) with numerous proteins, which has motivated the design of pharmacologically active photolabels. Combined with mass spectrometry, these have allowed the confirmation of suspected, and identification of previously unsuspected, targets and binding sites. m-Azi-propofol (Azi-Pm; Hall et al. (2010) J Med Chem 53:5667-5674) is a photoactive mimic of the intravenous anesthetic propofol (2,6-diisopropylphenol). Azi-Pm is physicochemically similar to propofol and pharmacologically comparable in terms of induction and recovery when administered to tadpoles. The photolysis of azi-Pm occurs at 370 nm (UVA), limiting damage to cellular macromolecules upon exposure. The resulting carbene radical is reactive and non-selective, and reliably reports anesthetic binding sites. We hypothesized that organisms exposed to UVA while anesthetized with azi-Pm would show prolonged recovery as anesthetic sites remain irreversibly occupied. We equilibrated albino Xenopus tadpoles with 4 μM azi-Pm in Petri dishes, exposed them to UVA, and monitored recovery of mobility after changing their water. Azi-Pm prolonged the recovery period of tadpoles in a manner dependent on duration of UVA exposure (two to ten-fold after three to twenty minutes UVA, respectively) with no toxicity up to 96 hours later. Control tadpoles exposed to propofol +/- UVA or azi-Pm alone recovered within 25 minutes with no significant differences. Armed with this new knowledge that azi-Pm-adducted targets contribute to immobility, we initiated a campaign to identify Xenopus neuronal proteins bound by tritiated azi-Pm at clinically relevant concentrations through in vivo photolabeling and mass spectrometry. Only a small number of neuronal targets are adducted, suggesting the combination of optoanesthesia and proteomics will become a valuable tool in the elucidation and verification of anesthetic mechanisms on the molecular level in tadpoles and ultimately the systems level as it is adapted to higher vertebrates.
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Pharmacology/Anesthetic Mechanisms #5 (29)

Norepinephrine Blocks Isoflurane-Induced Activation of Firing in Putative Sleep-Promoting VLPO Neurons

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Introduction: The ventrolateral preoptic nucleus (VLPO) of the hypothalamus has emerged as the prototypic natural sleep-promoting site and an intriguing target for anesthetics.1,2 Reciprocal inhibitory connections have been identified between VLPO and the major monoamine centers of the brain, forming the basis of a "flip-flop" switch.3 Electrophysiological studies have shown that the sleep-promoting neurons of VLPO are hyperpolarized by norepinephrine, a major neurotransmitter responsible for CNS arousal.4 We have previously demonstrated that sleep-promoting VLPO neurons characteristically display low threshold spiking (LTS) and are also depolarized by the volatile anesthetic isoflurane.5 Here we hypothesize that ex vivo and in vivo administration of norepinephrine will reverse the excitation of sleep-promoting VLPO neurons produced by isoflurane and should antagonize anesthetic hypnosis.

Methods: Hypothalamic brain slices containing VLPO were prepared from wild-type mice similar to that previously described.6,7 VLPO neurons were identified as the putative sleep-promoting type by the presence of low threshold spiking (LTS).4,8-9 Hypothalamic slices were exposed to 330μM isoflurane under current clamp conditions and subsequently exposed to a combination of 330μM isoflurane plus 100μM norepinephrine.10 The effects upon membrane characteristics including membrane potential and firing rates were measured. In parallel in vivo experiments, mice were chronically implanted with bilateral cannulas directed at VLPO. After 2 weeks of recovery, mice were stably anesthetized with 1.0% isoflurane. Over a 1-minute period 25nL of 5.75mM norepinephrine and 100μM reboxetine, a norepinephrine reuptake inhibitor, were infused bilaterally into VLPO. Behavioral responsiveness was continuously monitored in the gas-tight chamber.

Results: Whole cell recording demonstrated that isoflurane induced a significant 13.3±1.3mV depolarization and increased the firing rate of putative sleep-promoting LTS VLPO neurons. The isoflurane-induced excitation of these neurons was completely reversed by the concomitant administration of norepinephrine. While being exposed to a constant concentration of isoflurane, norepinephrine caused the putative sleep-promoting LTS VLPO neurons to cease firing and return to -55.8±1.8mV, a level indistinguishable from their baseline resting potential. Preliminary results from mice infused with norepinephrine/reboxetine, in which the cannula successfully targeted VLPO, suggest that a partial antagonism of the anesthetic state occurred. Prior to infusion, mice remained immobile. At a constant concentration of isoflurane, norepinephrine/reboxetine led to purposeful limb and tail movements and efforts to regain the righting reflex.

Conclusions: Exposure of putative sleep-promoting VLPO neurons to norepinephrine both ex vivo and in vivo counteracts the excitatory effects of isoflurane on these cells. The mechanisms by which isoflurane depolarized and norepinephrine hyperpolarized putative sleep-promoting LTS VLPO neurons are currently under investigation. Our data supports the notion that improved understanding of the neural circuits regulating arousal may lead to novel strategies for facilitating or delaying emergence from general anesthesia.

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Pharmacology/Anesthetic Mechanisms #6 (30)

Induction of General Anesthesia is Accompanied by Loss of Criticality in the Dynamics of the Brain

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Although millions of people undergo general anesthesia, the mechanisms responsible for this reversible loss of consciousness remain poorly understood. Surprisingly, at the level of the electroencephalogram (EEG) unconsciousness produced by different anesthetics is characterized by different signatures. While some anesthetics produce large amplitude low frequency oscillations in the EEG, others produce "activated" EEG characterized by high frequency oscillations. Thus, analysis of the frequency content of the EEG has been unable to provide a single conceptual framework to explain the nature of the processes underlying general anesthesia. Therefore, here we took a qualitatively different approach to the analysis of changes in brain dynamics that accompany induction of and emergence from anesthesia. We describe the spatiotemporal evolution of cortical local field potential (ECOG) using autoregressive models and apply this analysis to human subjects undergoing elective neurosurgery under target-controlled propofol administration and non-human primates undergoing induction and emergence from ketamine anesthesia. This methodology allows us to isolate dynamically critical modes – behavior present at the transition between stable and unstable regimes. It is known that such critical modes render the system most responsive to perturbations (e.g. sensory input) over a broad range of scales. We show that the dynamics in the awake brain are characterized by abundance of such critical modes. We show that this cannot be explained by the frequency content of the ECOG signal and depends critically on the correlated activity among different brain regions. Finally, we show that, despite the fact that anesthesia with propofol and ketamine produce different changes in the power spectrum, both states of unconsciousness are characterized by a reduction in the abundance of critical modes. Thus, loss of criticality in brain dynamics may reflect the general features of the anesthetized state regardless of the specifics of the anesthetic agent.

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