Syllabus

AUA 62nd Annual Meeting
April 23–25, 2015

Loews Vanderbilt Hotel

Nashville, Tennessee

hosted by

Vanderbilt University School of Medicine

AUA
Association of University Anesthesiologists

VANDERBILT UNIVERSITY

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Welcome to the Association of University Anesthesiologists 62nd Annual Meeting!

Welcome to the Association of University Anesthesiologists 62nd Annual Meeting hosted by the Vanderbilt University School of Medicine in Nashville, Tennessee. Over the next 3 days, you will have an invigorating intellectual and social experience. The *Meeting Planning Committee*, Drs. Sandberg, Emala, and Gaiser have developed an exciting program including a review of educational research, measurement of educational effectiveness, the trajectory of personalized medicine, and new original research from members and guests.

Annual Meeting Highlights include:

Thursday, April 23

The *Scientific Advisory Board (SAB) Program (Part 1) and Moderated Poster Discussion Session* will highlight original research from your peers and colleagues and research awards will be presented during Oral Presentations. During the break, be sure to visit the poster room to view all of the abstract submissions.

Friday, April 24

Friday is a full day packed with engaging presentations. The *Educational Advisory Board (EAB) Program (Part 1)* will address the *State of the Art for Education Research*. After the break, *EAB (Part 2)* will explore *Measuring Knowledge in Anesthesia* — a challenging topic for all involved in residency education. The afternoon session will include a *Mini-Symposium*, presented by SAB, entitled *Perioperative Genomics* followed by the President's Panel which explores *Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability* and the *Genomes, Phenomes, and Personalized Medicine: The Promise of Genomic Medicine in EHRs*.

Saturday, April 25

Saturday, another full-packed day, initiates in the morning with research awards presented to residents and junior faculty during their scientific presentations. A *Moderated Poster Discussion Session* will follow. The afternoon will give us the opportunity to hear from our Host who has put together an extraordinary panel showcasing Vanderbilt University.

Sincerely,

Thomas J.J. Blanck, PhD, MD
President, Association of University Anesthesiologists

Welcome to Nashville and the AUA 62nd Annual Meeting!

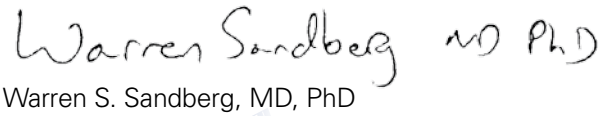
The Vanderbilt University Department of Anesthesiology is extremely pleased to host the 62nd Annual Meeting of the Association of University Anesthesiologists in Nashville, Tennessee. The Host Committee and AUA leadership have put together an exciting program for you.

Vanderbilt last hosted the AUA Annual Meeting in 2002, and in the past 12 years, Nashville has experienced a dramatic renaissance. We are now hailed as the "South's Red-Hot Town" (*Time* magazine), "One of the Top Five Travel Destinations to Visit in the World in 2013" (*Condé Nast Traveler*), and "One of the Top 50 Meeting Destinations in the United States" (Cvent). The city has countless bragging points – from fine dining to the best in cultural offerings. We look forward to sharing Nashville with you in person.

Vanderbilt University and our department have much to offer as well. Established in 1947, the Vanderbilt Department of Anesthesiology now operates one of the largest clinical programs in the country, providing service for more than 90,000 adult and pediatric anesthetic encounters annually. Our faculty will be sharing some of our scientific, clinical, and academic successes during the meeting, and we are excited to provide the opportunity for American Board of Anesthesiology Maintenance of Certification in Anesthesiology (MOCA) training before and after the meeting at our Center for Experiential Learning and Assessment. This state-of-the-art training facility is endorsed by the American Society of Anesthesiologists to deliver certified educational programs, including the simulation training that qualifies for MOCA credit.

This year, the AUA Host program focuses on the rapidly expanding field of perioperative genomics and personalized medicine and the significance of this approach to patient care as we strive to work more safely, efficiently, and wisely in times of continued fiscal constraint. Applying genomic approaches to our practice is critical in the identification of patients at high risk for complications so interventions that optimize outcomes can be implemented. We have invited key leaders in this arena to share their knowledge, and we are fortunate to have two giants in the field among our leadership at Vanderbilt. Dr. Jeff Balser, Vice Chancellor for Health Affairs and Dean of the School of Medicine at Vanderbilt, has been a national figure at the forefront of the movement toward personalized medicine since its inception. He will open the Mini-Symposium: *Perioperative Genomics* by addressing the "big picture" as it pertains to personalized medicine's dramatic implications for the healthcare of the future. Dr. Dan Roden, Assistant Vice Chancellor for Personalized Medicine at VUMC, will be a Mini-Symposium: *Perioperative Genomics* speaker. He will provide an overview of Vanderbilt's BioVU, now the country's largest collection of human DNA linked to searchable, electronic health information, as well as the Synthetic Derivative, and other genomics initiatives at Vanderbilt. Other speakers will address such topics as perioperative cardiovascular risk and pharmacogenomics, as well as important developments in electronic medical records.

In the decade since Vanderbilt last hosted the AUA Annual Meeting, the city of Nashville, our university, and healthcare have all experienced dramatic changes, and we look forward to sharing these transformations with you during your visit. The Host Planning Committee heartily thanks the many individuals who have collaborated to make this one of the best meeting programs ever, and we hope you enjoy your visit to Nashville.



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METROPOLITAN GOVERNMENT OF NASHVILLE AND DAVIDSON COUNTY

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April 23, 2015

Dear Annual Meeting Attendees:

It is a pleasure to welcome you to our great city for the AUA 62nd Annual Meeting. We are pleased that you chose Nashville to host such an important gathering.

While in Music City, I encourage you to take the time to enjoy the honky tonks on Broadway and discover the varied styles of music, art, food and culture that make Nashville unique. The Frist Center for the Visual Arts, the Country Music Hall of Fame and Museum and the Schermerhorn Symphony Center are just a few local sites well worth visiting. In addition, you can visit the Parthenon, one of our most beloved icons, located in beautiful Centennial Park near Vanderbilt University, your host institution.

I wish you great success in your practice and research in anesthesiology. I am certain that you will witness firsthand the southern hospitality and friendliness that our city is famous for. Thank you for choosing Nashville. We hope to see you back in years to come.

Regards,

Karl F. Dean
Mayor

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**Program Faculty are as of press time and subject to change.*

Continuing Medical Education (CME) Information

Activity Overview

Findings from new research and the evolution of anesthesiology practice based on emerging evidence create an inherent gap between existing practice and new practice models. The purpose of the Association of University Anesthesiologists (AUA) 62nd Annual Meeting is to provide a scientifically- based and clinically-oriented educational activity that will improve competence and performance in the anesthesiology specialty, resulting in improved patient care and outcomes.

Target Audience

The AUA 62nd Annual Meeting is designed to address the continuing medical education needs of anesthesiologists, anesthesiologists in training, and anesthesia investigators in academic, clinical and laboratory settings.

Educational Objectives

- Describe the latest developments in education research, measuring knowledge in the field anesthesia, and genomics.
- Consider recent research findings relative to anesthesiology and evaluate their application to the learner's professional practice.
- Develop strategies for integrating new knowledge and behaviors into their professional practice.
- Recognize gaps in their knowledge, behavior, and patient outcomes that may result in a need for additional education and training.

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the International Anesthesia Research Society (IARS) and the AUA. The IARS is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The International Anesthesia Research Society (IARS) designates this live activity for a maximum of *14 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure

The IARS and the AUA make every effort to develop CME activities that are scientifically based, accurate, current, and objectively presented. The IARS and the AUA have implemented mechanisms requiring everyone in a position to control content to disclose all relationships with relevant commercial interests. The IARS and the AUA provide these disclosures to learners in the Final Program and in advance of each session. The IARS and the AUA resolve any potential conflicts of interest prior to presentation of the activity. Individuals who refuse or fail to provide the required disclosures are disqualified from planning, managing, presenting, and evaluating the activity. Learners are asked to report any perceived commercial bias or lack of objectivity on the session evaluations.

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General Information

Welcome to the Association of University Anesthesiologists 62nd Annual Meeting at Loews Vanderbilt Hotel in Nashville, Tennessee!

Over the next three days, we hope you will take advantage of the wide variety of learning opportunities during the Educational Advisory Committee, Scientific Advisory Committee and Host Committee programs while networking with your peers and colleagues.

Headquarters Hotel & Education Program

Loews Vanderbilt Hotel
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All education sessions will take place at the Loews Vanderbilt Hotel.

The **Program Schedule**, included in your registration packet, will list the locations for all education sessions, food functions and special events.

REGISTRATION at Loews Vanderbilt Hotel

Badge Pick-Up and Registration Hours

Thursday, April 23

10:00 am – 4:30 pm	Symphony I Foyer
5:00 pm – 8:00 pm	Neely Foyer, Mezzanine Level

Friday, April 24

6:30 am – 6:00 pm	Symphony I Foyer

Saturday, April 25

6:30 am – 5:00 pm	Symphony I Foyer

Name Badges

Your registration packet includes your name badge which you must wear at all times while attending events. Only attendees with name badges will be admitted to meeting rooms and special events. If you misplace your badge, please visit the Registration Desk for a replacement.

CME Information: The International Anesthesia Research Society (IARS) designates this live activity for a maximum of 14 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Electronic Devices: Please silence all electronic devices during education sessions. Videotaping and recording of sessions is not allowed without written permission from the presenter(s).

Dress Code: The dress code for the AUA 62nd Annual Meeting is business / business casual.

Internet Availability: Complimentary wirelessinternet is available in all the AUA scheduled meeting rooms. Open your internet browser and click on the network labeled "AUA." When prompted for an access code, enter "62nd." Please no streaming or video downloading. Please note that the password is case sensitive. Internet **Network Name:** AUA; **Access Code:** 62nd

Smoke-Free Policy: Smoking is not permitted at any AUA-sponsored events. We respectfully require that you abide by our smoke-free policy.

Social Functions and Networking Events: Please remember to bring your business cards to all social events.

Special Services: If you have a special need please contact the AUA staff at AUA@iars.org.

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.

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:

Charles W. Emala, MD, Chair, Columbia University, New York, New York

Timothy Morey, MD, University of Florida, Gainesville, Florida

Peter Nagele, MD, MSc, Washington University in St. Louis, St. Louis, Missouri

Alina M. Grigore, MD, Cardiovascular Anesthesia Consultants, Las Vegas, Nevada

Roy Levitt, MD, University of Miami, Miami, Florida

Zhongcong Xie, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

Wei Chao, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

Y. S. Prakash, MD, PhD, Mayo Clinic, Rochester, Minnesota

Matthias Ludwig Riess, MD, PhD, Vanderbilt University, Nashville, Tennessee

Thomas Floyd, MD, Stony Brook University Medical Center, Stony Brook, New York

Peter Goldstein, MD, Weill Cornell Medical College, New York, New York

Randall Schell, MD, MACM, University of Kentucky, Nicholasville, Kentucky

Special Events & What to Do in Nashville

Special Events

THURSDAY, APRIL 23

Resident and Junior Faculty Meet and Greet Reception

5:00 pm to 6:00 pm, Loews Vanderbilt Hotel

The Resident and Junior Faculty Meet and Greet Reception gives residents and fellows an opportunity to meet their peers, mentors, and the AUA Council Members in an informal setting.

All Attendee Welcome Reception

6:00 pm to 8:00 pm, Loews Vanderbilt Hotel

Discover the vibrant energy of Nashville while networking with peers and colleagues at the All Attendee Welcome Reception to kick off the AUA 62nd Annual Meeting.

FRIDAY, APRIL 24

Free Night to Explore Nashville

Attendees are encouraged to check out all that Nashville has to offer on this free night. Experience the music scene, taste the local cuisine and visit the historic sites. Transportation will not be provided by AUA. Please see the bell stand at the Loews Vanderbilt Hotel for taxi service.

SATURDAY, APRIL 25

Resident Luncheon

11:45 am to 12:45 pm, Loews Vanderbilt Hotel

Tables will be reserved for residents, fellows and their sponsoring chair. Members of the AUA Council will be present to meet with these future leaders in academic anesthesiology. This luncheon is included in the Resident / Fellow registration fee.

Social Event Reception and Dinner

6:00 pm to 10:00 pm, Country Music Hall of Fame® and Museum

6:00 pm to 7:00 pm, Reception & Access to Museum

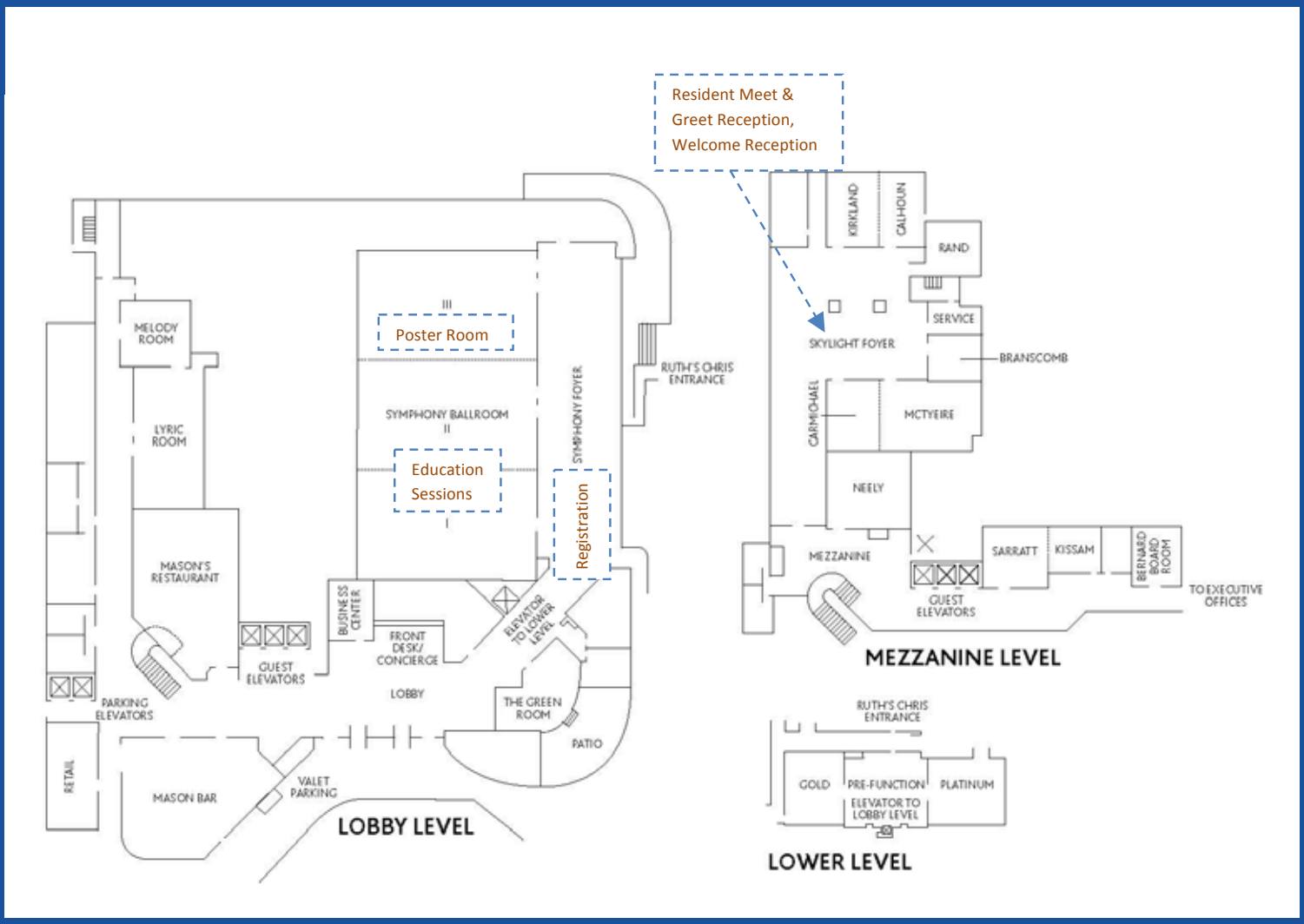
7:00 pm to 10:00 pm, Dinner

Join your friends and colleagues for a perfect ending to the AUA 62nd Annual Meeting, featuring the local flavors and live music of Nashville. Attendees will also have access to the museum during the reception. The Country Music Hall of Fame® and Museum has more than 2 million artifacts in its collection, showcasing one of our nation's foundational music forms. Don't miss this lively social event to close the meeting with live local music and all!

What to Do in Nashville

Discover the perfect harmony of history, events and attractions all culturally intertwined with the music that defines Nashville, Tennessee – Music City. As for dining, the city has become one of the South's hottest culinary destinations with some of the top chefs in the nation concocting dishes to delight every palate such as Virago, Sinema, Marché Artisan Foods, Prime 108, Catbird Seat, Etch, and Patterson House (just to name a few). For a list of noteworthy restaurants and entertainment options for your visit to Nashville, check out the AUA Annual Meeting website.

Loews Floor Plan



Travel Information

Headquarters Hotel

Loews Vanderbilt Hotel
2100 West End Avenue, Nashville, TN 37203

The Loews Vanderbilt captures Nashville's unique character with a mix of both old and new, beginning with the sound of modern music coming from a 1950s-style jukebox as you enter the lobby.

The recently renovated lobby includes a floor-to-ceiling fireplace and a stunning Hank Williams mural – created from classic images of famous country musicians.

These classics as well as many more features make for the perfect location for a meeting. In addition to all of these touches, the hotel is located just minutes from the city's most famous attractions.

All AUA activities will be conveniently located at the Loews Vanderbilt Hotel.

Travel Information

Nashville International Airport (BNA)
One Terminal Drive, Nashville, Tennessee

From the moment you step off the plane, you will be immersed in the music and art of Nashville. Nashville International Airport offers a changing line-up of live music and art installations throughout the airport and provide a gateway to the city and Tennessee. The Loews Vanderbilt Hotel is located a short, 15-minute drive from the Nashville International Airport.

Jarmon Transportation, the official shuttle of the Nashville International Airport, offers shuttle service to and from the airport to the Loews Vanderbilt Hotel for approximately $14 one way or $25 round trip. Taxi service costs approximately $27 one way from the airport to the Loews Vanderbilt Hotel. Rental cars are available at the airport as well.

Reservations can be made in person by phone at 615-275-0146, or online at **jarmontransportation.com**.

Nashville Restaurant Guide

Attendees may find dinner at a wide selection of restaurants near the Loews Vanderbilt Hotel (reservations are recommended). While Nashville has long been known for its expansive music scene, the talent and creativity of its culinary scene has recently put Nashville on the map. Nashville's creative spirit has certainly infiltrated into its kitchens, turning them into the chef's studio. From Southern fare to haute cuisine to quite literally everything in between, Nashville's palate offers it all.

Restaurants within Loews Vanderbilt

Mason's, 2100 West End Ave.
615-321-1990 • masons-nashville.com

Ruth's Chris Steak House, 2100 West End Ave.
615-320-0163 • ruthschris.com

Restaurants within Walking Distance

1808 Grille, 1808 West End Ave.
615-340-0012 • 1808grille.com

Adele's, 1210 McGavock St.
615-988-9700 • adelesnashville.com

Amerigo Italian Restaurant, 1920 West End Ave.
615-320-1740 • amerigo.net

Blackstone Restaurant & Brewery
1918 West End Ave.
615-327-9969 • blackstone-pub.com

Bound'ry Restaurant, 911 20th Ave. S
615-321-304 • boundrynashville.com

Café Coco, 210 Louise Ave.
615-321-2626 • cafecoco.com

City Fire American Oven and Bar
The Gulch, Downtown, 610 12th Ave. S
615- 401-9103 • cityfirenashville.com

Flyte World Dining and Wine, 718 Division St.
615-255-6200 • flytenashville.com

Hattie B's Hot Chicken, 112 19th Ave. S
615-678-4794 • hattieb.com

Jason's Deli, 2028 West End Ave.
615-340-9991 • jasonsdeli.com

Jimmy Kelly's Steakhouse, 217 Louise Ave.
615-329-4349 • jimmykellys.com

Magnolia South,1808 Hayes St.
615-840-6167 • magnoliasouthnashville.com

Midtown Café, 102 19th Ave S
615-320-7176 • midtowncafe.com

O'Sake Japanese Restaurant, 2204 Elliston Pl.
615-340-0058 • osaketn.com

Peg Leg Porker, 903 Gleaves St.
615-829-6023 • peglegporker.com

Sambuca, 601 12th Ave. S
615-248-2888 • sambucarestaurant.com

Samurai, 2209 Elliston Pl.
615-320-5438 • samurainashville.com

Seafood Sensation, 2719 Jefferson St.
615-678-1069

Tavern, 1904 Broadway
615-320-8580 • mstreetnashville.com/restaurants/tavern

The 404 Kitchen, 404 12th Ave. S
the404nashville.com

The Catbird Seat, 1711 Division St.
615-810-8200 • thecatbirdseatrestaurant.com

The Gold Rush, 2205 Elliston Pl.
615-321-1160 • goldrushnashville.com

The Row Kitchen & Pub, 110 Lyle Ave.
615-321-1224 • therownashville.com

Union Common, 1929 Broadway
615-329-4565 • unioncommon.com

Virago, 1126 McGavock St.
615-254-1902 • mstreetnashville.com/restaurants/virago

Watermark Restaurant, 507 12th Ave. S
615-254-2000 • watermark-restaurant.com

Whiskey Kitchen, 118 12th Ave. South
615-254-3029
mstreetnashville.com/restaurants/whiskey-kitchen

Program Schedule

THURSDAY, APRIL 23

10:00 am – 4:30 pm **Registration**

12:30 pm – 12:45 pm **Introduction and Welcome to the AUA 62nd Annual Meeting**
Thomas J. J. Blanck, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able: (1) To welcome members and guests to the 63rd annual AUA meeting; (2) To outline the academic program for the next two days; (3) To emphasize the social activities available on Thursday and Saturday nights; (4) To thank our hosts, the Vanderbilt University School of Medicine, and the AUA administrative staff for formulating a vibrant and well-organized meeting.

12:45 pm – 1:00 pm **Introduction and Welcome to the Host Program and Nashville**
Warren S. Sandberg, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Understand the transformative role of genomics-driven personalized medicine in customizing care for each individual patient; (2) Comprehend how to implement assessment and feedback systems that foster a culture of professionalism and safety in healthcare; (3) Evaluate the state of the art of research in anesthesia education; (4) Comprehend the measurement of developing knowledge in anesthesia learners; (5) Understand the utility of the Electronic Health Record as a repository of data informing clinically useful genomic and phenomic analyses and interventions; (6) Develop a generalized appreciation for where anesthesiology science and education fits into the community of scholars and the landscape of scholarship at major universities.

1:00 pm – 1:05 pm **Introduction and Welcome to the SAB Program**
Charles W. Emala, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize the emerging role of personalized medicine in perioperative medicine; (2) Describe how perioperative genomics will affect the approach to the cardiac surgical patient; (3) Describe how personalized medicine will impact considerations of drug metabolism; (4) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

1:05 pm – 2:00 pm **SAB Oral Session (Part 1)**
Moderators: Y. S. Prakash, MD, PhD and Wei Chao, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

Junior Faculty Research Award

- ***Pediatric Delirium in Critically Ill Infants and Preschool-Aged Children: Validation and Reliability of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)***
  Heidi A.B. Smith, MD, MSCi, Vanderbilt University, Nashville, Tennessee
- ***Latent Class Analysis of Neuropsychological Deficit after Exposure to Anesthesia in Early Childhood***
  Caleb Ing, MD, MS, Columbia University, New York, New York

Program Schedule

Margaret Wood Resident Research Award

- ***The Relative Effects of Dexmedetomidine and Propofol on Cerebral Blood Flow and Brain Oxygenation: A Noninferiority Study***
  Michael Kot, MD, Cleveland Clinic, Cleveland, Ohio
- ***The Elderly Brain Under Anesthesia: An Age-Dependent Analysis of Propofol- and Sevoflurane-Induced Electroencephalogram Dynamics***
  Patrick L. Purdon, PhD, Massachusetts General Hospital, Boston, Massachusetts

2:00 pm – 2:15 pm **Coffee Break & Poster Viewing and Discussion**

2:15 pm – 3:15 pm **SAB Oral Session (Part 1) Continued**
Moderators: Y. S. Prakash, MD, PhD and Wei Chao, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

- ***Selective Inhibition of the Calcineurin Interaction Site of TRPV1 Reduces Myocardial Infarct Size by Reducing Mitochondrial Calcium Influx***
  Eric R. Gross, MD, PhD, Stanford University, Stanford, California
- ***Proteomic Profiling and Multi-Color Flow Cytometry Reveal Species Specific and Hibernation-State Specific Differences in Innate Immunity, Susceptibility to Injury, and Response to Surgical Ischemia-Reperfusion between Rats and Arctic Ground Squirrels***
  Quintin J. Quinones, MD, PhD, Duke University, Durham, North Carolina
- ***Extracellular RNA Induces Inflammation via Toll-Like Receptor 7 and Contributes to Myocardial Infarction in a Mouse Model of Ischemia-Reperfusion Injury***
  Wei Chao, MD, PhD, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
- ***Acute Ischemic Albuminuria Mediates AKI in Mice after Cardiac Arrest and Cardiopulmonary Resuscitation***
  Michael P. Hutchens, MD, MA, Oregon Health & Science University, Portland, Oregon

3:15 pm – 4:45 pm **Moderated Poster Discussion Session**

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

5:00 pm – 8:00 pm **Registration**

5:00 pm – 6:00 pm **Resident and Junior Faculty Meet and Greet Reception**

6:00 pm – 8:00 pm **All Attendee Welcome Reception**

Program Schedule

FRIDAY, APRIL 24, 2015

6:30 am – 6:00 pm **Registration**

7:00 am – 8:00 am **Continental Breakfast**

8:00 am – 8:10 am **Introduction and Welcome to the EAB Program**
Robert R. Gaiser, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify quality research in education; (2) Apply statistical analysis for evaluation of knowledge in anesthesia; (3) Assist residents with the process of acquiring and measuring their anesthesia knowledge; (4) Scientifically evaluate research in education.

8:10 am – 9:30 am **EAB Program Session (Part 1): *State of the Art for Research in Education***

- ***Review of the Key Literature in Anesthesia***
  David J. Murray, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe the contributions of recent research to the anesthesia curriculum; (2) Provide an overview of how educational research is likely to change with directives and changes in measuring educational progress, certification examinations and maintenance of certification.

- ***Conducting Quality Research in Education***
  Matthew McEvoy, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Discuss current trends in educational research in anesthesiology; (2) Describe a translational research paradigm in educational research; (3) Discuss barriers to quality educational research; (4) Understand opportunities for the future of quality educational research in perioperative medicine.

- ***An Editor's Perspective of Research in Education***
  Steven Shafer, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Understand the tools that are used to assess performance in education research; (2) Understand the distinction between an education project and education research, and the critical role of reproducibility in that distinction; (3) Understand why *Anesthesia & Analgesia* has two venues to publication education research: *Anesthesia & Analgesia* for reproducible science, and *A&A Case Reports* for interesting N=1 (institution) Education Case Reports; (4) Understand the training required to obtain the necessary skills to formally study education as a process.

  Question & Answer

9:30 am – 10:00 am **Coffee Break & Poster Viewing and Discussion**

Program Schedule

10:00 am – 12:00 pm **EAB Program Session (Part 2): *Measuring Knowledge in Anesthesia***

- ***The Science of Psychometrics***
  Ann Harman, PhD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Understand the psychometric principles of validity, reliability and fairness; (2) Understand the processes used by the ABA to develop valid, reliable and fair examinations; (3) Understand the psychometric procedures used by the ABA to evaluate the technical measurement quality of its assessments; (4) Understand the three general types of standard-setting procedures used to establish performance standards for examinations as well as the specific standard-setting procedure used by the ABA.

- ***Use of the OSCE to Measure Anesthesia Knowledge***
  Brenda A. Bucklin, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Understand the use of OSCE's as a method of assessment in postgraduate education; (2) Understand the rationale for use of the OSCE in testing anesthesia knowledge; (3) Understand how the OSCE will be used to assess anesthesia knowledge; (4) Understand the content examined by the OSCE to assess anesthesia knowledge.

- ***Changes in the Exam Process to Measure Anesthesia Knowledge***
  James P. Rathmell, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe recent changes in the ABA examination aimed at assessment of knowledge related to the practice of anesthesiology; (2) Discuss the rationale behind the recent transition to the Staged Examination System; (3) Detail the differences between the Basic and Advanced portions of the Part 1 (written) examination.

12:00 pm – 1:00 pm **All Attendee Luncheon**

12:00 pm – 1:00 pm **EAB Luncheon**

12:00 pm – 1:00 pm **SAB Luncheon**

12:00 pm – 1:00 pm **President's Luncheon**

1:00 pm – 3:00 pm **Mini-Symposium: *Perioperative Genomics***

1:00 pm – 1:05 pm ***Introduction***
Moderator: Peter Nagele, MD

1:05 pm – 1:25 pm ***Personalizing Health in the Academic Medical Center***
Jeff Balser, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Understand the impact of personalizing care on the healthcare economy; (2) Become familiar with current strategies aimed at genomic medicine; (3) Understand the role health IT can play in personalized care.

Program Schedule

1:25 pm – 2:00 pm ***Engineering a Healthcare System for Discovery and Implementation in Personalized Medicine***
Dan Roden, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify ways in which electronic medical records can inform both research and patient care, and their interaction; (2) Understand the general relationship between genetic variant frequency and effect size; (3) Describe the potential advantages of a program of preemptive genetic testing.

2:00 pm – 2:20 pm ***Genomic Technology is Outpacing Utility This Decade, but Perhaps Not Next Decade***
Simon Body, MB ChB, MPH

Learner Objectives: After participating in this activity, the learner will be able to: (1) Understand the complex nature of inherited information acquired from parents and the Environment; (2) Understand several technologies required to measure this information; (3) Understand our limited knowledge of the impact of inherited information.

2:20 pm – 2:40 pm ***Genomics and Opioid Pharmacology***
Evan Kharasch, MD, PhD

2:40 pm – 3:00 pm ***Moderated Panel Discussion***
Moderator: Peter Nagele, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize the emerging role of personalized medicine in perioperative medicine; (2) Describe how perioperative genomics will affect the approach to the cardiac surgical patient; (3) Describe how personalized medicine will impact considerations of drug metabolism.

3:00 pm – 3:15 pm **Coffee Break & Poster Viewing and Discussion**

3:15 pm – 5:15 pm **President's Panel: *Frontiers in Medicine – Genomes to Organizations***

- ***Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability***
  William Cooper, MD, MPH
- ***Genomes, Phenomes, and Personalized Medicine: The Promise of Genomic Medicine in EHRs***
  Joshua C. Denny, MD, MS

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe the relationships between behaviors that undermine a culture of safety and suboptimal outcomes; (2) Articulate the essential elements of an organizational infrastructure for addressing behaviors that undermine a culture of safety; (3) Articulate the essential elements of three graduated levels of interventions for addressing behaviors that undermine a culture of safety.

Program Schedule

5:15 pm – 6:15 pm **AUA Annual Business Meeting**

6:15 pm – 11:00 pm **Free Night to Explore Nashville**
Transportation will not be provided by AUA. Please see the Loews Vanderbilt Hotel bell stand for taxi service.

SATURDAY, APRIL 25, 2015

6:30 am – 5:00 pm **Registration**

7:00 am – 8:00 am **Continental Breakfast**

8:00 am – 8:05 am **Introduction to the SAB Oral Session (Part 2)**

8:05 am – 9:00 am **SAB Oral Session (Part 2)**
Moderators: Zhongcong Xie, MD, PhD and Matthias Riess, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

Junior Faculty Research Award

- ***Isoflurane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway***
  Cyrus D. Mintz, MD, PhD, Johns Hopkins University School of Medicine, Baltimore, Maryland
- ***Carbon Monoxide Modulates Cytochrome Oxidase Activity and Oxidative Stress in the Developing Murine Brain During Isoflurane Exposure***
  Richard J. Levy, MD, FAAP, Columbia University Medical Center, New York, New York
- ***Astrocyte Specific Knockout of Hypoxia-Inducible Factor Impairs Hippocampal Learning after Mild Hypoxia***
  Cindy V. Leiton, PhD, Stony Brook University, Stony Brook, New York
- ***Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline***
  Niccolo Terrando, BSc (hons), DIC, PhD, Duke University, Durham, North Carolina

9:00 am – 9:15 am **Coffee Break**

9:15 am – 10:15 am **SAB Oral Session (Part 2) Continued**
Moderators: Zhongcong Xie, MD, PhD and Matthias Riess, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

Resident Travel Award

- ***Dexmedetomidine's Inhibitory Effects on Acetylcholine Release from Cholinergic Nerves in Guinea Pig Trachea: A Mechanism That Accounts for Its Clinical Benefit during Airway Irritation***
  Maya Mikami, MD, PhD, Columbia University College of Physicians and Surgeons, New York, New York

Program Schedule

Resident Travel Award

- ***Effects of Race and Common Genetic Variation on Therapeutic Response Disparities in Postoperative Atrial Fibrillation***
  Nazish K. Hashmi, MB, BS, Duke University Medical Center, Durham, North Carolina
- ***Do Potent Anesthetics Bind to All Five Transmembrane Subunit Interfaces in GABAA Receptors?***
  Stuart A. Forman, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts
- ***Selective Pharmacologic Targeting of the GABA-A α4 Subunit in Airway Smooth Muscle to Alleviate Bronchospasm***
  Gene T. Yocum, MD, Columbia University, New York, New York

10:15 am – 11:45 am **Moderated Poster Discussion Session**

Learner Objectives: After participating in this activity, the learner will be able to: (1) Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

11:45 am – 12:45 pm **All Attendee Luncheon**

11:45 am – 12:45 pm **Resident Luncheon**
Tables will be reserved for residents, fellows and their sponsoring chair. Members of the AUA Council will be present to meet with these future leaders in academic anesthesiology.

12:45 pm – 2:45 pm **Host Program Session (Part 1)**

12:45 pm – 1:45 pm ***Earth 2.0: The Quest for Other Worlds and The Diverse Scientists Who Find Them***
Keivan Stassun, PhD

1:45 pm – 2:45 pm ***Comparative Neurobiology: What We Can Learn From The Adaptations of Interesting Predators***
Kenneth Catania, PhD

2:45 pm – 3:00 pm **Coffee Break**

3:00 pm – 5:00 pm **Host Program Session (Part 2)**

3:00 pm – 4:00 pm ***What's A Guy Got to Do to Get A Meal Around Here? Vectors, Parasites and Homeostasis in Tropical Diseases***
David W. Wright, PhD

4:00 pm – 5:00 pm ***You Either Believe in Magic or You Believe in Math: The Changing Economics and Regulation of Health Care***
R. Lawrence Van Horn, PhD, MPH, MBA

6:00 pm – 10:00 pm **Social Event Reception & Dinner**
Country Music Hall of Fame® and Museum
Reception & Museum Access: 6:00 pm – 7:00 pm
Dinner: 7:00 pm – 10:00 pm
Museum access will be available to attendees during the reception.
Make sure to also check out the live local music at both the reception and dinner.

Program Materials

Thursday, April 23

SAB Oral Session (Part 1) Continued
2:15 pm - 3:15 pm

Extracellular RNA Induces Inflammation via Toll-Like Receptor 7 and Contributes to Myocardial Infarction in a Mouse Model of Ischemia-Reperfusion Injury
Wei Chao, MD, PhD

Friday, April 24

EAB Program Session (Part 1): State of the Art for Research in Education
8:10 am - 9:30 am

Review of the Key Literature in Anesthesia
David J. Murray, MD

Mini-Symposium: Perioperative Genomics
1:00 pm – 3:00 pm

Engineering a Healthcare System for Discovery and Implementation in Personalized Medicine
Dan Roden, MD

President's Panel: Frontiers in Medicine – Genomes to Organizations
3:15 pm – 5:15 pm

Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH

Saturday, April 25, 2015

SAB Oral Session (Part 2)
8:05 am - 9:00 am

Isoflorane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway
Cyrus Mintz, MD, PhD

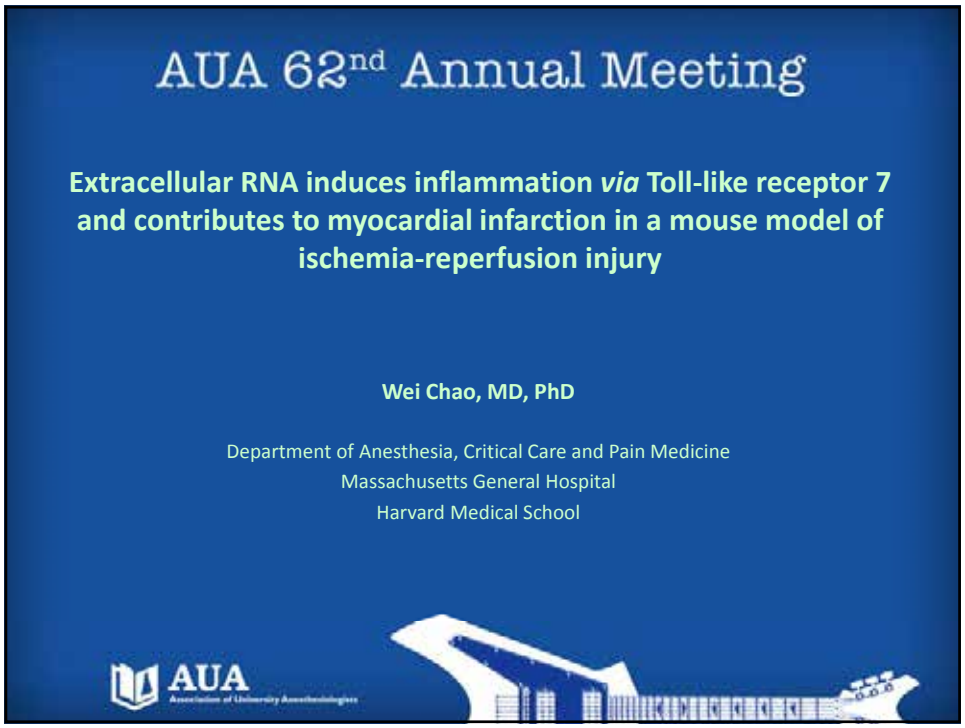
Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline
Niccolo Terrando, BSc (hons), DIC, PhD

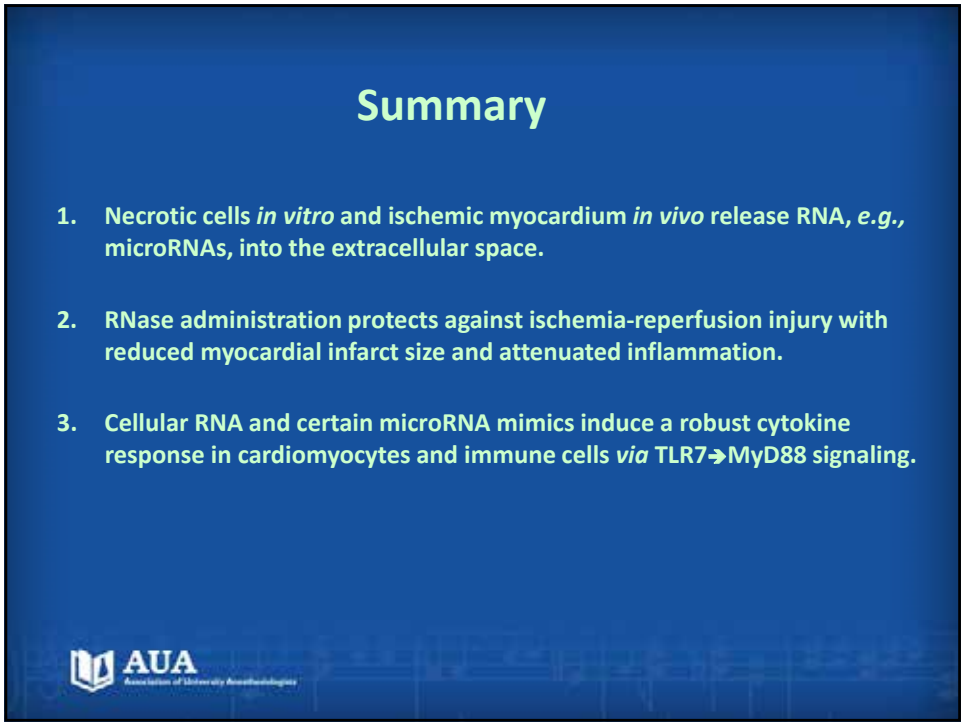
Notes:

Program Materials

Thursday, April 23

Extracellular RNA Induces Inflammation via Toll-Like Receptor 7 and Contributes to Myocardial Infarction in a Mouse Model of Ischemia-Reperfusion Injury
Wei Chao, MD, PhD

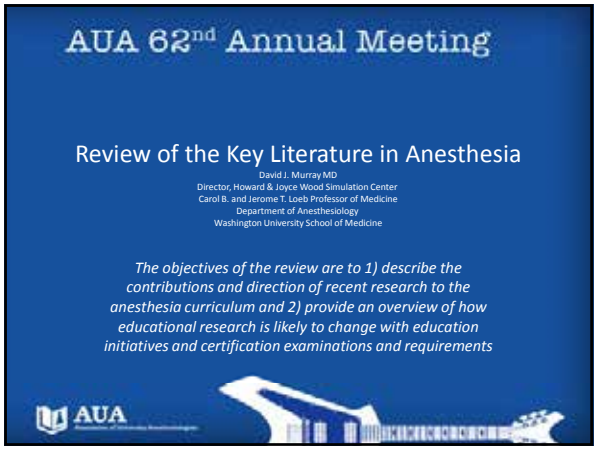


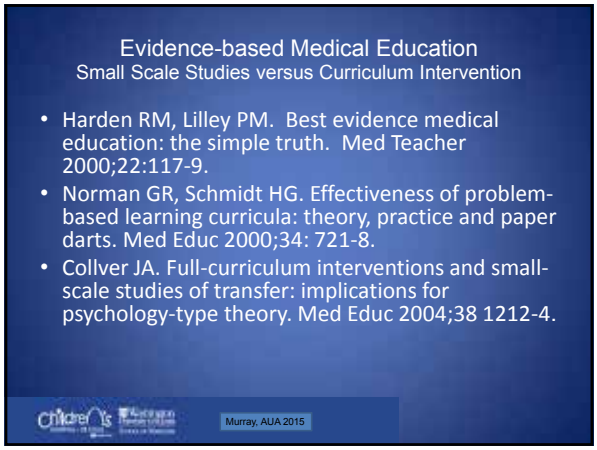


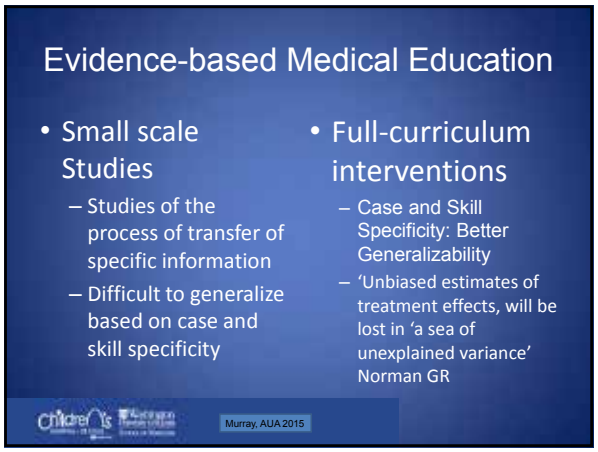
Program Materials

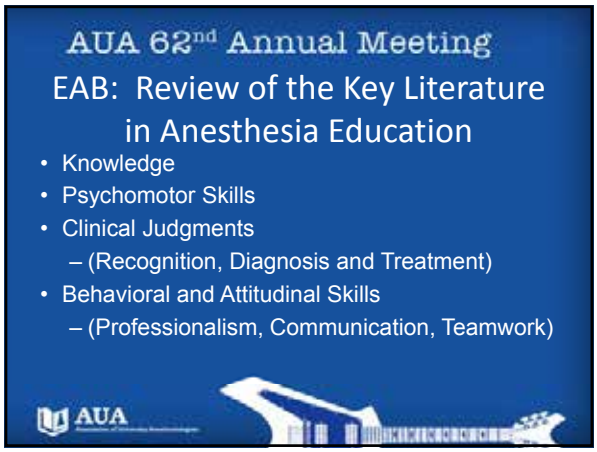
Friday, April 24

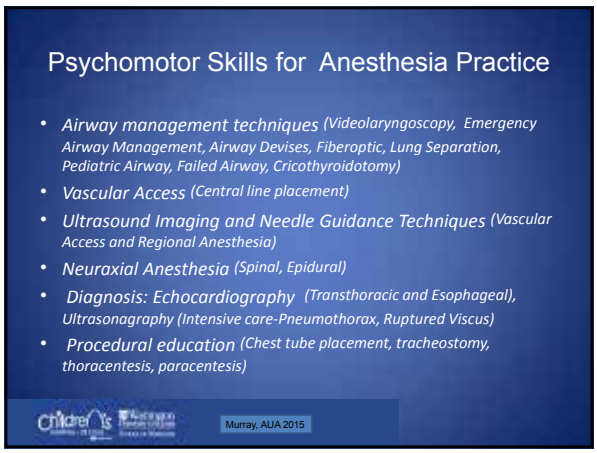
Review of the Key Literature in Anesthesia
David Murray, MD











Program Materials: Friday, April 24

Friday, April 24

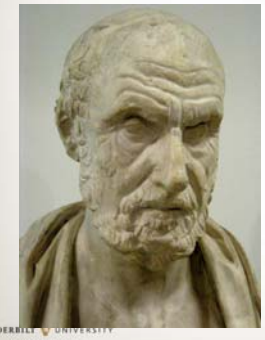
Engineering a Healthcare System for Discovery and Implementation in Personalized Medicine
Dan Roden, MD

VANDERBILT UNIVERSITY MEDICAL CENTER

Engineering a healthcare system for discovery and implementation in personalized medicine

Dan M. Roden, MD
Assistant Vice Chancellor for Personalized Medicine

Personalized medicine – not a new idea – (1)

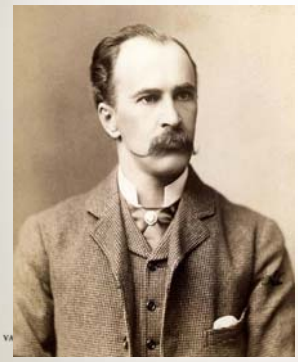


It is more important to know what sort of person has a disease than to know what sort of disease a person has.

Hippocrates

VANDERBILT UNIVERSITY MEDICAL CENTER

Personalized medicine – not a new idea – (2)



Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

The good physician treats the disease; the great physician treats the patient who has the disease.

Sir William Osler

Personalized medicine – not a new idea – (3)

endogenous and are not affected by diet, such as recent researches have revealed in increasing numbers. The differences of type which are so important in the selection of a blood for transfusion, and the idiosyncrasies with regard to drugs and articles of food, which are summed up in the proverbial saying that what is one man's meat is another man's poison, presumably have a chemical basis.

Upon chemical as upon structural variations the factors which make for evolution have worked and are working. Evidences of this are to be detected in many directions, as, for example, in the delicate selective power of the kidneys, in virtue of which they are enabled to hold back in the circulation the essential proteins of the blood but at the same time allow free passage to other proteins which are

VANDERBILT UNIVERSITY MEDICAL CENTER

1st ed.: 1909
2nd ed: 1923

Program Materials

Friday, April 24

Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH

Addressing Behaviors that Undermine a Culture of Safety, Reliability, and Accountability

Gerald B. Hickson, MD
Sr. Vice President for Quality, Safety and Risk Prevention
Assistant Vice Chancellor for Health Affairs
Joseph C. Ross Chair in Medical Education & Administration

1

Pursuing Reliability

Definition: "Failure free operation over time… effective, efficient, timely, pt-centered, equitable"

Requires:
– Vision/goals/core values
– Leadership/authority (modeled)
– A *safety* culture = willingness to report and address
  –Psychological safety
  –Trust

Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academies Press; 2001; Nolan et al. *Improving the Reliability of Health Care*. IHI Innovation Series. Boston: Institute for Healthcare Improvement; 2004; Hickson et al. Chapter 1: Balancing systems and individual accountability in a safety culture. In: Berman S., ed. *From Front Office to Front Line*. 2nd ed. Oakbrook Terrace, IL: Joint Commission Resources;2012:1-36.

2

Professionalism and Self-Regulation

- Professionals commit to:
  - *Technical and cognitive competence*
- Professionals also commit to:
  - *Clear and effective communication*
  - *Being available*
  - *Modeling respect*
  - *Self-awareness*
- Professionalism promotes *teamwork*
- Professionalism demands *self- and group regulation*

Hickson GB, Moore IN, Pichert JW, Benegas Jr M. Balancing systems and individual accountability in a safety culture. In: Berman S, ed. *From Front Office to Front Line*. 2nd ed. Oakbrook Terrace, IL: Joint Commission Resources;2012:1-36.

3

Checklists: The Keys to the Kingdom…

4

But wait…

The NEW ENGLAND JOURNAL of MEDICINE — Urbach DR, et al. Introduction of surgical safety checklists in Ontario, Canada. N Engl J Med. 2014 Mar 13;370(11):1029-38.

JAMA Surgery — Reames BN, et al. A Checklist-Based Intervention to Improve Surgical Outcomes in Michigan: Evaluation of the Keystone Surgery Program. JAMA Surg. 2015 Jan 14. doi: 10.1001/jamasurg.2014.2873. [Epub ahead of print].

- Conclusions:
  –Adjusted risk of death; surgical complications; SSIs; wound complications, 30-day mortality…

No Difference…

5

Case: "My Crackers"

A nurse observes:

Dr. X came into the nurses station and took my pack of crackers… I said, those are mine… he just looked at me and then said… "This is where I put MY crackers.", and turned and walked off.

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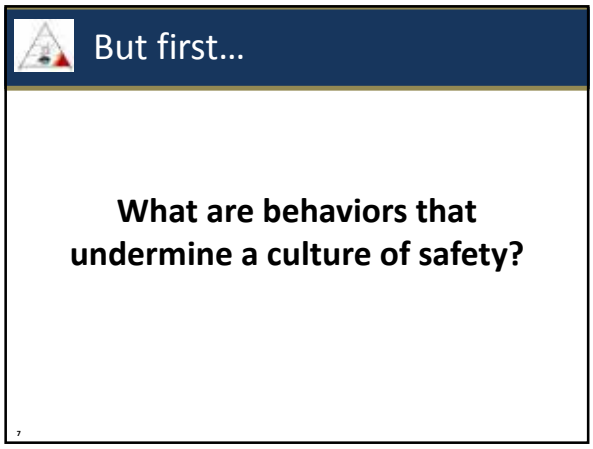
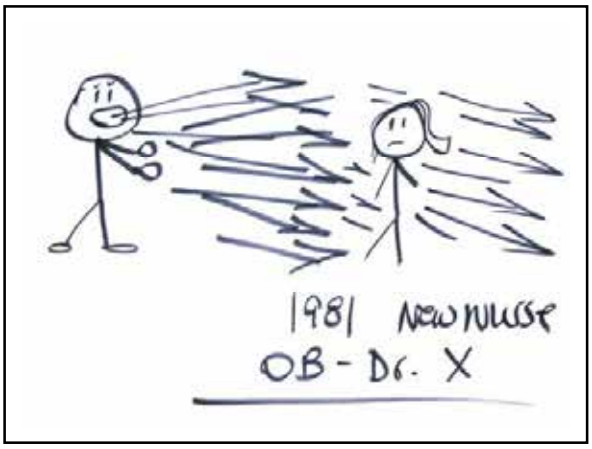
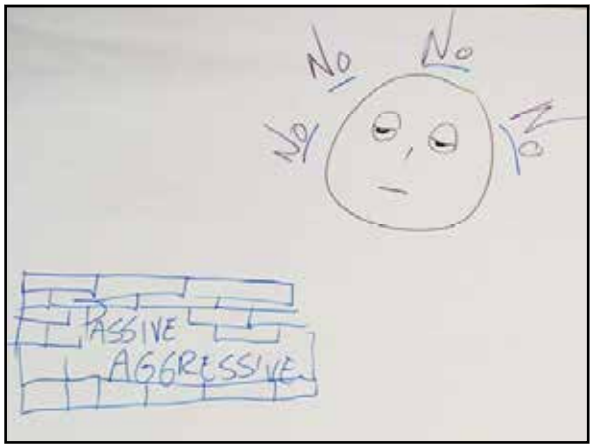
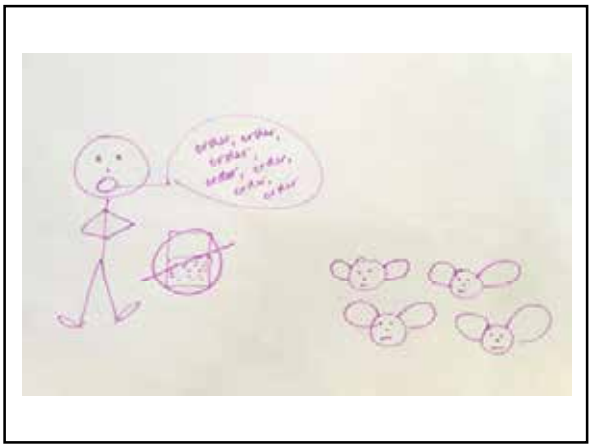
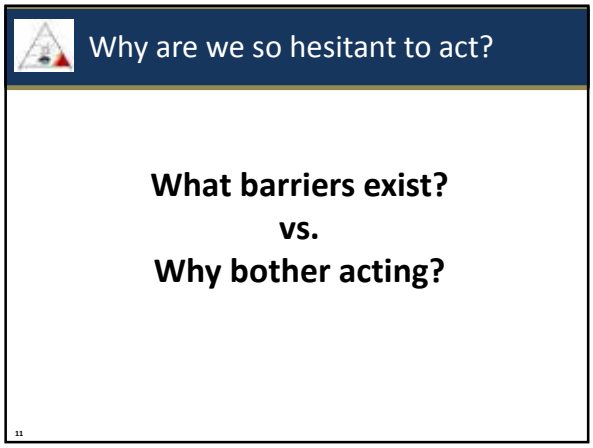
Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH

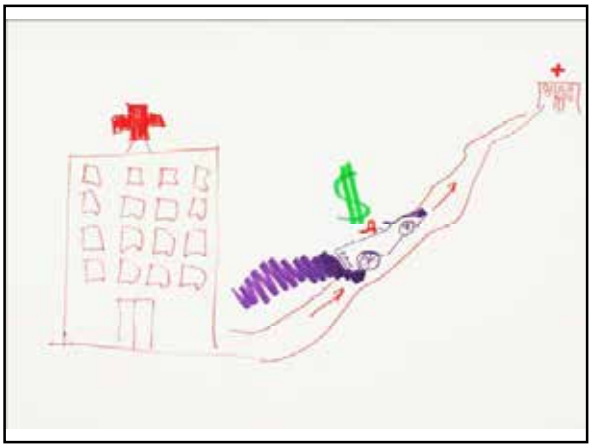












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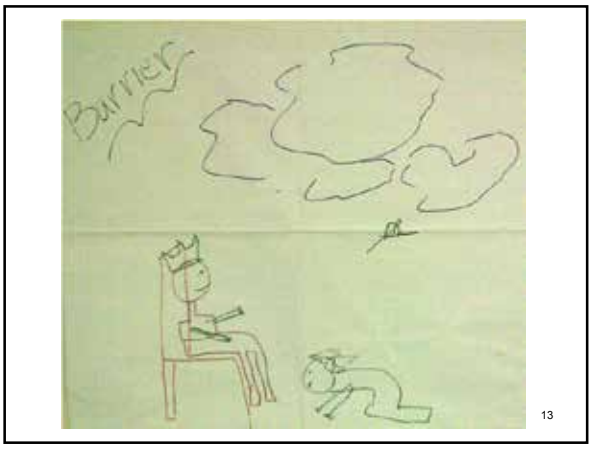
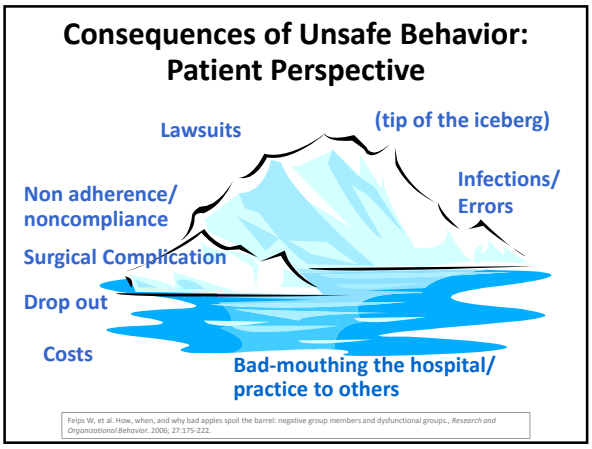
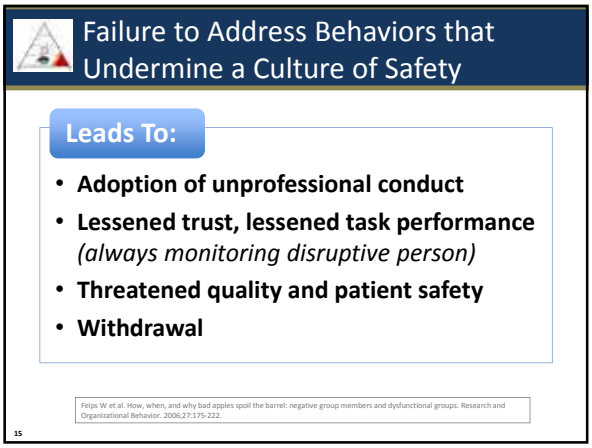
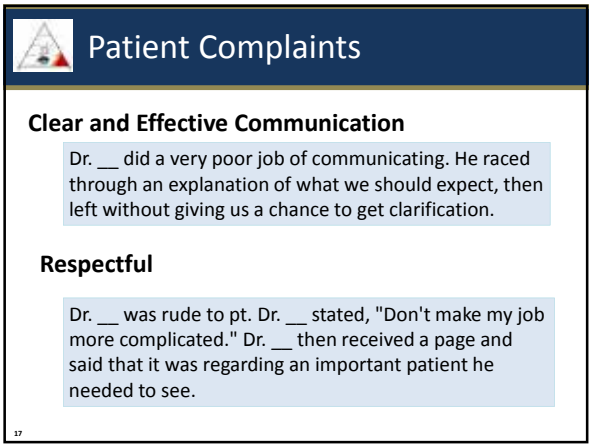
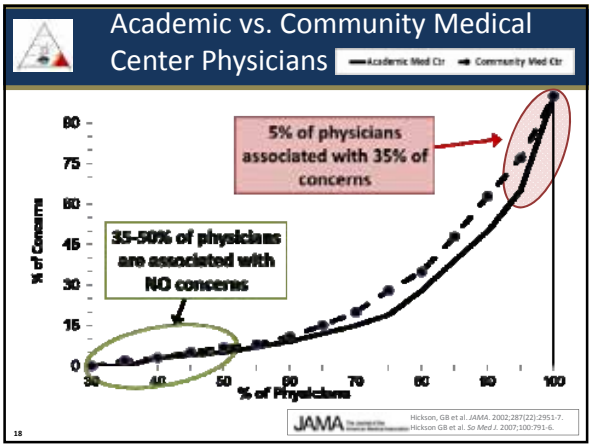
Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH











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Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH

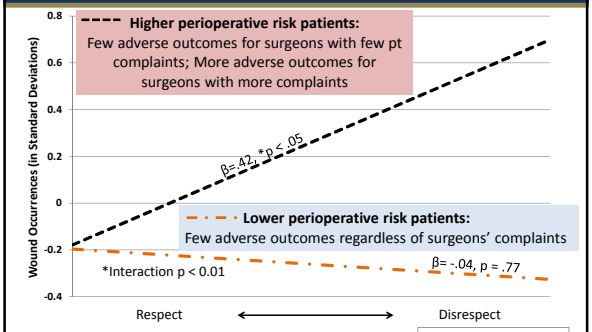
NSQIP and Pt Complaints

Risks	Patient Complaints	Outcomes
Preop Risk Factors	Comp Categories	Surgical Occurrences
ASA Class	Care & Treatment	Intraoperative
Priority Status	Communication	Wound
Wound Class	**Concern for Pt/Family**	Urinary
	Accessibility	CNS
	Billing w/C&T concern	Respiratory
		Other

Catron, Guillamondegui et al. Am J Med Qual, 2015, in press

19

Patient Complaints Moderate the Relationship Between Risk Factors and Surgical Outcomes *



*Wound depicted, same pattern for Urinary, Intraoperative, and Respiratory Occurrences. Analysis controls for # cases sampled.

Catron, Guillamondegui et al. Am J Med Qual, 2015, in press

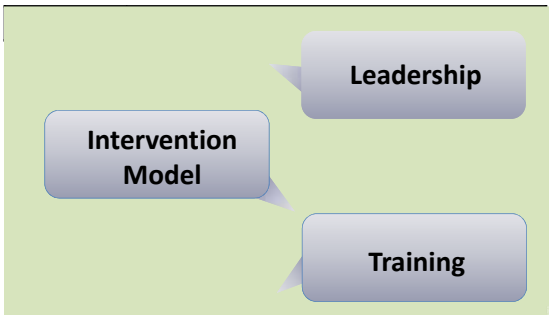
20

To "do something"
requires more than a commitment to professionalism and personal courage.

It requires a plan
(people, process and technology).

21

Critical Elements to Promote Accountability



Hickson GB, Pichert JW, Webb LE, Gabbe SG. A complementary approach to promoting professionalism: Identifying, measuring and addressing unprofessional behaviors. Acad Med. 2007 Nov;82(11):1040-1046. Hickson GB, Moore IN, Pichert JW, Benegas Jr M. Chapter 1: Balancing systems and individual accountability in a safety culture. In: Berman S, ed. From Front Office to Front Line. 2nd ed. Oakbrook Terrace, IL: Joint Commission Resources;2012:1-36.

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What Are "Surveillance Tools"?

Risk Event Reporting System	Patient Relations Department	Staff Concerns	Hand Hygiene Performance	Surgical Bundle Compliance

Hickson GB, Moore IN, Pichert JW, Benegas Jr M. Chapter 1: Balancing systems and individual accountability in a safety culture. In: Berman S, ed. *From Front Office to Front Line*. 2nd ed. Oakbrook Terrace, IL: Joint Commission Resources;2012:1-36.

23

Reports of Unprofessional Behavior

Anesth: Team attempted to do a time-out. Dr. X told everyone to "*listen closely*" and began whistling a tune…believe it was the Mickey Mouse theme song…

RN: Dr. X rushed…said to team setting up for surgery, "*Let's get going. Skip all the extra business and get the patient in here…*"

RN: Twice during consecutive surgeries Dr. X refused to do a time-out.

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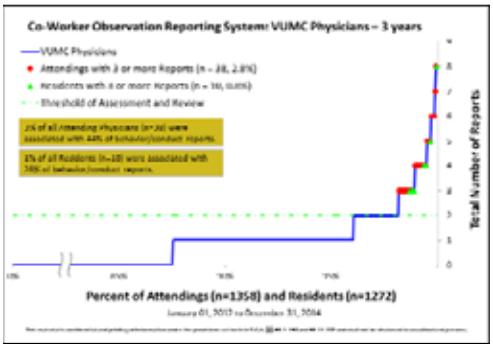
continued on page 33

Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH

Co-Worker Professionalism Reports about VUMC Physicians over a 3 Year Period



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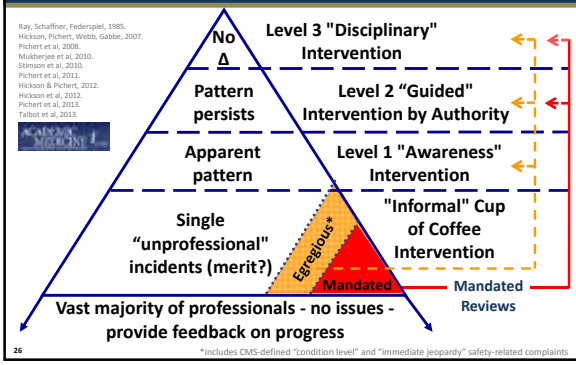
Promoting Professionalism Pyramid



26

Does any of this really work?

- Improves physicians' prescribing, clinical decision making[1]
- Reducing malpractice claims and expenses: By greater than 70%[2]
- Improving hand hygiene practices: From 50% to greater than 95% compliance[3]
- Addressing behaviors that undermine a culture of safety[4]

[1]Schaffner W, et al. JAMA 1983;250:1728-1732; Ray WA, et al. Am J Public Health 1987;77:1448-1450; Greco PJ, Eisenberg JM. New Engl J Med 1993;329:1271-1273
[2]Hickson et al. JAMA. 2002;287(22):2951-57; Hickson et al. South Med J. 2007;100(8):791-6; Pichert et al. In: Henriksen et al, editors. AHRQ; 2008: 421-30; Hickson & Pichert. In: Youngberg, editor. Jones and Bartlett Publishers; 2012: 347-68; Pichert et al. Jt Comm J Qual Patient Saf. 2013;39(10):435-46.
[3]Talbot et al. Infect Control Hosp Epidemiol. 2013; 34: 1129-36
[4]Dmochowski et al. Manuscript in preparation, 2014

27

Incurred Expense By Risk Category

Predicted Risk Category*	# (%) Physicians	Relative Expense*	% of Total Expense	Score (range)
1 (low)	**318 (49)**	**1**	**4%**	**0**
2	147 (23)	6	13%	1 - 20
3	76 (12)	4	4%	21 - 40
4	52 (8)	42	29%	41 - 50
5 (high)	**51 (8)**	**73**	**50%**	**>50**
Total	644 (100)		100%	

* In multiples of lowest risk group

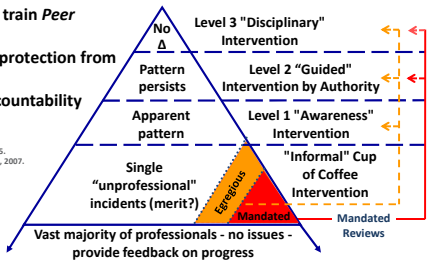
Moore, Pichert, Hickson, Federspiel, Blackford. *Vanderbilt Law Review*. 2006.

28

The PARS® Process

Share comparative feedback with tiered interventions using the *Pyramid for Promoting Reliability and Professional Accountability.*

- **Identify and train *Peer Messengers***
- **Position for protection from discovery**
- **Promote accountability**



References
- Ray, Schaffner, & Federspiel, 1985.
- Hickson, Pichert, Webb, & Gabbe, 2007.
- Pichert et al, 2008.
- Mukherjee et al, 2010.
- Stimson et al, 2010.
- Pichert et al, 2011.
- Hickson et al, 2012.
- Pichert et al, 2013.
- Talbot et al, 2013.

Adapted from Hickson, Pichert, Webb, & Gabbe. Acad Med. 2007. ©2013 Vanderbilt Center for Patient and Professional Advocacy

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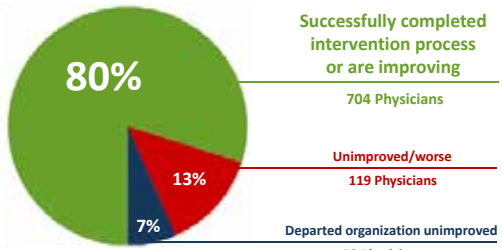
Awareness Interventions results: 00-15



Total number of high-risk physicians to date = 1170

Joint Commission Journal article honored with ABIM Foundation Professionalism Article Prize
"An Intervention Model that Promotes Accountability: Peer Messengers and Patient/Family Complaints" by James W. Pichert, Ilene N. Moore, Jan Karrass, Jeffrey S. Jay, Margaret W. Westlake, Thomas F. Catron and Gerald B. Hickson.

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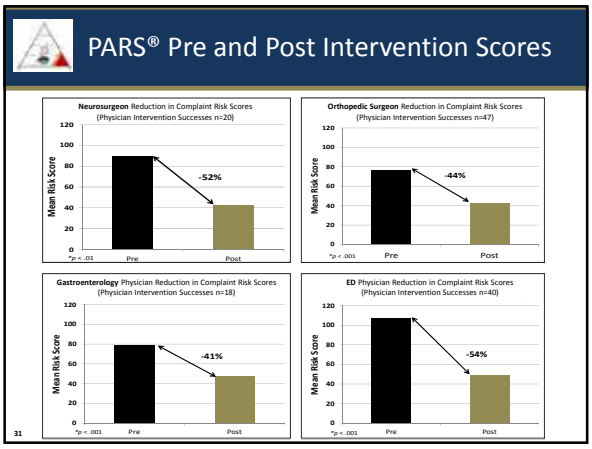
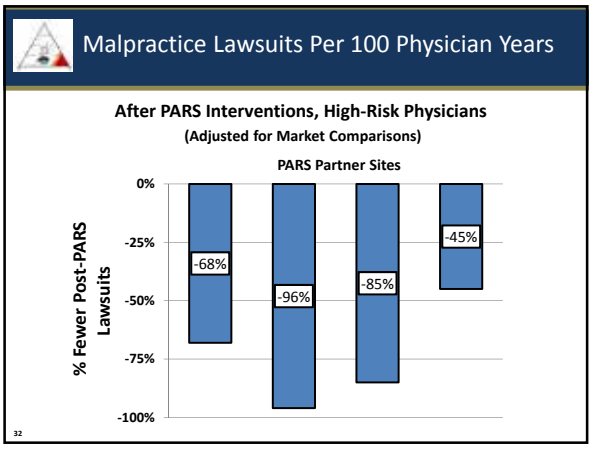
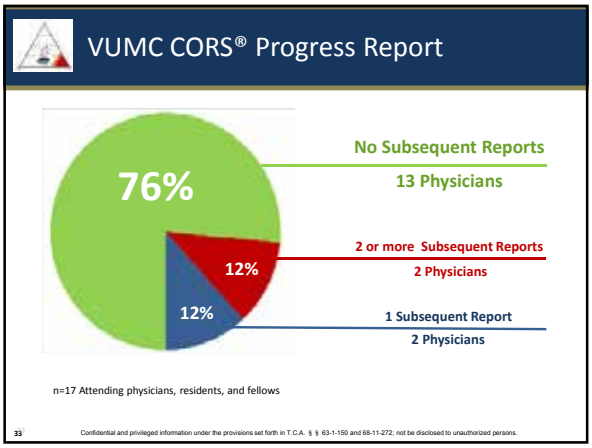
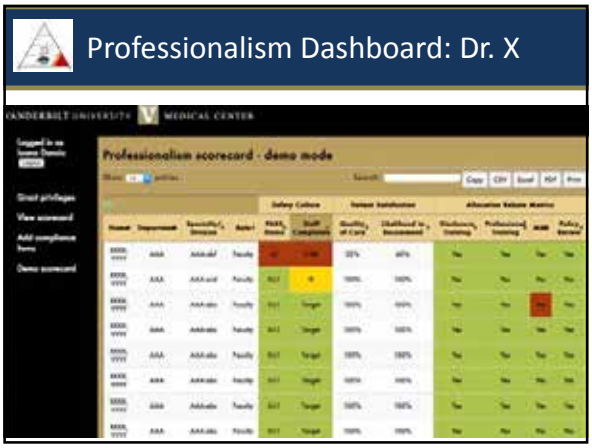
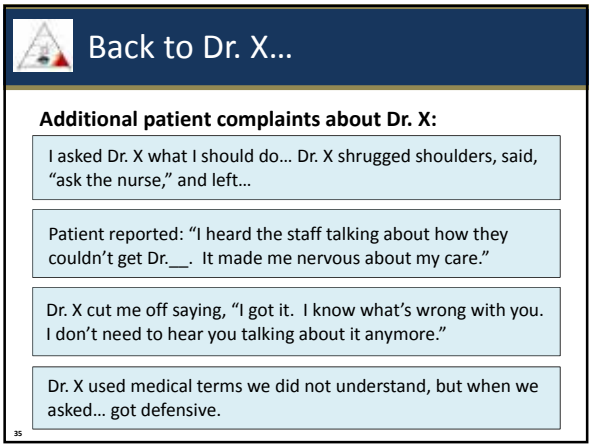
Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
William Cooper, MD, MPH

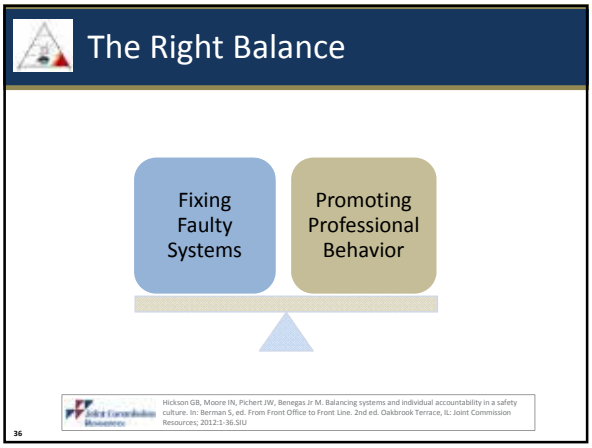












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Promoting Professional Accountability: Dealing with Behaviors that Undermine a Culture of Safety and Reliability
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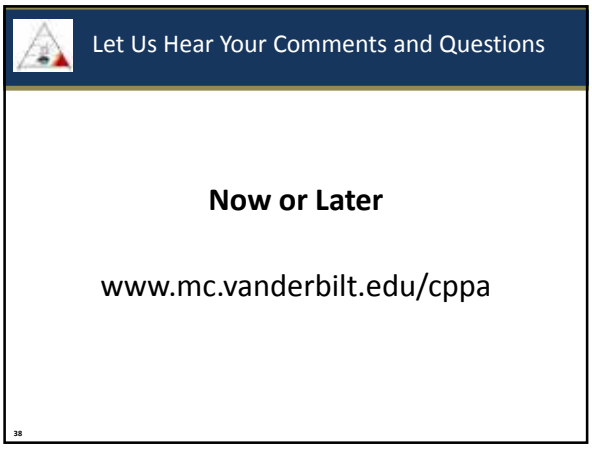
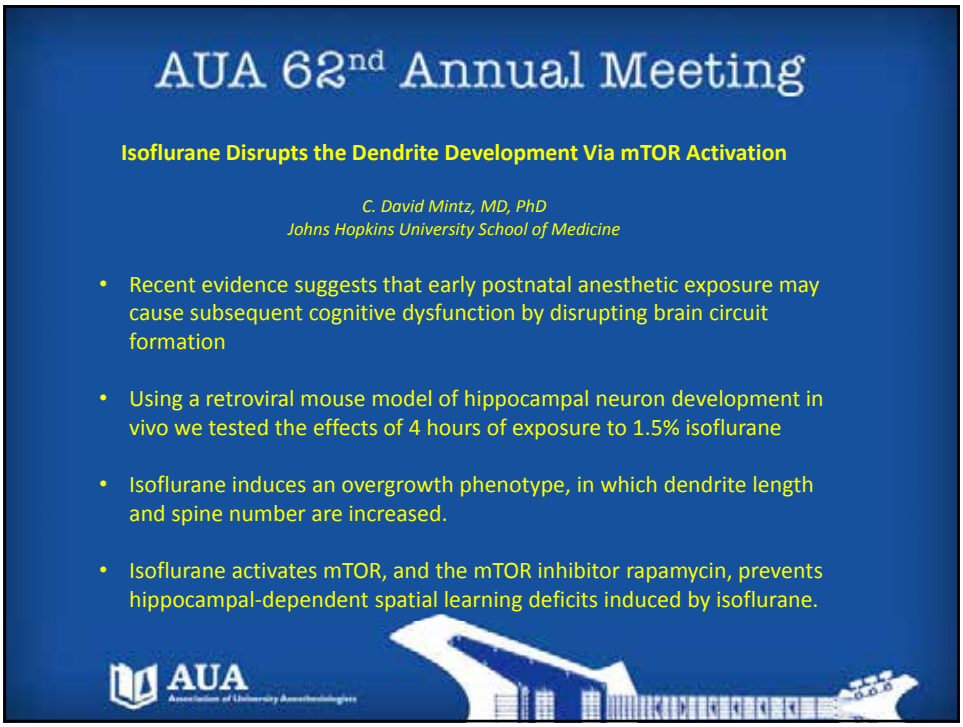
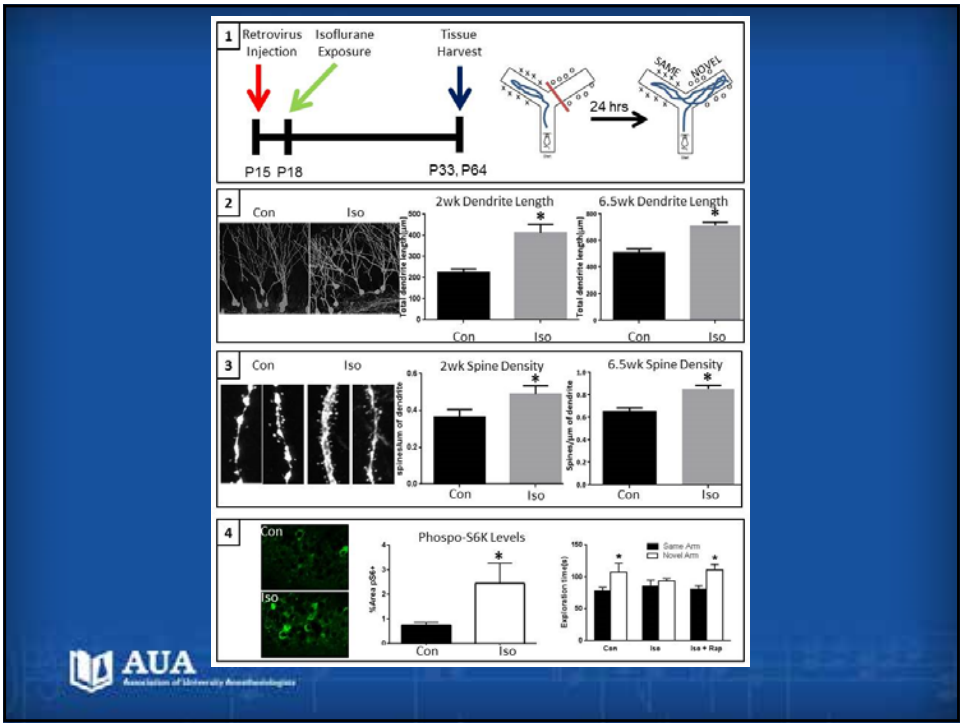


Program Materials

Saturday, April 25, 2015

Isoflorane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway
Cyrus Mintz, MD, PhD





Program Materials

Saturday, April 25, 2015

Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline
Niccolo Terrando, BSc (hons), DIC, PhD

Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline
Niccolo Terrando, Ph.D., Duke University, Durham, North Carolina

Overall objective:

To describe how specialized pro-resolving lipid mediators (SPM) can prevent surgery-induced neuroinflammation and cognitive decline after orthopedic surgery in a mouse model.

Intended learning outcomes:

1. To discuss the role of macrophage activity in mediating neuroinflammation and cognitive decline after peripheral surgery
2. To discuss novel evidence for maresin-1 (MaR-1), a macrophage-derived mediator of inflammation resolution, in modulating systemic and central inflammation
3. To elaborate on the pro-resolving effects of MaR1 on bone healing and its potential for novel clinical studies in POCD research

AUA
Association of University Anesthesiologists

2015 Abstract Award Winners

JUNIOR FACULTY RESEARCH AWARD	**OC 1 (61)** **Pediatric Delirium in Critically Ill Infants and Preschool-aged Children: Validation and Reliability of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)** Heidi A. B. Smith, MD, MSCi[1], D. Catherine Fuchs, MD[1], Mary Hamilton Chestnut, NP[1], Jennifer L. Thompson, MPH[1], Pratik P. Pandharipande, MD, MSCi[1] *[1]Vanderbilt University, Nashville, Tennessee*	*Oral Presentation:* **SAB Oral Session (Part 1)** Thursday, April 23, 2015 1:00 pm – 3:15 pm *Poster Discussion:* **Moderated Poster Discussion Outcomes** Thursday, April 23, 2015 3:15 pm – 4:45 pm
JUNIOR FACULTY RESEARCH AWARD	**Tox Cogn Dysfx 55 (28)** **Isoflurane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway** Cyrus D. Mintz, MD, PhD[1], Danye Jiang, BS[1], Yun K. Ryu, PhD[2], Sanghee Lim, MS[1], Minhye Kwak, MS[1] *[1]Johns Hopkins Hospital, Baltimore, Maryland* *[2]Columbia University, New York, New York*	*Oral Presentation:* **SAB Oral Session (Part 2)** Saturday, April 25, 2015 8:00 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Toxicity and Cognitive Dysfunction** Saturday, April 25, 2015 10:15 am – 11:45 am
MARGARET WOOD RESIDENT RESEARCH AWARD	**Clin Neuro 31 (43)** **The Relative Effects of Dexmedetomidine and Propofol on Cerebral Blood Flow and Brain Oxygenation: A Noninferiority Study** Michael Kot, MD[1], Ehab Farag MD, FRCA[1], Attila Podolyak, MD[1], Daniel Sessler, MD[1], Edward Mascha, PhD1, Andrea Kurz, MD[1] *[1]Cleveland Clinic, Cleveland, Ohio*	*Oral Presentation:* **SAB Oral Session (Part 1)** Thursday, April 23, 2015 1:00 pm – 3:15 pm *Poster Discussion:* **Moderated Poster Discussion Clinical Neuroscience** Thursday, April 23, 2015 3:15 pm – 4:45 pm
RESIDENT TRAVEL AWARD	**CS/Metab 22 (62)** **Dexmedetomidine's Inhibitory Effects on Acetylcholine Release from Cholinergic Nerves in Guinea Pig Trachea: A Mechanism That Accounts for Its Clinical Benefit during Airway Irritation** Maya Mikami, MD, PhD[1], Yi Zhang, MD[1], Charles W. Emala, MD[1] *[1]Columbia University College of Physicians and Surgeons, New York, New York*	*Oral Presentation:* **SAB Oral Session (Part 2)** Saturday, April 25, 2015 8:00 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Cell Signaling/Metabolism** Saturday, April 25, 2015 10:15 am – 11:45 am
RESIDENT TRAVEL AWARD	**OC 4 (52)** **Effects of Race and Common Genetic Variation on Therapeutic Response Disparities in Postoperative Atrial Fibrillation** Nazish K. Hashmi, MB, BS[1], Mary Cooter, PhD[1], Yi-Ju Li, PhD[1], Miklos Kertai, MD, PhD[1], Mihai V. Podgoreanu, MD, FASE[1] *[1]Duke University Medical Center, Durham, North Carolina*	*Oral Presentation:* **SAB Oral Session (Part 2)** Saturday, April 25, 2015 8:00 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Outcomes** Saturday, April 25, 2015 10:15 am – 11:45 am

Junior Faculty Research Award

OC 1 (61)

Pediatric Delirium in Critically Ill Infants and Preschool-Aged Children: Validation and Reliability of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)

Heidi A. B. Smith, MD, MSCi[1], D. Catherine Fuchs, MD[1], Mary Hamilton Chestnut, NP[1], Jennifer L. Thompson, MPH[1], Pratik P. Pandharipande, MD, MSCi[1]

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Introduction: Delirium occurs in up to 80% of critically ill adults and is associated with worse outcomes including long-term cognitive impairment and death. Among critically ill pediatric cohorts, however, delirium remains poorly understood due to limited availability of valid delirium tools for all ages. The Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) is a highly valid delirium screening tool for critically ill children ≥ 5 years of age (1). Due to variations in cognitive and language development, infants and preschool-aged children create unique challenges for delirium assessment. The objectives of this study are to determine 1) the validity and reliability of a delirium instrument for critically ill infants and preschool-aged children, 2) the prevalence of pediatric delirium, and 3) the frequency of motoric delirium subtypes.

Methods: An interdisciplinary team comprised of pediatric anesthesiology/critical care, neurodevelopmental pediatrics, and psychiatry created the PreSchool Confusion Assessment Method for the ICU (psCAM-ICU) based on the hierarchical design of the pCAM-ICU that requires: 1) fluctuation or change in mental status, 2) inattention, and 3) either signs of a disorganized brain or an altered level of consciousness for delirium diagnosis. We enrolled patients 6 months to 5 years of age, admitted to the PICU of a tertiary medical center, regardless of diagnosis. Patients with hearing/visual impairments, non-English speaking, moribund, or surrogate refusal of consent, were excluded. Enrolled patients were independently assessed for delirium daily by the research team, using the psCAM-ICU, and the reference standard, a psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criterion. The paired independent delirium assessments had to occur ≤ 3 hours apart. The reference standard designated motoric subtypes including: hyperactive, hypoactive, or mixed, based on the pattern of observed behaviors consistent with delirium. Reliability was assessed using simultaneous scoring of the psCAM-ICU by two research team members in a blinded fashion. We determined specificity, sensitivity, negative predictive value (NPV), and positive predictive value (PPV) using clustered bootstrapping by patient, since multiple delirium assessments were conducted on individual patients.

Results: A total of 631 independent delirium assessments were completed on 300 enrolled patients with a median age of 20 months (IQR 10,37). Compared with the reference standard for delirium diagnosis, the psCAM-ICU performed with a specificity of 91% (95%CI 90,93), sensitivity of 75% (72,78), NPV of 86% (84,88), and PPV of 84% (81,87). The psCAM-ICU was highly reliable with a kappa statistic of 0.79 (0.76,0.83). Among patients on mechanical ventilation, the psCAM-ICU demonstrated a specificity of 96% (93,99) and a sensitivity of 81% (77,85). The psCAM-ICU detected delirium in 44% of the cohort. Rates of delirium were 56% in patients ≤ 2 years of age versus 35% in patients 2-5 years of age. The majority of patients with delirium demonstrated the hypoactive subtype (64%) of delirium, while the mixed (29%) and hyperactive (7%) subtypes were less frequently observed.

Conclusion: The psCAM-ICU is a valid and reliable delirium screening tool in critically ill infants and preschool-aged children. Delirium is extremely common in the pediatric critical care population. The hypoactive subtype is the most frequent behavioral pattern observed in critically ill infants and children with delirium. Delirium monitoring using the psCAM-ICU will promote further study of delirium in the PICU setting including understanding potential risk factors and related outcomes.

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1. Diagnosing delirium in critically ill children: Validity and reliability of the Pediatric Confusion Assessment Method for the Intensive Care Unit. Smith HA, et al. Crit Care Med 201; 39:150-7

Junior Faculty Research Award

Tox Cogn Dysfx 55 (28)
Isoflurane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway

Cyrus D. Mintz, MD, PhD[1], Danye Jiang, BS[1], Yun K. Ryu, PhD[2], Sanghee Lim, MS[1], Minhye Kwak, MS[1]

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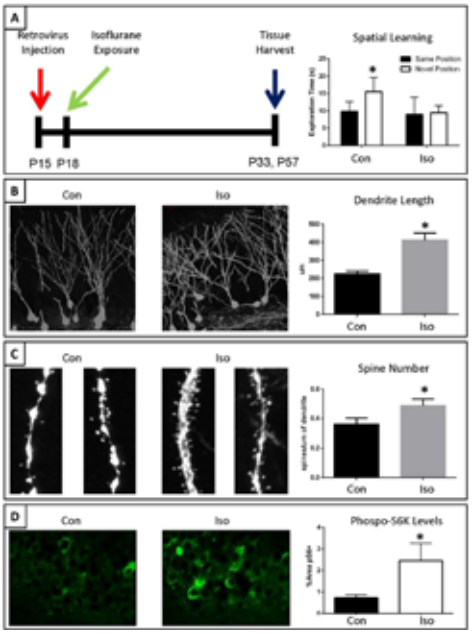
Introduction: Epidemiologic studies have raised concerns that pediatric exposure to anesthetics may have lasting adverse effects on cognitive function (1), and studies in animal models show that anesthetic exposure during development causes chronically reduced performance in behavioral tests of learning (2). It has been hypothesized that developmental anesthetic exposure may cause a lasting effect on cognitive function by disrupting the generation of brain circuits, a process which requires appropriate, coordinated development of axons and dendrites. Previously we have shown that anesthetics interfere with the development of axons (3). Here we investigate the effects of isoflurane on dendrite development in vivo in the mouse hippocampus.

Methods: A murine retrovirus that specifically infects newborn neurons and expresses GFP was stereotaxically injected into the dentate gyrus (DG) at P15. Mice were treated for 4 hours with 1.5% isoflurane. Groups consisted of naïve controls, single exposure (P18), or multiple exposure (P18, P20, P22). After harvest (on P33 or P57), brain sections were immunolabeled labeled for GFP. A minimum of 50 neurons from 5 animals per condition were imaged by confocal microscopy, and morphological measurements were made using NeuroLucida. Quantitative immunofluorescence was performed for phospho-S6 kinase (p-S6k) and analyzed with Metamorph. A 24 hour latency object-place recognition test was used to evaluate spatial learning.



Results: To determine the effects of anesthetics on dendrite development, we employed a retroviral strategy to label selected newborn DG neurons with GFP for systematic examination of their development in vivo (Fig A, left). We conducted behavioral testing to validate our model, in which exposure occurred at P18 to allow for successful retroviral injection. We found that anesthetic exposed animals displayed substantial deficits in recognizing novel positioning of an object (Fig A, right), indicating a learning impairment. Morphological analysis of individual neurons showed striking overgrowth of dendrites in the anesthetic groups. Dendrite length (Fig B) and spine number (Fig C) were markedly increased, as were branch number and complexity (not shown). These findings occurred at two and a half weeks (Fig B, C) and were sustained at six weeks (not shown). Multiple exposures yielded more dramatic effects than single exposures (not shown). These rather surprising findings are reminiscent of the morphological changes of Fragile X Mental Retardation, a disorder mediated by increased activity in the mTOR pathway, a signaling system implicated in a variety of neurodevelopmental disorders. We measured levels of p-S6K, a well-known marker of mTOR activation, and found a two-fold increase two weeks after a single isoflurane exposure (Fig D).

Conclusion: These data are the first in evidence of a lasting disruption of dendrite development in vivo caused by anesthetic exposure. The observed pathologic overgrowth, which may be mediated by mTOR activation, represents a novel mechanism by which anesthetics interfere with the development of brain circuits.

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Margaret Wood Resident Research Award

Clin Neuro 31 (43)
The Relative Effects of Dexmedetomidine and Propofol on Cerebral Blood Flow and Brain Oxygenation: A Noninferiority Study

Michael Kot, MD[1], Ehab Farag MD, FRCA[1], Attila Podolyak, MD[1], Daniel Sessler, MD[1], Edward Mascha, PhD[1], Andrea Kurz, MD[1]

[1]Cleveland Clinic, Cleveland, Ohio

Background: Dexmedetomidine is considered a promising sedative agent in the perioperative period. However, its vasoconstrictive effect on cerebral blood vessels1, 2, 3 without concomitant reduction in cerebral metabolic oxygen consumption makes its safety in the patients with neurological diseases is uncertain4, 5. Therefore, we tested the hypothesis that dexmedetomidine is noninferior to propofol with regards cerebral blood flow velocity and brain oxygenation.

Methods: Patients were randomized to receive either dexmedetomidine or propofol during deep brain stimulator insertion procedures using the sleep awake sleep technique. Both dexmedetomidine and propofol were given using target control infuser in varying doses during the procedure (Dex was infused to achieve plasma level of 0.8-1ng/ml, and propofol was infused to achieve plasma level of 2-3mcg/ml). After electrode insertion and before microelectrode testing Dex was reduced to 0.4ng/ml and propofol was stopped. Both the cerebral blood flow velocities and brain oxygenation were measured by trans-cranial Doppler and near infrared spectroscopy before procedure, with peak level, at lowest level, at peak level after restarting infusion and in PACU.

Statistical Analysis

Primary outcome: We tested the joint hypothesis that dexmedetomidine was noninferior to propofol both in terms of cerebral blood flow velocity and brain oxygenation during DBS surgery. We specified an a priori noninferiority ratio of 0.80 for each outcome, so that noninferiority would be claimed for an outcome if the mean for dexmedetomidine was no more than 20% lower (worse) than that of propofol. A relative difference of 20% or less was a priori deemed to be clinically unimportant.

Secondary outcome: We evaluated the effect of dexmedetomidine and propofol on pulsatility index, cerebral perfusion pressure, OAA/S, number of hypertensive episodes during DBS surgery and number of apneic episodes during DBS surgery. We defined the outcome variable for pulsatility index, cerebral perfusion pressure and OAA/S as the corresponding measurements at the first zenith during DBS surgery.

Separate linear regression models were built (after log transformation) to estimate the effect of dexmedetomidine and propofol on pulsatility index and cerebral perfusion pressure while including baseline measurements as a covariate. Furthermore, the two groups were compared on OAA/S, number of hypertensive episodes and number of apneic episodes using student t-test and Wilcoxon rank-sum test as appropriate.

Results: Dexmedetomidine was found noninferior to propofol on both cerebral blood flow and brain oxygenation, confirming our primary hypothesis. For cerebral flood flow the estimated ratio of means (dexmedetomidine / propofol) was 0.94 (90% CI: 0.84, 1.05), P = 0.011, and significantly greater than the a priori noninferiority ratio of 0.8. For brain oxygenation the estimated ratio of means (dexmedetomidine / propofol) was 0.99 (90% CI: 0.96, 1.02), P < 0.001, also significantly greater than 0.8. Superiority was not found for either primary outcome. In secondary analyses dexmedetomidine was found superior to propofol on the Observer's Assessment of Alertness/Sedation (OAA/S) scale, with difference of medians of 1 (1.0, 3.0), P<0.001, but not on pulsatility index, cerebral perfusion pressure, or number of either hypertensive or apneic episodes during DBS surgery.

Conclusions: The effect of dexmedetomidine is no more than 20% worse than propofol on brain oxygenation and cerebral blood flow during awake deep-brain stimulator insertion.

continued on page 30

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Table 1. Demographics and baseline characteristics for dexmedetomidine and propofol patients

Factor	Dexmedetomidine (N = 23)	Propofol (N = 21)	STD
Age, years.	65.4 ± 6.8	63.5 ± 10.5	0.22
Gender, Female, N (%)	5 (22)	3 (14)	0.19
Race, Caucasian, N (%)	21 (91)	21 (100)	-0.44
BMI	26.5 ± 4.9	28.6 ± 5.7	-0.39
ASA Status[a]			0.32
II	5 (25)	8 (40)	
III	15 (75)	12 (60)	
Medical history, yes, N(%)			
Parkinson	16 (70)	16 (76)	-0.15
Essential tremor	8 (35)	6 (29)	0.13
Use of drug, yes, N (%)			
Antiparkinson	20 (87)	16 (76)	0.28
Antihypertensive	13 (57)	12 (57)	0.01
Lead implantation placements, N (%)			-0.42
STN	16 (70)	16 (76)	
VIM	4 (17)	1 (5)	
Thalamic	3 (13)	4 (19)	
Year of Surgery, N (%)			0.13
2011	5 (22)	4 (19)	
2012	11 (48)	13 (62)	
2013	7 (30)	4 (19)	
Baseline measurements			
FVm, cm/sec	47.9 ± 9.3	49.1 ± 11.1	-0.12
Pulsatility index	1.0 [0.9, 1.2]	0.9 [0.8, 1.1]	0.52
Cerebral Perfusion pressure[b]	47.4 [39.5, 60.7]	51.8 [48.0, 62.2]	-0.44

ASA = American Society of Anesthesiologists; STD = standardized difference; BMI = body mass index; FVm = cerebral blood flow velocity; STN = subthalamic nucleus; VIM = ventrointermediate nucleus of thalamus

[a] There were 4 missing values in preoperative ASA status.

[b] There were 3 missing values in baseline measurement of cerebral perfusion pressure.

Table 2. Effect of dexmedetomidine versus propofol on primary outcomes of mean cerebral blood flow velocity and oxygenation using one-sided noninferiority tests.

Primary outcome*	Dexmedetomidine	Propofol	Ratio of geometric means (90% CI) (Dexmedetomidine vs. Propofol)	p**
Mean cerebral blood flow velocity[a], cm/sec	39.9 [31.5, 47.0]	45.4 [37.0, 48.0]	0.94 (0.84, 1.05)	0.011
Brain oxygenation[b], %	72.7 [70.0, 75.3]	73.5 [70.3, 76.6]	0.99 (0.96, 1.02)	<0.001

* Both primary outcomes followed a log-normal distribution, so a log transformation was implemented. The corresponding effect size was thus specified as ratio of geometric means.

** 1-tailed test whether ratio of geometric means is greater than the a priori noninferiority ratio of means (dexmedetomidine divided by propofol) of 0.8. Since noninferiority was required for both outcomes, no adjustment for having two primary outcomes was needed; significance criterion was $P < 0.05$.

[a] There was 1 missing value in the dexmedetomidine group, so we assigned the observed minimum (worst) blood flow velocity to that patient to be conservative. Comparisons were adjusted for baseline measurements.

[b] There were 4 missing values in the dexmedetomidine group, so we assigned the observed minimum (worst) brain oxygenation to those patients to be conservative.

Table 3. Perioperative measurements for dexmedetomidine and propofol patients (N=44)

Variable	Dexmedetomidine (N = 23)	Propofol (N = 21)	STD
Mean cerebral blood flow, cm/sec			
Preoperative	47.9 ± 9.3[b]	49.1 ± 11.1[a]	-0.12
First peak dose	40.5 ± 7.9[a]	45.4 ± 17.0	-0.37
Lowest dose	40.7 ± 7.7[b]	43.1 ± 10.7[b]	-0.25
Second peak dose	44.3 ± 13.8[c]	48.2 ± 13.9[b]	-0.28
PACU	46.7 ± 10.5	55.0 ± 18.1[b]	-0.56
Mean arterial pressure, mmHg			
Preoperative	89.7 ± 16.1[d]	99.5 ± 11.3[b]	-0.70
First peak dose	89.8 ± 12.4[a]	80.9 ± 12.6	0.71
Lowest dose	83.5 ± 9.8[a]	89.0 ± 10.0[b]	-0.56
Second peak dose	82.5 ± 8.9[c]	79.9 ± 13.0[b]	0.23
PACU	79.4 ± 11.6[e]	87.1 ± 15.2[f]	-0.57
Systolic blood pressure, mmHg			
Preoperative	133.7 ± 21.5[d]	133.7 ± 33.0[b]	0.00
First peak dose	122.0 ± 15.4[a]	107.7 ± 27.3	0.65
Lowest dose	113.3 ± 13.0[a]	124.6 ± 15.7[b]	-0.78
Second peak dose	115.0 ± 12.9[c]	110.2 ± 14.7[b]	0.35
PACU	113.4 ± 14.9[e]	120.7 ± 17.5[f]	-0.45

Standardized difference (STD): the difference in means or proportions divided by the pooled standard deviation.

N missing values: [a]=1, [b]=2, [c]=3, [d]=4, [e]=6, [f]=9

Resident Travel Award

CS/Metab 22 (62)
Dexmedetomidine's Inhibitory Effects on Acetylcholine Release from Cholinergic Nerves in Guinea Pig Trachea: A Mechanism That Accounts for its Clinical Benefit during Airway Irritation

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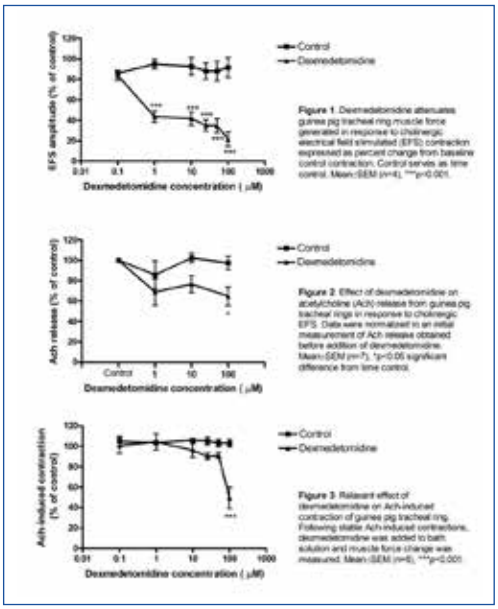
Introduction: Laryngospasm, bronchospasm and cough are adverse events during intubation and extubation of the airway. These airway events occur in part by irritant-induced neuronal modulation of airway tone. The parasympathetic nerves originate from airway-related vagal preganglionic neurons, and after synapsing at parasympathetic ganglia release acetylcholine (Ach) from post-ganglionic cholinergic nerves. The release of Ach is dysregulated in some animal models of asthma [1] and possibly in human asthmatics [2], suggesting a mechanistic basis for clinically observed reflex-induced bronchoconstriction following airway manipulation. The clinical utility of opioids, local anesthetics or alpha-2 agonists in reducing airway responses during awake intubation or emergence from anesthesia may be explained by activation of pre-junctional receptors on postganglionic parasympathetic nerves resulting in decreased Ach release. We questioned whether remifentanil, lidocaine or dexmedetomidine attenuated Ach release from electrically field stimulated (EFS)-nerves in guinea pig trachea.



Methods: Studies were approved by the institutional IACUC. Tracheal rings were isolated from male guinea pigs under pentobarbital anesthesia and suspended in organ baths filled with a physiological buffer. EFS was applied (DC current: 30Hz, 24V, 0.5msec pulse width in single 10sec trains) +/- cumulatively increasing concentrations of dexmedetomidine while measuring airway smooth muscle (ASM) contractile force. In the separate experiments, buffer was supplemented with 0.1μM atropine, 10μM guanethidine and 0.1μM neostigmine and 2Hz EFS was applied +/- remifentanil, lidocaine or dexmedetomidine. Organ bath buffer was collected and lyophilized (FreeZone 2.5 Plus, Labconco) and reconstituted in 500μl water. Ach was measured using a choline/acetylcholine quantitation kit (Sigma-Aldrich). Tracheal rings were also contracted with exogenous Ach, and after a sustained contraction was established, dexmedetomidine was added to the buffer to measure direct ASM relaxation.

Results: Dexmedetomidine (1-100μM) attenuated EFS-induced tracheal ring contraction (Figure 1) and Ach release (Figure 2) while lidocaine (10μM - 1mM) and remifentanil (0.1 – 10μM) did not. Dexmedetomidine at high concentrations (100μM) also attenuated muscle force induced by the exogenous addition of the contractile agonist Ach (Figure 3). Tetrodotoxin, known to abolish nerve release of Ach, attenuated EFS-induced Ach release in a dose-dependent manner and served as a positive control.

Conclusion: The alpha-2 agonist dexmedetomidine reduced EFS-induced contraction and Ach release consistent with the presence of inhibitory alpha-2 adrenergic receptors on the prejunctional side of the postganglionic parasympathetic nerve [3]. Lidocaine and remifentanil, which are frequently used clinically to reduce airway reflexes, did not effect EFS-induced Ach release. Dexmedetomidine at high concentrations attenuated the contractile response to exogenous Ach suggesting that dexmedetomidine's clinical effect on attenuating airway responses may not be limited to its effect on neurotransmission. Our findings provide a plausible mechanism for the observed utility of dexmedetomidine in attenuating airway reactivity during awake airway instrumentation.

References

1. Am J Physiol 1994; 266: L263-270
2. Neuroimmunomodulation 1999; 6: 145-159
3. Life Sciences 1981; 28: 2981-2986

Resident Travel Award

OC 4 (52)

Effects of Race and Common Genetic Variation on Therapeutic Response Disparities in Postoperative Atrial Fibrillation

Nazish K. Hashmi, MB, BS[1], Mary Cooter, PhD[1], Yi-Ju Li, PhD[1], Miklos Kertai, MD, PhD[1], Mihai V. Podgoreanu, MD, FASE[1]

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Background: Variability in perioperative beta-blocker (BB) responsiveness can be attributed to differences in drug metabolism and genetic polymorphisms in the adrenergic signaling pathway. Over 80 polymorphisms have been identified in the CYP2D6 enzyme, involved in the hepatic metabolism of BB. Race-associated differences in cardiac surgical outcomes, both short-term (postoperative atrial fibrillation, PoAF) and long-term (mortality and event-free survival), are well known, and may be associated with genetic variation in BB pharmacokinetics and drug targets that can potentially explain variability in racially based responses to BB therapy. Accumulating evidence suggests that such pharmacogenomic variations may contribute to increased adverse effects (hypotension and bradycardia) or reduced efficacy of BB. We hypothesized that race-associated differences in incidence of PoAF following CABG could be in part explained by therapeutic response disparities to perioperative BB administration, that are pharmacogenomically mediated.

Table A. Racial distribution of selected signaling pathway alleles

	AA subjects (N=140)	EA subjects (N=2532)		
New onset PoAF (%)	14	28		
Gene, amino acid or nucleotide position, SNP reference (rs) number, proxy SNP	AA MAF	EA MAF	AA vs EA MAF	AA vs EA effect on sympathetic signaling
ADRB1 Arg389Gly (rs1801253-rs740746*)	0.32 Gly	0.28 Gly	~14% ↑Gly	↓ADRB1
ADRB1 Ser49Gly (rs1801252-rs10885530*)	0.1 Gly	0.13 Gly	-	-
ADRB2 Gly16Arg (rs1042713*)	0.49 Arg	0.37 Arg	~24% ↑Arg	↓ADRB2
ADRB2 Gln27Glu (rs1042714*)	0.23 Glu	0.42 Glu	~24% ↓Glu	↓ADRB2
ADRB2 T-47C 5'UTR (rs1042711-rs2082382*)	0.14 C	0.43 C	~67% ↓C	↓ADRB2
ADRB3 Trp64Arg (rs4994-rs7004842*)	0.22 Arg	0.08 Arg	~1.8-fold ↑Arg	↓ADRB3
GNB3 C825T (rs5443-rs2238114*)	0.43 T	0.29 T	~48% ↑T	↑ ADR drive
CYP2D6 G1146A (*4) (rs1800716-rs3892097*)	0.07 C	0.19 C	~63% ↓C	↓poor BB metab.
CYP2D6 C100T (*10) (rs1065852-rs5758637*)	0.38 T	0.22 T	~73% ↑T	-
CYP2D6 G4180C (rs1135840-rs7245*)	0.26 C	0.44 C	~41% ↓C	↓poor BB metab.
4q25 (rs2200733)	0.15 G	0.12 G	-	-
4q25 (rs10033464)	0.22 C	0.09 C	-	-

Table B. Multivariable predictors of new onset PoAF

Variable	OR (95% CI), p
Race (AA vs EA)	0.48 (0.28-0.78), p=0.003
Afib risk index	P<0.0001
Age	1.06 (1.05-1.08), p=3.4x10^{-11}
COPD	1.39 (1.11-1.76), p=0.004
Preop BB	1.22 (1.01-1.48), p=0.03
Race x preop BB	NS
COPD	1.39 (1.11-1.76), p=0.004
ADRB2 5'UTR -47C*	2 (1.02-3.93), p=0.04
ADRB2 5'UTR -47C x preop BB#	0.67 (0.46-0.98), p=0.04
4q25 rs2200733 A#	0.66 (0.50-0.87), p=0.003

PoAF, postoperative atrial fibrillation; AA, African ancestry; EA, European ancestry; SNP, single nucleotide polymorphism; MAF, minor allele frequency; UTR, untranslated region; ADR, adrenergic; BB, beta-blocker; BB metab., beta-blocker metabolizer; *proxy SNP (from 1000 genomes); #, in EA subjects only

Methods: We analyzed a cohort of N=3014 ethnically diverse patients (AA, African ancestry; EA, European ancestry) who underwent CABG with CPB (PREVENT-IV trial), and had extensive covariate and outcome information collected per study protocol. Genetic information was available for 1480 patients. The primary outcome was incidence of new onset PoAF.

Results: AA subjects showed half the incidence of PoAF compared to EA (14 vs 28%, p<0.0002, Table A). The predicted impact of observed AA vs EA differences in minor allele frequencies is consistent with a significant decrease in cardiac adrenergic signaling (Table A). In multivariate analyses, race, age, COPD, and preoperative BB, but not the interaction between race-BB, were independently associated with incident PoAF. In EA subjects, a common functional SNP in the regulatory region of ADRB2 was associated with reduced PoAF in patients on BB (Table B).

Conclusion: Compared to EA, AA race is associated with significantly lower incidence of PoAF, and with allele frequency-based genetic profiles that would predict: 1) reduced signaling through both β1 and β2 adrenergic signaling pathways (protective effect against developing and natural progression of PoAF), yet 2) attenuated therapeutic responses to BB (receptor downregulation, lower incidence of CYP2D6 poor metabolizer). Follow-up analyses include an expanded cohort of AA to improve power of genetic association tests.

References

1. Am J Physiol 1994; 266: L263-270
2. Neuroimmunomodulation 1999; 6: 145-159
3. Life Sciences 1981; 28: 2981-2986

Oral Presentations

Thursday, April 23, 2015

SAB Oral Session (Part 1)

Moderators: Y. S. Prakash, MD, PhD and Wei Chao, MD, PhD

JUNIOR FACULTY RESEARCH AWARD

OC 1 (61) • Pediatric Delirium in Critically Ill Infants and Preschool-aged Children: Validation and Reliability of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)

Heidi A. B. Smith, MD, MSCi[1], D. Catherine Fuchs, MD[1], Mary Hamilton Chestnut, NP[1], Jennifer L. Thompson, MPH[1], Pratik P. Pandharipande, MD, MSCi[1]

[1]Vanderbilt University, Nashville, Tennessee. *See Page 39 for complete abstract.*

Clin Neuro 30 (7) • Latent Class Analysis of Neuropsychological Deficit after Exposure to Anesthesia in Early Childhood

Caleb Ing, MD, MS[1], Melanie M. Wall, PhD[1], Charles J. DiMaggio, PhD, MPH, PA-C[1], Andrew J. O. Whitehouse, PhD[2], Guohua Li, MD, PhD[1], Lena S. Sun, MD[1]

[1]Columbia University, New York, New York; [2]Telethon Kids Institute, Subiaco, WA, Australia

MARGARET WOOD RESIDENT RESEARCH AWARD

Clin Neuro 31 (43) • The Relative Effects of Dexmedetomidine and Propofol on Cerebral Blood Flow and Brain Oxygenation: A Noninferiority Study

Michael Kot, MD[1], Ehab Farag MD, FRCA[1], Attila Podolyak, MD[1], Daniel Sessler, MD[1], Edward Mascha, PhD1, Andrea Kurz, MD[1]

[1]Cleveland Clinic, Cleveland, Ohio. *See Page 41-42 for complete abstract.*

Clin Neuro 32 (84) • The Elderly Brain Under Anesthesia: An Age-Dependent Analysis of Propofol- and Sevoflurane-Induced Electroencephalogram Dynamics

Patrick L. Purdon, PhD[1], Kara J. Pavone, BS[1], Oluwaseun Akeju, MD[2], Anne C. Smith, PhD[1], Ken Solt, MD[1], Emery N. Brown, MD, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Massachusetts Institute of Technology, Cambridge, Massachusetts

Organ Inj 65 (70) • Selective inhibition of the Calcineurin Interaction Site of TRPV1 Reduces Myocardial Infarct Size by Reducing Mitochondrial Calcium Influx

Eric R. Gross, MD, PhD[1], Carl M. Hurt, MD, PhD[1], Bryce A. Small, BS[1]

[1]Stanford University, Palo Alto, California

Organ Inj 64 (67) • Proteomic Profiling and Multi-Color Flow Cytometry Reveal Species Specific and Hibernation-State Specific Differences in Innate Immunity, Susceptibility to Injury, and Response to Surgical Ischemia-Reperfusion between Rats and Arctic Ground Squirrels

Quintin J. Quinones, MD, PhD[1], Qing Ma, MD, PhD[1], Michael P. Smith, MS[1], Janet Staats, BS[1], Brian M. Barnes, PhD[2], Mihai V. Podgoreanu, MD[1]

[1]Duke University, Durham, North Carolina; [2]University of Alaska Fairbanks, Fairbanks, Alaska

Organ Inj 63 (64) • Extracellular RNA Induces Inflammation via Toll-Like Receptor 7 and Contributes to Myocardial Infarction in a Mouse Model of Ischemia-Reperfusion Injury

Wei Chao, MD, PhD[1, 2], Yan Feng, MD, PhD[1], Hongliang Chen, MD[1], Lin Zou, MD, PhD[1], Ganqiong Xu, MD[1], Jingping Wang, MD, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Harvard Medical School, Boston, Massachusetts

Organ Inj 62 (49) • Acute Ischemic Albuminuria Mediates AKI in Mice after Cardiac Arrest and Cardiopulmonary Resuscitation

Michael P. Hutchens, MD, MA[1], Mizuko Ikeda, MD, PhD[1], Sharon Anderson, MD[1]

[1]Oregon Health & Science University, Portland, Oregon

Oral Presentations

Saturday, April 25, 2015

SAB Oral Session (Part 2)

Moderators: Moderators: Zhongcong Xie, MD, PhD and Matthias Riess, MD, PhD

JUNIOR FACULTY RESEARCH AWARD

Tox Cogn Dysfx 55 (28) • Isoflurane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway

Cyrus D. Mintz, MD, PhD[1], Danye Jiang, BS[1], Yun K. Ryu, PhD[2], Sanghee Lim, MS[1], Minhye Kwak, MS[1]

[1]Johns Hopkins Hospital, Baltimore, Maryland; [2]Columbia University, New York, New York. *See Page 40 for complete abstract.*

Tox Cogn Dysfx 54 (4) • Carbon Monoxide Modulates Cytochrome Oxidase Activity and Oxidative Stress in the Developing Murine Brain During Isoflurane Exposure

Richard J. Levy, MD, FAAP[1], Ying Cheng, MS[1], Ying Cheng, MS[2]

[1]Columbia University, New York, New York; [2]Children's National Medical Center, Washington DC

Tox Cogn Dysfx 56 (54) • Astrocyte Specific Knockout of Hypoxia-Inducible Factor Impairs Hippocampal Learning after Mild Hypoxia

Cindy V. Leiton, PhD[1], Ying Wang, PhD[1], Elyssa Chen, PhD[1], Kristy Conn, DVM[1], Joher Sheikh, BS[1], Thomas Floyd, MD[1]

[1]Stony Brook University, Stony Brook, New York

Tox Cogn Dysfx 57 (66) • Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline

Niccolo Terrando, BSc (hons), DIC, PhD[1], Ting Yang, MD, PhD[1], Andrei Chagin, PhD[1], Katerina Akassoglou, PhD[2]

[1]Duke University, Durham, North Carolina; [2]Gladstone Institute of Neurology, UCSF, San Francisco, California

RESIDENT TRAVEL AWARD

CS/Metab 22 (62) • Dexmedetomidine's Inhibitory Effects on Acetylcholine Release from Cholinergic Nerves in Guinea Pig Trachea: A Mechanism That Accounts for its Clinical Benefit during Airway Irritation

Maya Mikami, MD, PhD[1], Yi Zhang, MD[1], Charles W. Emala, MD[1]

[1]Columbia University College of Physicians and Surgeons, New York, New York. *See Page 43 for complete abstract.*

RESIDENT TRAVEL AWARD

OC 4 (52) • Effects of Race and Common Genetic Variation on Therapeutic Response Disparities in Postoperative Atrial Fibrillation

Nazish K. Hashmi, MB, BS[1], Mary Cooter, PhD[1], Yi-Ju Li, PhD[1], Miklos Kertai, MD, PhD[1], Mihai V. Podgoreanu, MD, FASE[1]

[1]Duke University, Durham, North Carolina. *See Page 44 for complete abstract.*

CS/Metab 20 (3) • Do Potent Anesthetics Bind to All Five Transmembrane Subunit Interfaces in GABAA Receptors?

Stuart A. Forman, MD, PhD[1], Alex T. Stern, BS[1], Deirdre S. Stewart, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts

CS/Metab 21 (24) • Selective Pharmacologic Targeting of the GABA-A α4 Subunit in Airway Smooth Muscle to Alleviate Bronchospasm

Gene T. Yocum, MD, MPH[1], Ryo Wakita, DDS, PhD[1], Michael R. Rajesh, Stephen, PhD[2], James M. Cook, PhD[2], Charles W. Emala, MD, MS[1], George Gallos, MD[1]

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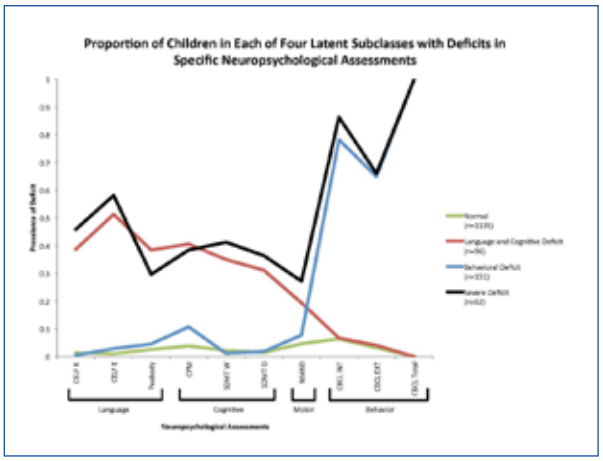
Oral Presentations

Clin Neuro 30 (7)
Latent Class Analysis of Neuropsychological Deficit after Exposure to Anesthesia in Early Childhood

Caleb Ing, MD, MS[1], Melanie M. Wall, PhD[1], Charles J. DiMaggio, PhD, MPH, PA-C[1], Andrew J. O. Whitehouse, PhD[2], Guohua Li, MD, PhD[1], Lena S. Sun, MD[1]

[1]Columbia University, New York, New York; [2]Telethon Kids Institute, Subiaco, WA, Australia

Introduction: Over the last decade, the safety of anesthetic agents in children has been questioned with some studies reporting an association between early anesthetic exposure and long-term deficit.1 It is however unclear if this association is found in all children or if only specific subgroups of children may be vulnerable.2 Latent class analysis (LCA) is a statistical method that can be used to identify discrete subgroups of clinical phenotypes.3 We used LCA of specific neurodevelopmental outcomes to characterize subgroups of children potentially vulnerable to anesthesia.



Methods: Data were obtained from the Western Australian Pregnancy Cohort Study (Raine) (2868 children born 1989-1992) and results of neuropsychological (NP) assessments at age 10 years, including language (Peabody Picture Vocabulary [PPV], Clinical Evaluation of Language Fundamentals: Receptive [CELF-R] and Expressive [CELF-E]), cognition (Colored Progressive Matrices [CPM], Symbol Digit Modality Test: Oral [SDMT-O] and Written [SDMT-W]), motor function (McCarron Assessment of Neuromuscular Development [MAND]) and behavior (Child Behavior Checklist: Internalizing [CBCL-INT], Externalizing [CBCL-EXT], and Total behavior [CBCL-T]) were assessed. Children were evaluated for anesthesia exposure before age 3, and only those who had all available NP test results at age 10 were included in the analysis. Based on LCA of the NP tests, the cohort was divided into mutually exclusive subclasses of cognitive deficits. Using a multivariable polytomous logistic regression model, we determined the strength of association between anesthesia exposure and each latent class, and also adjusted for demographics, perinatal health status, and comorbid diseases.

Results: A total of 1444 children were included in the analysis. LCA indicated that a four-class model provided the best fit. Thus, four clinically meaningful groups were identified: 1) Normal: little or no deficits, (n=1135, 78.6%), 2) Behavioral deficits: high probability for behavioral deficits, low probability for other deficits. (n= 151, 10.5%), 3) Language and Cognitive deficits: high probability for language, cognitive and motor deficits and low probability for behavioral deficits (n=96, 6.6% of cohort) and 4) Severe deficits: high probability for deficits in all NP domains (n=62, 4.3%) (Figure 1). Children with Language and Cognitive deficits had significantly higher odds of prior anesthesia exposure vs Normal children [adjusted odds ratio (aOR), 2.35 (95% CI, 1.36 – 4.07)], while those with Behavioral or Severe deficits were comparable to Normal children [aOR, 0.90 (95% CI, 0.54 – 1.52), and aOR, 0.91 (95% CI, 0.41 – 2.04) respectively] with respect to anesthesia exposure. There were no differences in patient-specific characteristics among the three classes of children with deficits.

Discussion: Applying LCA to results of NP tests at age 10 years in the Raine cohort, we identified four subgroups of children. Children with isolated deficits in language and cognition were associated with prior exposure to anesthesia, but children with severe deficits, who had language and cognitive in addition to behavioral deficits, were not associated with exposure. Our results suggest that specific subgroups of children may be at risk for developing neuropsychological deficits after anesthesia exposure while other subgroups may not be at risk. Additional studies however are needed to better identify demographic and other patient characteristics as risk factors for this vulnerability.

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Oral Presentations

Organ Inj 65 (70)

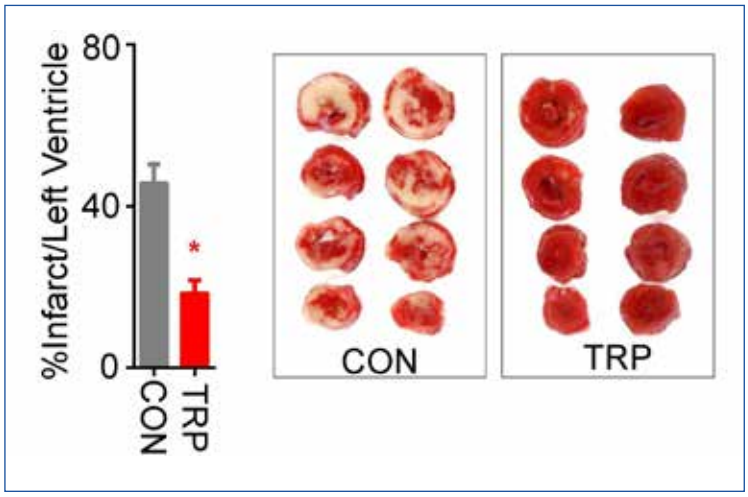
Selective Inhibition of the Calcineurin Interaction Site of TRPV1 Reduces Myocardial Infarct Size by Reducing Mitochondrial Calcium Influx

Eric R. Gross, MD, PhD[1], Carl M. Hurt, MD, PhD[1], Bryce A. Small, BS[1]

[1]*Stanford University, Palo Alto, California*

Introduction: The transient receptor potential vanilloid 1 (TRPV1) channel is a calcium ion channel mediating heat, pain and noxious stimuli that is modulated by calcineurin [1, 2]. TRPV1 knockout mice sustain greater myocardial damage after ischemia-reperfusion injury [3]. However, controversy exists whether TRPV1 is present and functional in the cardiac myocyte [4]. Therefore, we characterized the TRPV1 channel in the cardiac myocyte and further determined how the interaction of calcineurin with TRPV1 effects myocardial injury.

Methods: We used PCR and western blot, immunofluorescence, and calcium-labeled indicator dyes to characterize TRPV1 in left ventricle-derived H9C2 cells and primary neonatal cardiomyocytes. TRPV1 function was assessed by using the TRPV1 agonist, capsaicin (0.1-10μM) and measuring the intensity of Rhod-2 and Fura-2, dyes specific for mitochondrial and cytoplasmic calcium flux, respectively. A subset of experiments prior to capsaicin administration were given the selective calcineurin inhibitor, FK506 (1μM, 10 minutes prior to capsaicin). We also performed in silico modeling to predict the interaction site between calcineurin and TRPV1 and synthesized a peptide, TRP, against this interaction site. In vitro studies with TRP were performed with a calcineurin activity assay kit. For isolated heart studies, male Sprague-Dawley rats 8 weeks of age were subjected to 30 minutes of ischemia followed by 90 minutes reperfusion, receiving either the peptide, TRP (1μM), or vehicle for 10 minutes prior to ischemia. Infarct size was assessed by triphenyltetrazolium staining.



Results: TRPV1 was present in H9C2 cells and primary cardiomyocytes by qPCR and western blot. Immunofluorescence revealed TRPV1 mainly localized to the endoplasmic reticulum. In both cell types, activation by capsaicin (0.1-10μM) caused dose-dependent changes in mitochondrial calcium influx, with minimal cytoplasmic entry of calcium from the plasma membrane. The capsaicin-induced mitochondrial calcium influx was blocked by the specific calcineurin antagonist, FK506. A peptide against the predicted calcineurin-TRPV1 interaction site, TRP, inhibited calcineurin activity versus vehicle when assessed in vitro using a calcineurin activity assay kit (0.46±0.03* vs. 0.77±0.02, nmol phosphate, n=3/group, *P<0.05). Further, subjecting rats to an isolated heart protocol the TRP peptide (1μM, infused over 10 minutes prior to ischemia) reduced infarct size when compared to vehicle treated control hearts (CON), (Figure, Left; CON: 53±4% vs. TRP: 19±3%* %infarct/left ventricle; n=6/group, mean±SEM, *P<0.01, Right: 2 representative infarct size images for CON and TRP groups; tissue stained red is viable tissue).

Conclusion: Our results suggest TRPV1 is present and functional in the cardiac myocyte. Further, we discovered a novel calcineurin interaction site of TRPV1 with a peptide against this site reducing myocardial infarct size. Disrupting specific protein-protein interactions with TRPV1 may provide a novel strategy to design therapeutics for cardioprotection by limiting mitochondrial calcium influx.

References

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3. Circulation, 112 (2005), 3617-23
4. European Journal of Pharmacology, 746 (2015), 180-5

Oral Presentations

Clin Neuro 32 (84)
The Elderly Brain Under Anesthesia: An Age-Dependent Analysis of Propofol- and Sevoflurane-Induced Electroencephalogram Dynamics

Patrick L. Purdon, PhD[1], Kara J. Pavone, BS[1], Oluwaseun Akeju, MD[2], Anne C. Smith, PhD[1], Ken Solt, MD[1], Emery N. Brown, MD, PhD[1]

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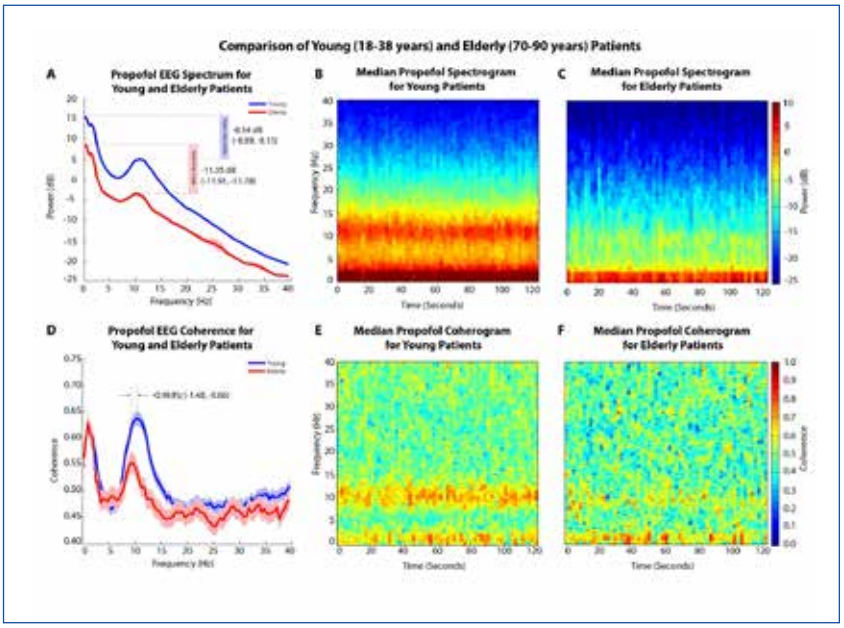
Anesthetic drugs act at sites within the brain that undergo profound changes during typical aging. We postulated that anesthesia-induced brain dynamics observed in the electroencephalogram (EEG) would change with age. We analyzed the EEG in 155 subjects aged 18 to 90 in which propofol (n=60) or sevoflurane (n=95) were administered as the primary anesthetic. The EEG spectrum and coherence were estimated over a 2-minute period of stable anesthetic maintenance. Age-related effects were characterized by analyzing power and coherence as a function of age using linear regression, by characterizing the probability of burst suppression during anesthetic maintenance as a function of age, and by comparing the spectrum and coherence in young (18-38 years) versus elderly (70-90 years) patients.



Power across all frequency bands decreased significantly with age for both propofol and sevoflurane (linear regression, P<0.01 for all bands and drugs). Fig. 1 shows a comparison of the spectrum and coherence in young vs. elderly patients for propofol. Similar results were observed under sevoflurane. EEG oscillations in elderly patients were ~2- to 3-fold smaller in amplitude than those for younger adults (Fig. 1A-C). The qualitative form of the EEG appeared similar regardless of age, showing prominent alpha (8-12 Hz) and slow (0.1-1 Hz) oscillations. However, alpha band dynamics showed specific age-related changes. In elderly patients compared to young, alpha power decreased more than slow oscillation power, characterized in terms of the alpha-slow ratio (Fig. 1A; 95% bootstrapped confidence intervals in parentheses). In addition, alpha band coherence (Fig. 1D-F) and peak frequency were significantly lower (Fig. 1D). Elderly patients were also more likely to experience burst suppression (Pr(elderly > young) > 0.95 for both propofol and sevoflurane, Markov-Chain Monte Carlo analysis of difference in burst suppression probability).

These profound age-related changes in the EEG are consistent with known neurobiological and neuroanatomical changes that occur during typical aging, including reduced brain volume, cortical thinning, and decreased synaptic density. Reductions in brain volume and cortical thinning would reduce EEG power independent of frequency, and thus could explain the age-dependent reduction in EEG power across all frequency bands. Age-dependent changes in alpha band coherence and peak frequency, however, likely reflect age-dependent changes in underlying brain circuit function. Anesthesia-induced coherent alpha waves are thought to be a GABA-mediated thalamocortical oscillations. Thus, the unique age-related alpha band effects that we have observed may reflect functional changes in GABA-dependent thalamocortical circuits. Age-dependent changes in burst suppression probability also likely reflect age-related changes in underlying neurobiology. Commercial EEG-based depth-of-anesthesia indices do not account for age, and are therefore likely to be inaccurate in elderly patients. In contrast, monitoring the unprocessed EEG and its spectrogram can account for age and individual patient characteristics, and could be used to more precisely establish and maintain general anesthetic and sedative brain states in elderly patients.

Oral Presentations

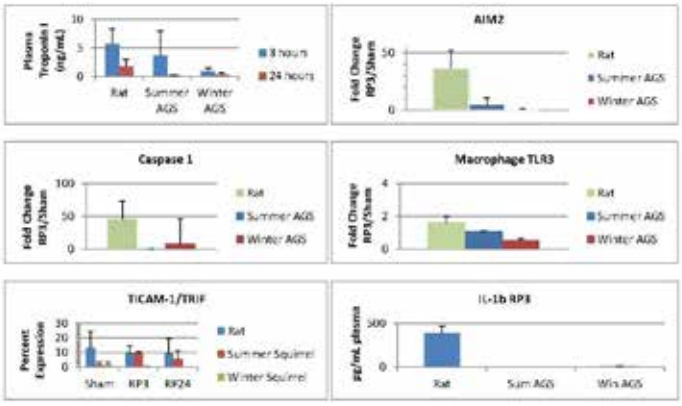
Organ Inj 64 (67)

Proteomic Profiling and Multi-Color Flow Cytometry Reveal Species Specific and Hibernation-State Specific Differences in Innate Immunity, Susceptibility to Injury, and Response to Surgical Ischemia-Reperfusion between Rats and Arctic Ground Squirrels

Quintin J. Quinones, MD, PhD[1], Qing Ma, MD, PhD[1], Michael P. Smith, MS1, Janet Staats, BS[1], Brian M. Barnes, PhD[2], Mihai V. Podgoreanu, MD[1]

[1]Duke University, Durham, North Carolina; [2]University of Alaska Fairbanks, Fairbanks, Alaska

Introduction: Hibernation is a natural molecular adaptation to extreme environmental conditions with important implications for perioperative organ protection. We have previously shown in a surgical model of ischemia and reperfusion (I/R) robust cardioprotection in hibernating arctic ground squirrels (AGS) compared to rats. Although hibernating animals undergo significant natural immunomodulation, a phenomenon conserved among distinct species, innate immune activity in hibernators has not been characterized.1 We hypothesized that the hibernator cardioprotective phenotype is accompanied by altered expression of innate immune pattern-recognition receptors (PRRs) and inflammatory pathways.



Methods: With IACUC approval, left ventricular (LV) myocardium, peripheral blood monocytes (PBMC), and plasma were collected from rat, summer AGS, and winter AGS after sham, 3h or 24h I/R. Label-free proteomic profiling was conducted on LV myocardial samples for unbiased cross-species protein quantitation. PBMC and plasma were analyzed by 4-panel multicolor flow cytometry and multiplex cytokine assay. Differences in flow cytometric markers of innate immune response were assessed across 3 groups (rats, winter AGS, summer AGS) and 3 time-points (sham, RP3 3 hour, and RP24 24hours) after I/R injury. In the marker-by-marker analysis, the outcome variable was the integrated median fluorescence (combining marker density on a single cell with the relative abundance of cell types expressing that marker). In the cell subset analysis, unbiased cell subsets with similar patterns of marker expression were identified across samples using a hierarchical Dirichlet process mixture model for clustering events and used as the dependent variable. ANOVA will test for main and interaction effects.

Results: Plasma troponin I detection confirmed greater I/R injury in rat compared to AGS. Proteomic profiling of LV myocardium detected multiple differences including higher expression of MyD88 dependent toll-like receptors (TLR) in rat compared to AGS; average levels of TLRs were 1.8 fold higher in rat compared with hibernating AGS. Analysis of PBMCs confirmed that the changes observed in myocardium are consistent in immune effector cells. Rats have increased inflammasome activation (AIM2, caspase 1) compared with summer AGS or winter AGS, which correlate with increased myocardial injury observed in the rat. Comparison of summer AGS with winter AGS and rat reveals increased expression of PRRs (AIM2,TLR3,TLR4), increased signal transduction along the TLR3/TICAM1 axis, and increased cytokine production in the rat compared with AGS.

Conclusion: Using a proteomic and multicolor flow cytometry approach we interrogated innate immunity in rat vs. AGS following surgical I/R. Several patterns emerged – compared to AGS, rats experience robust inflammasome activation in response to I/R as evidenced by >30-fold increases in AIM2 and Caspase 1. Hibernation state differences in innate immunity exist, including reduced expression of PRRs TLR3 and TLR4; additionally signaling via TLR 3 and 4 is greatly dampened in winter AGS due to nearly absent expression of TICAM1, which is preserved in summer AGS. As a result, circulating immune effector cells in winter AGS have an abrogated response to DAMPs compared to cells from summer AGS or rat, as evidenced by reduced cytokine production. Molecular switches that regulate innate immunity are difficult to manipulate, and given their importance in the pathogenesis of organ dysfunction in perioperative and critical care settings, understanding key events in immunomodulation naturally invoked by hibernators have high translational relevance.

References

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Oral Presentations

Organ Inj 63 (64)

Extracellular RNA Induces Inflammation via Toll-Like Receptor 7 and Contributes to Myocardial Infarction in a Mouse Model of Ischemia-Reperfusion Injury

Wei Chao, MD, PhD[1, 2], Yan Feng, MD, PhD[1], Hongliang Chen, MD[1], Lin Zou, MD, PhD[1], Ganqiong Xu, MD[1], Jingping Wang, MD, PhD[1]

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Introduction: We have recently reported that extracellular RNA (exRNA) associated with injured cells induces a cytokine response in cardiomyocytes and that eliminating circulating exRNA with exogenous RNase confers cardiac protection against myocardial ischemia/reperfusion (I/R) injury (1). However, the molecular mechanism by which exRNA exhibits its pro-inflammatory effect in cardiomyocytes and how exRNA contributes to myocardial I/R injury is unknown.

Methods: I/R model: Mice were subjected to Sham procedure or coronary occlusion for 45 min followed by reperfusion. exRNA extraction and quantification: RNA in culture media and mouse sera was extracted using Trizol LS and quantified using Quant-iT RNA assay kit. Circulating microRNA (miRNA) array: 68 miRNAs of a Cardiology Panel in the plasma samples were quantified using Fireplex circulating miRNA assay kit without RNA extraction. Cytokines: cytokine proteins in culture media were measured by ELISA or Luminex multiplex immunoassay. Cytokine genes in cells were detected by qRT-PCR.

Results: Twenty-four hours after hypoxia/serum-deprivation (H/SD), medium RNA in cardiomyocyte cultures rose from 12 ng/ml to approx. 600 ng/ml. In vivo, 24 h after I/R injury, serum RNA level was increased from 183±34 to 344±68 ng/ml. Plasma miRNA array data indicate that 38 out of 68 miRNAs were significantly increased by at least two-fold 4 h after myocardial I/R compared to Sham mice, including the muscle-specific miRNAs, namely miR-208, miR-499, and miR-133. To test the role of exRNA in inflammation, cardiomyocytes and immune cells (neutrophils and macrophages) were treated with total RNA of cardiac origin or miRNA mimics selected from the miRNA array panel. Purified RNA and six miRNA mimics (miR-34a, -122, -133a, 142a, -146a, -208a) were found to induce MIP-2 production in a dose-dependent manner. The effects were abolished by pre-treatment of RNase, but not DNase. The RNase effect was specific towards RNA/miRNA as it had no effect on Pam3cys (a TLR2 ligand)-induced MIP-2 production. Moreover, RNA-induced cytokine secretion, both in cardiomyocytes and immune cells, was significantly inhibited by a specific TLR7 antagonist. Consistent with this, genetic deletion of TLR7 or MyD88 (an adaptor for TLR7/8 signaling), but not TLR3 or Trif, markedly inhibited RNA-induced cytokine response. Similarly, miRNA-induced cytokine production was completely diminished in TLR7- or MyD88-deficient macrophages. Finally, i.p. injection of RNA or miRNA mimics induced acute peritonitis as characterized by IL-6 production and neutrophil activation.

Conclusion: Our data demonstrate that 1) RNAs, including many miRNAs, are released from hypoxic cardiomyocytes in vitro and ischemic myocardium in vivo; 2) exRNAs, both purified RNA of cardiac origin and miRNA, induce cytokine production through TLR7-MyD88 signaling; 3) exRNA induces acute inflammation after i.p injection.

References

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Oral Presentations

Organ Inj 62 (49)

Acute Ischemic Albuminuria Mediates AKI in Mice after Cardiac Arrest and Cardiopulmonary Resuscitation

Michael P. Hutchens, MD, MA[1], Mizuko Ikeda, MD, PhD[1], Sharon Anderson, MD[1]

[1]*Oregon Health & Science University, Portland, Oregon*

Introduction: Acute kidney injury complicates 300,000 surgical procedures yearly (1,2). Even mild cases increase risk of mortality by a factor of 8 (3). Mechanisms of AKI are incompletely understood and there is no therapy or prevention. AKI rapidly and transiently increases urinary albumin concentration (4), which is correlated with severity. We previously found that glomerular permeability to macromolecules is rapidly and transiently (maximal 2h following resuscitation) increased by cardiac arrest and cardiopulmonary resuscitation (CA/CPR), a model of whole-body ischemia (5). As albumin is a tubular toxin, glomerular hyperfiltration of albumin in the ischemic state could contribute to tubular epithelial cell death, the hallmark of AKI. We hypothesized that transient albuminuria, induced by ischemia (acute ischemic albuminuria, AIA), mediates acute kidney injury. We tested this hypothesis using CA/CPR in mice.

Methods: All mice in these studies were C57Bl/6 male mice and all studies IACUC approved. CA/CPR was induced as described (5) using potassium chloride, mice were resuscitated after 8 minutes of CA. We measured urine albumin concentration with ELISA. Because primary urine is subject to albumin secretion and reabsorption by injured tubular epithelium, we also examined the primary urine of Bowmans space, measuring filtration of albumin 2h after CA/CPR or sham with in-vivo 2-photon microscopy with ratiometric quantification of Alexa594 bovine serum albumin and FITC-dextran with MW 500 kD. Glomerular VE-cadherin was assessed using immunofluorescence and confocal microscopy. To test the renal effect of albumiin after ischemia, mouse serum albumin, 8mg, or the osmotic control Ficoll-70, also 8mg, was administered intravenously in equivalent volume 15 minutes after resuscitation from CA. Glomerular permeability to macromolecules was measured 2h after CA/CPR using urine and serum fluorescence following administration of TRITC-Ficoll-70. Results are reported as mean±SD and 2-tailed p values determined with Student's test.

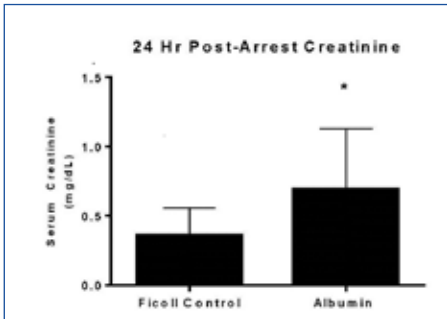

Figure 1: 8 mg (320 mg/kg) mouse serum albumin, administered after CA/CPR, worsens renal injury compared with osmotic control Ficoll-70. n=10-11/gr, p<0.05

Results and Major Findings:

1. CA/CPR massively increases 24h urine albumin excretion (pre-CA/CPR 0.5±0.6, post-CA/CPR 936±1150 mg/dL, n >35/gr, p<0.0001).
2. CA/CPR increased primary urine β for albumin (sham 0.2±0.04, CA/CPR 0.4±0.03, n=3/gr, p<0.05).
3. Glomerular endothelial VE-cadherin distribution, a determinant of glomerular permeability, is altered by CA/CPR (mean glomerular VE-cadherin fluorescence signal in sham 53±13 arbitrary fluorescence units [AFU], CA/CPR 95±11 AFU, n=3/gr, p<0.05).
4. Administration of albumin worsens renal injury after CA/CPR compared with osmotic control Ficoll-70 (serum creatinine [sCr] 0.4±0.1 control vs 0.7±0.1, n=10-11/gr, p<0.05, Figure 1).
5. Post-arrest administration of estradiol reduced glomerular permeability measured 2h after CA/CPR (β, vehicle 0.9±0.2, estradiol 0.5±0.2, n=5-7/gr, p<0.01) , and also reduced renal injury measured 24 h after CA/CPR (sCr vehicle 1.0±0.6, estradiol 0.5±0.5 mg/dL, n=11-13,p<0.05).

Conclusion: We conclude that CA/CPR, a model of whole-body ischemia-reperfusion injury, is associated with glomerular hyperfiltration of macromolecules including albumin. Administration of exogenous albumin in a clinically-relevant dose during this permeable phase resulted in increased renal injury compared with osmotic control. Estradiol administration reduced glomerular permeability to macromolecules, and also reduced tubular injury as measured by serum creatinine. We conclude that acute ischemic albuminuria mediates AKI in mice and that interventions which reduce ischemic glomerular permeability may ameliorate AKI.

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Oral Presentations

Tox Cogn Dysfx 54 (4)

Carbon Monoxide Modulates Cytochrome Oxidase Activity and Oxidative Stress in the Developing Murine Brain During Isoflurane Exposure

Richard J. Levy, MD, FAAP[1], Ying Cheng, MS[2]

[1]Columbia University Medical Center, New York, New York; [2]Children's National Medical Center, Washington DC

Introduction: Anesthetics induce widespread neurodegeneration in the developing mammalian brain via the oxidative stress-associated mitochondrial apoptosis pathway. Dysregulation of cytochrome oxidase (CcOX), the terminal oxidase of the electron transport chain, results in reactive oxygen species (ROS) formation and isoflurane has been shown to activate this enzyme. Carbon monoxide (CO), a modulator of CcOX, is of interest because children routinely rebreathe CO during low-flow anesthesia. CO has the potential to either inhibit or stimulate CcOX, resulting in ROS formation or prevention of oxidative stress depending on the mitochondrial transmembrane potential. We hypothesized that CO would limit anesthesia-induced oxidative stress in the developing murine brain via CcOX modulation. We aimed to determine the effect of low concentration CO on CcOX kinetics during exposure to isoflurane with a focus on lipid peroxidation.

Methods: The care of animals was in accordance with NIH and IACUC guidelines. 7 day old male CD-1 mice underwent 1-hour exposure to 0 ppm (air), 5 ppm, or 100 ppm CO with or without isoflurane (2%). Immediately after exposure, forebrain mitochondria were isolated, fatty acid peroxidation was assessed by colorimetric determination of thiobarbituric acid reactive substances (TBARS), steady-state CcOX kinetic activity was determined using spectrophotometry, and immunoblot analysis was performed for CcOX subunit I (the active site). In a separate cohort, CcOX was extracted and immunoblot analysis performed for phosphotyrosine. Five to six animals per cohort were evaluated. Significance was set at $P < 0.05$ and assessed with ANOVA and post hoc Tukey's Test.

Results: Exposure to isoflurane or CO alone significantly increased TBARS within forebrain mitochondria. However, combined exposure resulted in TBARS that were significantly lower than those seen following concentration-matched CO exposure alone. Steady-state forebrain CcOX activity significantly increased following exposure to isoflurane or CO alone in a dose-dependent fashion for CO. On the other hand, combined exposure to isoflurane with CO resulted in a paradoxical reduction in enzyme kinetics in a concentration-dependent manner for CO. Levels of TBARS correlated strongly and significantly with CcOX activity. There were no changes seen in steady-state levels of CcOX I protein indicating post-translational modification as an etiology for changes in enzyme activity. Immunoblot analysis for phosphotyrosine demonstrated a 57 kD band in each cohort suggesting tyrosine phosphorylation of CcOX subunit I. Steady-state levels of phosphotyrosine significantly decreased following exposure to 5 ppm CO. However, exposure to 100 ppm CO alone and combined exposure to isoflurane with CO significantly increased tyrosine phosphorylation of CcOX.

Conclusion: The findings indicate that isoflurane and low concentration CO independently cause oxidative stress and activate CcOX in the developing forebrain. The strong correlation between lipid peroxidation and CcOX activity suggests a role for CcOX dysregulation in ROS production. Interestingly, when both isoflurane and CO were inspired simultaneously, the combined exposure limited lipid peroxidation within mitochondria and prevented CcOX activation in a dose-dependent manner for CO. Our findings indicate differential effects of CO on tyrosine phosphorylation depending on concentration and a synergistic effect of combined exposure to CO with isoflurane. Taken together, the data suggest that CO modulates CcOX via tyrosine phosphorylation in the developing brain during isoflurane exposure, thereby limiting ROS production. These effects could have implications for the development of low-flow anesthesia in children in order to prevent anesthesia-induced oxidative stress.

Oral Presentations

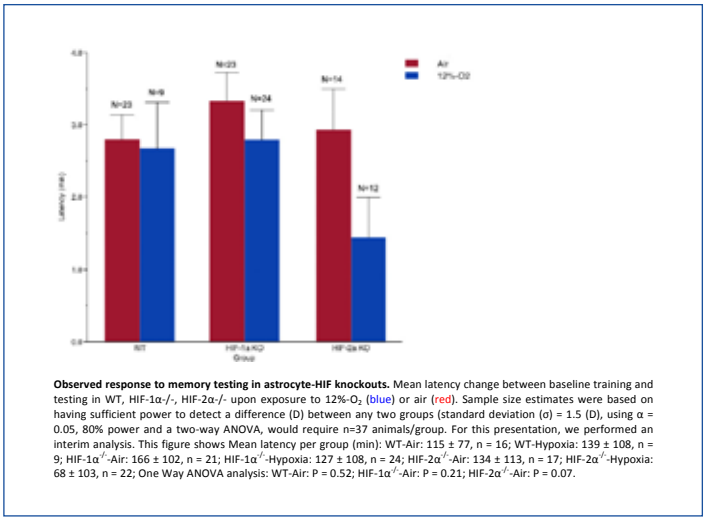
Tox Cogn Dysfx 56 (54)

Astrocyte Specific Knockout of Hypoxia-Inducible Factor Impairs Hippocampal Learning after Mild Hypoxia

Cindy V. Leiton, PhD[1], Ying Wang, PhD[1], Elyssa Chen, PhD[1], Kristy Conn, DVM[1], Joher Sheikh, BS[1], Thomas Floyd, MD[1]

[1]Columbia University Medical Center, New York, New York; [2]Children's National Medical Center, Washington DC

Abstract Body: Aging is the primary risk factor for postoperative cognitive dysfunction yet the mechanism remains elusive. We previously demonstrated that acute isovolemic anemia, commonly seen with major surgery, elicits memory impairment in aged but not in young chronically hypertensive rats. Aging, chronic cerebrovascular disease, and acute anemia expose the brain to greater degrees of hypoxia. Aging is also associated with a diminished capacity of cells to express Hypoxia Inducible Factor (HIF), the master regulator of the cellular response to hypoxia. HIF supports the adjustment to hypoxic challenges and maintains the integrity of key trophic and metabolic processes, including those related to memory. Astrocytes support synaptic plasticity through a host of neurotrophic and metabolic pathways, and HIF-2β is the predominant HIF form in astrocytes. Here, we test the hypothesis that astrocyte HIF-2β supports memory under hypoxic stress. Astrocyte-specific HIF-1β & HIF-2β Knockouts (KO) were generated by cross-breeding mice carrying the loxP-flanked conditional alleles of HIF-1β or HIF-2β to GFAP-Cre transgenic mice in C57BL/6 background. Wild type C57BL/6 mice were used as controls. Novel hippocampal learning and memory were tested in 3-5 mo. old animals using a Passive Avoidance (PA) paradigm: animals are placed in a light-dark chamber, where upon entering the dark side, a 3 sec., 3 mA foot shock is induced, and exposure to either 21%- O2 (air) or 12%-O2 (hypoxia) environment for 6 h follows. 24 h after training, mice are tested for memory retention where the time from entering into the PA chamber to the foot shock is recorded (latency). Shorter latency identifies poorer memory. We conducted an interim analysis and found an observable trend in learning impairment in both HIF-1β-/- & HIF-2β-/- groups after exposure to hypoxia that is not seen in WT (Figure). Long Term Potentiation (LTP), an electrophysiological correlate of memory formation used to test synaptic activity in brain slices obtained from WT and KO animals was found to be reduced in hippocampal slices from HIF-2β-/- mice exposed to hypoxia (135±4% in hypoxia, n=5 slices, 5 mice; versus 189±4% in room air, n=5 slices, 5 mice; p <0.001). Interim analysis of LTP activity across WT, HIF-1β-/- & HIF-2β-/- groups further showed that LTP was more severely compromised in HIF-2β-/- animals than in HIF-1β-/- animals, consistent with the predominance of HIF- 2β versus HIF-1β in astrocytes. Finally, molecular correlates of synaptic plasticity were measured after PA testing: a) Erythropoietin increased in WT control, & HIF-1β -/-, but not in HIF-2β-/- upon hypoxia, b) PA training-induced brain derived neurotrophic factor (BDNF) mRNA and protein expression were reduced under hypoxia in both HIF-2β-/- and HIF-1β-/-, and c) activity-regulated cytoskeleton-associated protein (Arc) mRNA and protein expression were diminished under hypoxia in HIF-2β-/- > HIF-1β-/-. Together, these data support the hypothesis that astrocytic HIF-2β supports learning and memory under hypoxic stress and offer mechanistic insight into age-related memory impairment under hypoxic challenges that exist postoperatively and in chronic disease states such as anemia, heart failure, and pulmonary disease.



Observed response to memory testing in astrocyte-HIF knockouts. Mean latency change between baseline training and testing in WT, HIF-1α-/-, HIF-2α-/- upon exposure to 12%-O_2 (blue) or air (red). Sample size estimates were based on having sufficient power to detect a difference (D) between any two groups (standard deviation (σ) = 1.5 (D), using α = 0.05, 80% power and a two-way ANOVA, would require n=37 animals/group. For this presentation, we performed an interim analysis. This figure shows Mean latency per group (min): WT-Air: 115 ± 77, n = 16; WT-Hypoxia: 139 ± 108, n = 9; HIF-1$\alpha^{-/-}$-Air: 166 ± 102, n = 21; HIF-1$\alpha^{-/-}$-Hypoxia: 127 ± 108, n = 24; HIF-2$\alpha^{-/-}$-Air: 134 ± 113, n = 17; HIF-2$\alpha^{-/-}$-Hypoxia: 68 ± 103, n = 22; One Way ANOVA analysis: WT-Air: P = 0.52; HIF-1$\alpha^{-/-}$-Air: P = 0.21; HIF-2$\alpha^{-/-}$-Air: P = 0.07.

Oral Presentations

Tox Cogn Dysfx 57 (66)

Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline

Niccolo Terrando, BSc (hons), DIC, PhD[1], Ting Yang, MD, PhD[1], Andrei Chagin, PhD[1], Katerina Akassoglou, PhD[2]

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Introduction: Cognitive decline following surgery and acute illness is a common complication without defined etiology. Using a murine model of orthopedic surgery we previously elucidated how impaired resolution of inflammation contributes to the pathogenesis of cognitive decline, including changes in synaptic plasticity, neuroinflammation and subsequent memory dysfunction (1, 2). Herein we describe how a specific family of structurally distinct macrophage (MΦ)-derived mediators, Maresin 1 (MaR1, 7R,14S-dihydroxy-docosa-4Z,8E,10E,12Z,16Z,19Z-hexaenoic acid) (3), stimulate overall resolution signalling after surgery. Because specialized pro-resolving mediators (SPM) provide both anti-inflammatory and pro-resolving actions without being immunosuppressive (4), we tested the hypothesis that targeting Mβ trafficking into the brain using synthetic MaR1 may reduce neuroinflammation and improve cognitive outcome without impairing bone healing after orthopedic surgery.

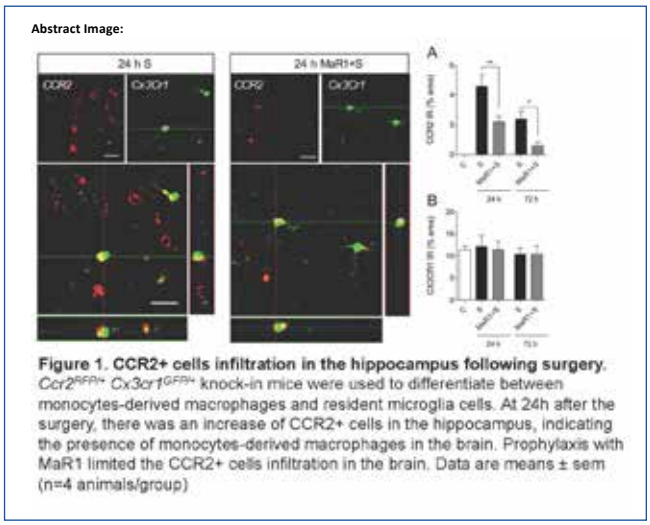

Figure 1. CCR2+ cells infiltration in the hippocampus following surgery. *Ccr2$^{RFP/+}$ Cx3cr1$^{GFP/+}$* knock-in mice were used to differentiate between monocytes-derived macrophages and resident microglia cells. At 24h after the surgery, there was an increase of CCR2+ cells in the hippocampus, indicating the presence of monocytes-derived macrophages in the brain. Prophylaxis with MaR1 limited the CCR2+ cells infiltration in the brain. Data are means ± sem (n=4 animals/group)

Methods: 12-wk-old male C57BL/6 and Ccr2RFP/+ Cx3cr1GFP/+ mice were randomly assigned as: 1) untreated control animals with analgesia, 2) surgery (an open tibial fracture of the left hind leg with intramedullary fixation) under isoflurane general anesthesia and postoperative analgesia, 3) surgery with preemptive MaR1 treatment (IP bolus, 100 ng dose/mouse), or 4) MaR1 alone. Separate cohorts of animals were used to perform systemic and central inflammatory analyses, blood brain barrier dysfunction and MΦ infiltration, microarray gene expression in the hippocampus, behavior using trace fear conditioning (TFC) and bone healing analyses.

Results: Using Ccr2RFP/+ Cx3cr1GFP/+ knock-in mice to investigate monocyte/microglia subset trafficking, we found a novel role for MaR1 in preventing infiltration of monocytes in the hippocampus and stimulating both anti-inflammatory and pro-resolving pathways after surgery. The neuroinflammation (microglia activation and astrogliosis) sustained until 72h in the surgical group with saline, however mice treated with MaR1 showed significantly reduced signs of neuroinflammation. At 24h, the peak of neuroinflammation, we found an increase in CCR2+ cells in the CA1 – CA3 area of the hippocampus, which was attenuated by prophylaxis with MaR1 (Figure 1). Freezing time as assessed by TFC was significantly improved in animals receiving MaR1 compared to surgery ($p<0.05$), indicating a better memory outcome following treatment. This was also highlighted using a microarray approach on hippocampal tissue showing relative recovery upon the treatment with MaR1 in biological pathways involving both neurological system processes and cognition. Systemically, MaR1 treatment reduced pro-inflammatory cytokines (IL-6, IL12 and KC/GRO) levels at 24h ($p<0.001$, $p<0.05$ and $p<0.01$ respectively) post surgery but further enhancing the production of anti-inflammatory IL-10 ($p<0.01$). Looking at the bone repair process, the area of the cartilage callous surrounding the fracture site was not reduced by treatment with MaR1, thus not impairing overall healing.

Conclusion: Overall, administration of MaR1 and SPM in the perioperative period may provide a safe and effective therapeutic option to modulate the inflammatory sequelae, limiting the neuroinflammatory response and cognitive dysfunction after trauma.

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Oral Presentations

CS/Metab 20 (3)

Do Potent Anesthetics Bind to All Five Transmembrane Subunit Interfaces in GABAA Receptors?

Stuart A. Forman, MD, PhD[1], Alex T. Stern, BS[1], Deirdre S. Stewart, PhD[1]

[1]*Massachusetts General Hospital, Boston, Massachusetts*

Introduction: Several potent intravenous general anesthetics, including etomidate (ETO), propofol (PROP), alphaxalone (ALPHAX), and pentobarbital (PB), produce their effects by enhancing the activity of GABAA receptors in the central nervous system. Photolabeling α1β2/3γ2L GABAA receptors with anesthetic analogs has located binding sites at transmembrane interfaces between M3 (+) and M1 (-) helices of adjacent subunits (Figure 1). ETO analogs photolabel residues in the two β+/α- interfaces (1), while a barbiturate photolabel, mTFD-MPAB, incorporates at homologous residues in the α+/β- and γ+/β- interfaces (2). PROP inhibits photolabeling by both ETO analogs and mTFD-MPAB (2), and a PROP photolabel binds at all four of the above interfaces (3). A neurosteroid photolabel incorporates in β-M3 (4), but ALPHAX does not inhibit other photolabels. To date, no anesthetic photolabels have identified a site in the fifth, α+/γ- transmembrane interface. We hypothesized that either PROP or ALPHAX might bind in this interface.

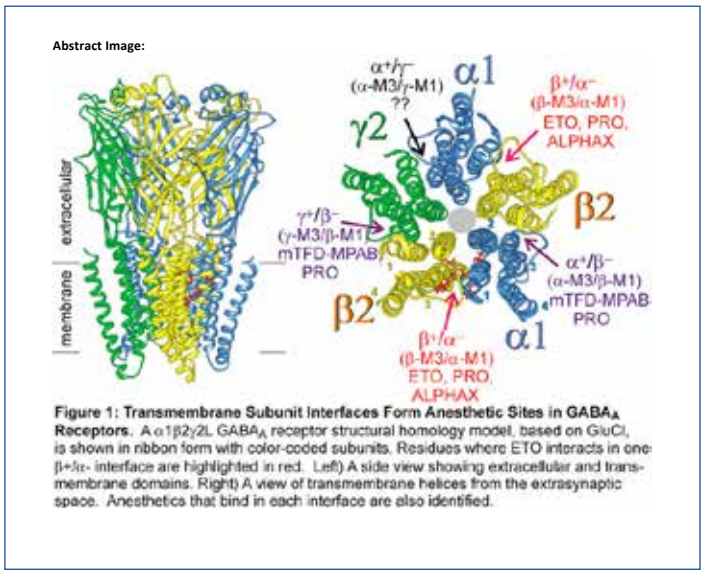

Figure 1: Transmembrane Subunit Interfaces Form Anesthetic Sites in $GABA_A$ Receptors. A α1β2γ2L $GABA_A$ receptor structural homology model, based on GluCl, is shown in ribbon form with color-coded subunits. Residues where ETO interacts in one β+/α- interface are highlighted in red. Left) A side view showing extracellular and transmembrane domains. Right) A view of transmembrane helices from the extrasynaptic space. Anesthetics that bind in each interface are also identified.

Methods: The γ2L homologs of established anesthetic contacts in α-M1 and β-M1, γ2L-I242 and γ2L-L246, were mutated to tryptophan and cysteine. The mutant γ2L subunits were co-expressed with wild-type α1 and β3 subunits in Xenopus oocytes. Two-microelectrode voltage-clamp electrophysiology was used to test receptor function and pharmacological properties, including spontaneous gating, GABA EC50 and efficacy, and modulation by ETO, PROP, ALPHAX, and PB. Cysteine mutants were exposed to para-chloromercuribenzene sulfonate (pCMBS), a reagent that covalently modifies free sulfhydryls. Rates of modification in the presence of pCMBS+GABA vs. pCMBS+GABA+anesthetic at 2 x anesthetic EC50 were compared.

Results: The γ2L-L246W mutation conferred spontaneous gating and increased GABA sensitivity compared to wild-type receptors, while retaining sensitivity to the modulating effects of all four anesthetics. Substituted cysteines at both β2L-I242 and L246 were accessible to pCMBS, and covalent modification enhanced gating in response to low GABA. However, none of the four anesthetics significantly reduced the rate of modification at γ2L-I242C or L246C.

Conclusion: The properties of γ-M1 tryptophan mutants and the effect of pCMBS modification at γ2L-I242C are similar to those in α-M1 homologs, indicating that the α+/γ- transmembrane interface is coupled to receptor gating, and forms a cavity where small molecules can enter. Thus, the α+/γ- transmembrane interface, like the other transmembrane subunit interfaces, is a potential anesthetic binding site. However, cysteine modification-protection suggests that none of the tested anesthetics significantly occupy the α+/γ- site at concentrations that occupy other sites. We plan to test whether smaller flexible drugs like alcohols or volatiles interact with this site.

References

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Oral Presentations

CS/Metab 21 (24)

Selective Pharmacologic Targeting of the GABA-A α4 Subunit in Airway Smooth Muscle to Alleviate Bronchospasm

Gene T. Yocum, MD[1], Ryo Wakita, DDS, PhD[1], Michael R. Rajesh, Stephen, PhD[2], James M. Cook, PhD[2], Charles W. Emala, MD, MS[1], George Gallos, MD[1]

[1]Columbia University, New York, New York; [2]University of Wisconsin-Milwaukee, Milwaukee, Wisconsin

Introduction: Bronchoconstriction remains a significant global health problem. We previously demonstrated that airway smooth muscle (ASM) cells express GABA-A receptors, which are heteropentameric ligand-gated chloride channels best known for their role in central nervous system (CNS) inhibitory neurotransmission, and that GABA-A agonists lead to acute airway smooth muscle relaxation [1]. Among the α subunits, ASM GABA-A receptors express only α4 and α5 [2], providing an opportunity for selective pharmacologic targeting to avoid CNS depression. We hypothesized that novel GABA-A ligands with enhanced selectivity for the α4 subunit would acutely relax ASM.

Methods: Novel positive allosteric modulators of the GABA-A receptor with enhanced α4 subunit selectivity were synthesized (CMD-45, Xhe-III-74). Organ bath experiments were conducted using mouse tracheal rings from wild type (WT) and global GABA-A α4 subunit (gabra4) KO mice and human tracheal smooth muscle strips. During continuous force monitoring, all ASM samples were contracted with an EC50 concentration of acetylcholine and then exposed to concentration ranges of CMD-45 and Xhe-III-74. To determine the effect of these ligands on ASM intracellular calcium, immortalized human ASM cells were loaded with a fluorescent calcium indicator in vitro, pretreated with CMD-45 or Xhe-III-74, and then exposed to histamine during continuous fluorescent recording.

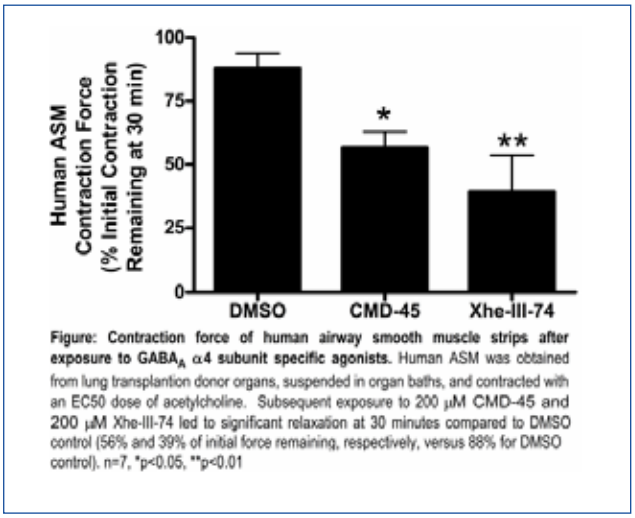

Figure: Contraction force of human airway smooth muscle strips after exposure to $GABA_A$ α4 subunit specific agonists. Human ASM was obtained from lung transplantion donor organs, suspended in organ baths, and contracted with an EC50 dose of acetylcholine. Subsequent exposure to 200 μM CMD-45 and 200 μM Xhe-III-74 led to significant relaxation at 30 minutes compared to DMSO control (56% and 39% of initial force remaining, respectively, versus 88% for DMSO control). n=7, *p<0.05, **p<0.01

Results: CMD-45 significantly relaxed precontracted WT mouse tracheal rings at 50, 75, and 100 μM ($p<0.05$, n=4). Significant relaxation in gabra4 KO tracheal rings was only achieved at the highest concentration of CMD-45 (100uM), and the relaxation was significantly greater in WT mice at this concentration ($p<0.01$, n=4). Xhe-III-74 led to significant relaxation in WT and gabra4 KO rings at 10, 25, and 50 μM, though the relaxation in the WT rings was greater than gabra4 KO at 25 μM ($p<0.05$, n=7). Furthermore, Xhe-III-74 and CMD-45 significantly relaxed precontracted human ASM compared to vehicle (39% and 56% of initial force remaining at 30 min respectively versus 88% for DMSO, $p<0.05$, n=7; Figure). In vitro, pretreatment of human ASM cells with CMD-45 and Xhe-III-74 significantly inhibited histamine-induced increases in intracellular calcium concentration ([Ca2+]i) by 20% and 25% respectively (n=8, $p<0.01$). This magnitude of inhibition is consistent with the proportion of Gq-protein coupled receptor-mediated [Ca2+]i increase attributed to external Ca2+ entry in ASM cells (as opposed to SR Ca2+ release).

Conclusion: Positive GABA-A modulators with enhanced selectivity for the α4 subunit relax contracted mouse and human ASM in organ bath experiments in an α4 subunit-selective manor. Limited relaxation in gabra4 KO tracheal rings suggests that high concentrations of these ligands may affect GABA-A receptors containing other α subunits. Consistent with a plasma membrane potential effect on external calcium entry, these ligands inhibited histamine-induced increases in [Ca2+]i. Selective targeting of the GABA-A α4 subunit may be a novel therapeutic pathway to treat acute bronchoconstriction while avoiding CNS depression, which is largely mediated by α1, α2, and/or α3 subunit-containing GABA-A receptors

References

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Moderated Poster Discussion Rounds

POSTER TOPICS	POSTER BOARD NUMBERS
Outcomes	1-6 & 9-14
Education	7, 8, 15, 16
Cell Signaling/Metabolism	17*, 18-26, 27*, 28, 29
Clinical Neuroscience	30-35
Clinical and Basic Pain	36-42
Clinical Management	43-46
Basic Neuroscience	47-53
Toxicity and Cognitive Dysfunction	54-61
Organ Injury	62-65, 80-81, 82*
Clinical Interventions and Outcomes	66-79

**Poster Withdrawn*

Poster Presentations Schedule

Thursday, April 23, 2015 • 3:15 pm - 4:45 pm

Moderated Poster Discussion: Outcomes
Moderators: Timothy Morey, MD

JUNIOR FACULTY RESEARCH AWARD

OC 1 (61) • Pediatric Delirium in Critically Ill Infants and Preschool-Aged Children: Validation and Reliability of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)

Heidi A. B. Smith, MD, MSCi[1], D. Catherine Fuchs, MD[1], Mary Hamilton Chestnut, NP[1], Jennifer L. Thompson, MPH[1], Pratik P. Pandharipande, MD, MSCi[1]

[1]Vanderbilt University, Nashville, Tennessee. *See Page 39 for complete abstract.*

OC 2 (65) • Lack of Association Between Routine ACEI Use and Acute Renal Injury After Non-Cardiac Surgery in Patients Given Hydroxyethyl Starch Solutions

Omar Dyara, DO[1], Ehab Farg, MD[1], Maged Argalious, MD[1], Andrea Kurz, MD[1], Praveen Chahar, MD[1]

[1]Cleveland Clinic Foundation, Cleveland, Ohio

OC 3 (73) • Improved Modeling of Post-operative Acute Kidney Injury Using Latent Variable Mixture Models: Overcoming the Null-Bias of Serum Creatinine Change

Loren E. Smith, MD, PhD[1], Derek K. Smith, DDS[1], Frederic T. Billings IV, MD, MSc[1]

[1]Vanderbilt University, Nashville, Tennessee

OC 9 (74) • Length of Stay and Readmission for Cardiac Surgery

Zachary A. Turnbull, MD[1], Natalia S. Ivascu, MD[1], Hugh C. Hemmings, MD, PhD[1], Andrea Poon, BS[2], Elizabeth Lemoine, BA[1], Peter M. Fleischut, MD[1]

[1]Weill Cornell Medical College, New York, New York; [2]Rutgers Robert Wood Johnson Medical School, Newark, New Jersey

OC 10 (8) • Unplanned Rehospitalizations within 30 days of Hospital Discharge for Survivors of Critical Illness

May Hua, MD[1], Michelle Ng Gong, MD, MSc[2], Joanne Brady, PhD[1], Hannah Wunsch, MD, MSc[1, 3]

[1]Columbia University, New York, New York; [2]Montefiore Medical Center, Bronx, New York; [3]Sunnybrook Health Sciences Centre, Toronto, Canada

OC 11 (10) • Medical Follow-Up in the Year After Surgery and Subsequent Survival Among a National Cohort of Surgical Patients

Robert B. Schonberger, MD, MA[1], Feng Dai, PhD[1], Cynthia Brandt, MD, MPH[1], Matthew M. Burg, PhD[1]

[1]Yale University, New Haven, Connecticut

Poster Presentations Schedule

Moderated Poster Discussion: Education
Moderators: Robert Gaiser, MD and Randall Schell, MD, MACM

Edu 7 (19) • Assessing the Assessment: Psychometric Analysis of Scoring Instruments for the Assessment of Anesthesia Non-Technical Skills

Scott C. Watkins, MD[1], David Roberts, BS[1], Matthew McEvoy, MD[1], John Boulet, PhD[1], Matthew Weinger, MD[1]

[1]Vanderbilt University, Nashville, Tennessee

Edu 8 (26) • Evaluating Peer-to-Peer Performance of Anesthesiology Critical Care Fellows in a Busy Multifaceted Fellowship Using Data Envelopment Analysis: A Case Study

Vikram Tiwari, PhD[1], Avinash B. Kumar, FCCM, FCCP[1]

[1]Vanderbilt University, Nashville, Tennessee

Edu 15 (42) • Evaluation of a Neonatal Resuscitation Teaching Curriculum in a Low-Resource Environment

Camile Lyon, MD[1], Mary Chang, MD[2], Deborah Askamit, RN[2], John Sampson, MD[2], David Janiszewski, MPA[3]

[1]Vanderbilt University, Nashville, Tennessee; [2]Johns Hopkins University, Baltimore, Maryland; [3]Doctors for United Medical Missions, Havre de Grace, Maryland

Edu 16 (57) • A PACU Handover Training Initiative – The Curriculum Design

Arna Banerjee, MD[1], Matthew B, Weinger, MD[1], Jason M. Slagle, PhD[1]

[1]Vanderbilt University Medical Center, Nashville, Tennessee

Poster Presentations Schedule

Moderated Poster Discussion: Cell Signaling/Metabolism
Moderators: Matthias Riess, MD, PhD, and Charles Emala, MS, MD

CS/Metab 18 (30) • Regulation of Neutrophil Mobilization and Recruitment by the TLR4 agonist Monophosphoryl Lipid A: Cellular and Molecular Mechanisms

Antonio Hernandez, MD[1], Julia Bohannon, PhD[1], Liming Luan, PhD[1], Benjamin Fensterheim, BS[1], Edward Sherwood, MD, PhD[1]

[1]Vanderbilt University, Nashville, Tennessee

CS/Metab 19 (32) • Melanopsin Mediates Light-Dependent Relaxation In Blood Vessels [1]

Gautam Sikka, MD[1], Dan E. Berkowitz, MB, BCh[1], Daniel Nyhan, MB, BCh[1], Patrick G. Hussman, PhD[2], Larrisa A. Shimoda, PhD[1], Solomon H. Snyder, MD, PhD[1]

[1]Johns Hopkins Hospital, Baltimore, Maryland; [2]National Institute of Health, Bethesda, Maryland

CS/Metab 26 (36) • A Novel Mechanism for Cardioprotection by Intralipid

Matthias L. Riess, MD, PhD[1], Michael E. Larson, BS[2], John G. Krolikoski, BS[2], Dorothee Weihrauch, PhD[2]

[1]TVHS VA Medical Center, Nashville, Tennessee; [2]Medical College of Wisconsin, Milwaukee, Wisconsin

CS/Metab 28 (68) • Characterization of Cytochrome P450 Reductase Mutants that Control Its Activity with Cytochrome P450 50

Lucy Waskell, MD, PhD[1, 2], Jung-Ja P. Kim, PhD[3], Freeborn Rwere, PhD[1], Chuanwu Xia, PhD[3], Sangchoul Im, PhD[1]

[1]University of Michigan, Ann Arbor, Michigan; [2]Ann Arbor VAMC, Ann Arbor, Michigan; [3]Medical College of Wisconsin, Milwaukee, Wisconsin

CS/Metab 29 (72) • General Anesthetic-Mediated Effects on Autophagy Determine Cell Survival

Huafeng Wei, MD, PhD[1], Gongyi Ren, PhD[1], Yachun Zhou, MD, PhD[1], Li Liang, MD[1], Chunxia Liu, MD, PhD[1], Maryellen Eckenhoff, PhD[1]

[1]University of Pennsylvania, Phildelphia, Pennsylvania

Poster Presentations Schedule

Moderated Poster Discussion: Clinical Neuroscience
Moderators: Roy Levitt, MD and Jianguo Cheng, MD, PhD

Clin Neuro 30 (7) • Latent Class Analysis of Neuropsychological Deficit after Exposure to Anesthesia in Early Childhood

Caleb Ing, MD, MS[1], Melanie M. Wall, PhD[1], Charles J. DiMaggio, PhD, MPH, PA-C[1], Andrew J. O. Whitehouse, PhD[2], Guohua Li, MD, PhD[1], Lena S. Sun, MD[1]

[1]Columbia University, New York, New York; [2]Telethon Kids Institute, Subiaco, WA, Australia. *See Page 47 for complete abstract.*

MARGARET WOOD RESIDENT RESEARCH AWARD

Clin Neuro 31 (43) • The Relative Effects of Dexmedetomidine and Propofol on Cerebral Blood Flow and Brain Oxygenation: A Noninferiority Study

Michael Kot, MD[1], Ehab Farag MD, FRCA[1], Attila Podolyak, MD[1], Daniel Sessler, MD[1], Edward Mascha, PhD[1], Andrea Kurz, MD[1]

[1]Cleveland Clinic, Cleveland, Ohio. *See Page 41-42 for complete abstract.*

Clin Neuro 32 (84) • The Elderly Brain Under Anesthesia: An Age-Dependent Analysis of Propofol- and Sevoflurane-Induced Electroencephalogram Dynamics

Patrick L. Purdon, PhD[1], Kara J. Pavone, BS[1], Oluwaseun Akeju, MD[2], Anne C. Smith, PhD[1], Ken Solt, MD[1], Emery N. Brown, MD, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Massachusetts Institute of Technology, Cambridge, Massachusetts. *See Page 44 for complete abstract.*

Clin Neuro 33 (5) • Role of Surgery Requiring Anesthesia in Postoperative Cognitive Impairment

Christopher G. Hughes, MD[1], Mayur B. Patel, MD, MSCi[1], Timothy D. Girard, MD, MSCi[1], Sunil K. Geevarghese, MD, MSCi[1], Brett C. Norman, MD, MPH[1], Pratik P. Pandharipande, MD, MSCil[1]

[1]Vanderbilt University School of Medicine, Nashville, Tennessee

Clin Neuro 34 (55) • Validity of Neuromonitoring in Aneurysm Surgery

Deepika Razia, MBBS[1], Ramachandram Ramani, MD[1], Kenneth Fomberstein, MD[1], Brooke Callahan, DABNM[1]

[1]Yale University, New Haven, Connecticut

Clin Neuro 35 (59) • Effects of Anesthesia, Surgery, and APOE4 on Brain Atrophy in Older Adults

Katie J. Schenning, MD, MPH[1], Charles Murchison, MS[1], Nora Mattek, MPH[1], Jeffrey Kaye, MD[1], Joseph Quinn, MD[1]

[1]Oregon Health & Science University

Poster Presentations Schedule

Moderated Poster Discussion: Basic Neuroscience
Moderators: Y.S. Prakash, MD, PhD

Basic Neuro Sci 47 (39) • The Importance of Body Posture for Waste Removal via the Brain-Wide Glymphatic Pathway

Helene Benveniste, MD, PhD[1], Hedok Lee, PhD[1], Mei Yu, BS[1], Tian Feng, MS[1], Rany R. Makaryus, MD[1]

[1]Stony Brook Medicine, Stony Brook, New York

Basic Neuro Sci 48 (40) • Peroxiredoxin-1 is a Novel Danger Signal Involved in Neurotoxic Microglial Activation After Experimental Cardiac Arrest

Ines P. Koerner, MD, PhD[1], Mizuko Ikeda, MD, PhD[1], Sarah Mader, BS[1]

[1]Oregon Health & Science University, Portland, Oregon

Basic Neuro Sci 49 (41) • The Parabrachial Nucleus Mediates Respiratory Rate Depression from Intravenous Remifentanil

Astrid G. Stucke, MD[1], Justin R. Miller, PhD[1], Edward J. Zuperku, PhD[1,2], Francis A. Hopp, MS[2], Eckehard A. Stuth, MD[1,3]

[1]Medical College of Wisconsin, Milwaukee, Wisconsin; [2]Zablocki VA Medical Center, Milwaukee, Wisconsin; [3]Children's Hospital of Wisconsin, Milwaukee, Wisconsin

Basic Neuro Sci 50 (53) • The Role of Increased Branched-Chain Amino Acids in the Blood on Brain Extracellular Fluid Glutamate Concentrations in Naive Rats

Shaun E. Gruenbaum, MD[1], Ronnie Dhaher, PhD[1], Tore Eid, MD, PhD[1]

[1]Yale University, New Haven, Connecticut

Basic Neuro Sci 51 (77) • O-GlcNac Glycosylation in Schwann Cells for Myelin Maintenance and Axon Survival

Sungsu Kim, PhD[1], Jeffrey Milbrandt, MD, PhD[1]

[1]Washington University, St. Louis, Missouri

Basic Neuro Sci 52 (79) • Transcriptional Profiling of K+ Channel Expression Patterns (in Mice) Identifies Kcnh8 as Potential Key Regulator of Circadian Rhythms

Aaron J. Norris, MD, PhD[1], Daniel Granados-Fuentes, PhD[1], Jeanne Nerbonne, PhD[1], Erik Herzog, PhD[1]

[1]Washington University, St. Louis, Missouri

Basic Neuro Sci 53 (82) • A Predictable Sequence Of Brain Stem Network Reactivation In Rodents Anesthetized With Either Propofol Or Isoflurane

Paul S. Garcia, MD, PhD[1,2], Jonathan A. Fidler, BS[1,2]

[1]Emory University, Atlanta, Georgia, [2]Atlanta VA, Atlanta, Georgia

Poster Presentations Schedule

Moderated Poster Discussion: Organ Injury
Moderators: Wei Chao, MD, PhD

Organ Inj 62 (49) • Acute Ischemic Albuminuria Mediates AKI in Mice after Cardiac Arrest and Cardiopulmonary Resuscitation

Michael P. Hutchens, MD, MA[1], Mizuko Ikeda, MD, PhD[1], Sharon Anderson, MD[1]

[1]Oregon Health & Science University, Portland, Oregon. *See Page 52 for complete abstract.*

Organ Inj 63 (64) • Extracellular RNA Induces Inflammation via Toll-Like Receptor 7 and Contributes to Myocardial Infarction in a Mouse Model of Ischemia-Reperfusion Injury

Wei Chao, MD, PhD[1,2], Yan Feng, MD, PhD[1], Hongliang Chen, MD[1], Lin Zou, MD, PhD[1], Ganqiong Xu, MD[1], Jingping Wang, MD, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Harvard Medical School, Boston, Massachusetts. *See Page 51 for complete abstract.*

Organ Inj 64 (67) • Proteomic Profiling and Multi-Color Flow Cytometry Reveal Species Specific and Hibernation-State Specific Differences in Innate Immunity, Susceptibility to Injury, and Response to Surgical Ischemia-Reperfusion between Rats and Arctic Ground Squirrels

Quintin J. Quinones, MD, PhD[1], Qing Ma, MD, PhD[1], Michael P. Smith, MS[1], Janet Staats, BS[1], Brian M. Barnes, PhD[2], Mihai V. Podgoreanu, MD[1]

[1]Duke University, Durham, North Carolina, [2]University of Alaska Fairbanks, Fairbanks, Alaska. *See Page 50 for complete abstract.*

Organ Inj 65 (70) • Selective Inhibition of the Calcineurin Interaction Site of TRPV1 Reduces Myocardial Infarct Size by Reducing Mitochondrial Calcium Influx

Eric R. Gross, MD, PhD[1], Carl M. Hurt, MD, PhD[1], Bryce A. Small, BS[1]

[1]Stanford University, Palo Alto, California. *See Page 48 for complete abstract.*

Organ Inj 80 (12) • Hyperoxic Resuscitation Improves Survival but Worsens Neurologic Outcome in a Rat Polytrauma Model of Traumatic Brain Injury Plus Hemorrhagic Shock

Gary Fiskum, PhD[1]

[1]University of Maryland, Baltimore, Maryland

Organ Inj 81 (37) • Even Protective Ventilation Can Cause Acute Lung Injury in a Mouse Model of Chronic Obstructive Pulmonary Disease

Laurence E. Ring, MD[1], Jeanine M. D'Armiento, MD, PhD[1]

[1]Columbia University, New York, New York

Poster Presentations Schedule

Moderated Poster Discussion: Clinical Interventions and Outcomes
Moderators: Peter Nagele, MD and Peter Goldstein, MD

Clin Int OC 70 (9) • Nitrous Oxide for Treatment-Resistant Major Depression: a Proof-of-Concept Trial

Peter Nagele, MD, MSc[1], Andreas Duma, MD, MSc[1], Michael Kopec, MS[1], Charles Zorumski, MD[1], Charles Conway, MD[1]

[1]Washington University, St. Louis, Missouri

Clin Int OC 71 (13) • Peripheral Venous Waveform Analysis for Detecting Acute Intraoperative Blood Loss

Susan Eagle, MD[1], Bantayehu Sileshi, MD[1], Richard Boyer, MD, PhD candidate[1], Kyle Hocking, PhD[1], Franz Baudenbacher, PhD[1], Andrew Shaw, MD[1]

[1]Vanderbilt University, Nashville, Tennessee

Clin Int OC 72 (14) • Spinal Anesthesia for Lumbar Spine Surgery: Overall Drug Utilization and the Need for Hemodynamic Support

Richard W. Anderson, MD[1], Robert Peterfreund, MD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts

Clin Int OC 73 (16) • Myocardial Injury after Electroconvulsive Therapy: A Prospective Cohort Study

Andreas Duma, MD, MSc[1], Swatilika Pal, MBBS, MS[2], Mitch G. Scott, Prof[3], Charles R. Conway, Assoc Prof[3], Peter Nagele, MD, MSc[3]

[1]Medical University of Vienna, Wien, Austria; [2]Saint Louis University, St. Louis, Missouri; [3]Washington University in St. Louis, St. Louis, Missouri

Clin Int OC 74 (25) • Choice of Intravenous Crystalloid Therapy and Major In-Hospital Outcomes among Adult Patients Undergoing Cardiac Surgery

Karthik Raghunathan, MD, MPH[1], Victor S. Khangulov, PhD[2], Fred Peyerl, PhD[2], Andrew D. Shaw, MB, FRCA, FFICM, FCCM[3]

[1]Duke University, Durham, North Carolina; [2]Boston Strategic Partners, Boston, Massachusetts; [3]Vanderbilt University, Nashville, Tennessee

Clin Int OC 75 (31) • Alarm Limits for Intraoperative Drug Infusions: A Report from the Multicenter Perioperative Outcomes Group (MPOG)

Mitchell F. Berman, MD, MPH[1], Leon Freudzon, MD[2], Sachin Kheterpal, MD, MBA[3], Shuang Wang, PhD[1]

[1]Columbia University, New York, New York; [2]Yale University, New Haven, Connecticut; [3]University of Michigan, Ann Arbor, Michigan

Clin Int OC 76 (33) • Identifying Patients at Risk for Escalation of Care after Rapid Response Activation

Liza M. Weavind, MDDCh, MMHC[1], Colleen M. Kiernan, MD[1], Melissa K. Stewart, MD, BS[1]

[1]Vanderbilt University Medical Center, Nashville, Tennessee

Clin Int OC 79 (86) • The Effect of High-Dose Cholecalciferol Supplementation on Perioperative Vitamin D Status in Colorectal Surgery Patients: A Randomized, Placebo-Controlled, Pilot Trial

Sadeq A. Quraishi, MD, MHA, MMSc[1,2], Caitlin M. McCarthy, BA[1,2], Joseph S. Needleman, BS, BA[1,2], Erica D. Herzon, RN[1,2], David L. Berger, MD[1,2], Carlos A. Camargo, Jr, MD, DrPH[1,2]

[1]Massachusetts General Hospital, Boston, Massachusetts, [2]Harvard Medical School, Boston, Massachusetts

Poster Presentations Schedule

Saturday, April 25, 2015 • 10:15 am - 11:45 am

Moderated Poster Discussion: Outcomes
Moderators: Alina Grigore, MD and Peter Nagele , MD

RESIDENT TRAVEL AWARD

OC 4 (52) • Effects of Race and Common Genetic Variation on Therapeutic Response Disparities in Postoperative Atrial Fibrillation

Nazish K. Hashmi, MB, BS[1], Mary Cooter, PhD[1], Yi-Ju Li, PhD[1], Miklos Kertai, MD, PhD[1], Mihai V. Podgoreanu, MD, FASE[1]

[1]Duke University Medical Center, Durham, North Carolina. *See Page 44 for complete abstract.*

OC 5 (11) • Surgical Risk Predictions Are Not Meaningfully Improved by Including the Intraoperative Course: An Analysis of the Risk Quantification Index, Present-On-Admission Risk Model, and Surgical Apgar Score

Jonathan P. Wanderer, MD, MPhil[1], Maxim A. Terekhov, MS[1], Jesse M. Ehrenfeld, MD, MPH[1]

[1]Vanderbilt University, Nashville, Tennessee

OC 6 (18) • Interaction Effects of Acute Kidney Injury, Acute Respiratory Failure, and Sepsis on 30-day Postoperative Mortality in Patients Undergoing High-Risk Intra-abdominal General Surgical Procedures

Minjae Kim, MD, MS[1], Joanne Brady, PhD[1], Guahua Li, MD, DrPH[1]

[1]Columbia University Medical Center, New York, New York

OC 12 (20) • Effects of Intra-Operative Positive End-Expiratory Pressure on the Postoperative Respiratory Complications in Patients Undergoing Craniotomy: A Retrospective Study

Yandong Jiang, MD, PhD[1], Shujie Liu, PhD[1], Zhenbo Su, PhD[2], Jun Oto, PhD[1], Christopher T. Chenelle, BS[1], Robert M. Kacmarek, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]China-Japan Union Hospital Jilin University, Jilin, China

OC 13 (21) • Intraoperative Normoxia, Oxidative Damage, and Organ Injury following Cardiac Surgery

Frederic T. Billings IV, MD, MSc[1]

[1]Vanderbilt University, Nashville, Tennessee

OC 14 (27) • Epidemiology of Critical Care Admissions in a Tertiary Hospital of Sub-Saharan Africa

Meghan Prin, MD[1], Julia Sobol, MD, MPH[1]

[1]Columbia University College of Physicians & Surgeons, New York, New York

Poster Presentations Schedule

Moderated Poster Discussion: Cell Signaling/Metabolism
Moderators: Matthias Riess, MD, PhD

CS/Metab 20 (3) • Do Potent Anesthetics Bind to All Five Transmembrane Subunit Interfaces in GABAA Receptors?

Stuart A. Forman, MD, PhD[1], Alex T. Stern, BS[1], Deirdre S. Stewart, PhD[1]

[1]Massachusetts General Hospital. *See Page 56 for complete abstract.*

CS/Metab 21 (24) • Selective Pharmacologic Targeting of the GABA-A α4 Subunit in Airway Smooth Muscle to Alleviate Bronchospasm

Gene T. Yocum, MD, MPH[1], Ryo Wakita, DDS, PhD[1], Michael R. Rajesh, Stephen, PhD[2], James M. Cook, PhD[2], Charles W. Emala, MD, MS[1], George Gallos, MD[1]

[1]Columbia University, New York, New York, [2]University of Wisconsin-Milwaukee, Milwaukee, Wisconsin. *See Page 57 for complete abstract.*

RESIDENT TRAVEL AWARD

CS/Metab 22 (62) • Dexmedetomidine's Inhibitory Effects on Acetylcholine Release from Cholinergic Nerves in Guinea Pig Trachea: A Mechanism that Accounts for Its Clinical Benefit during Airway Irritation

Maya Mikami, MD, PhD[1], Yi Zhang, MD[1], Charles W. Emala, MD[1]

[1]Columbia University College of Physicians and Surgeons, New York, New York. *See Page 43 for complete abstract.*

CS/Metab 23 (75) • Discovery of AMPA Receptor GluA4 Subunit Expression in Mouse and Human Epidermal Keratinocytes

Takeshi Irie, MD, PhD[1], David Cabañero, DVM, PhD[2], Zare Melyan, PhD[3], David M. Owens, PhD[3], Jose A. Moron, PhD[3]

[1]Memorial Sloan Kettering Cancer Center, New York, New York; [2]Univeritat Pompeu Fabra, Barcelona, Spain; [3]Columbia University Medical Center, New York, New York

CS/Metab 24 (83) • Drosomycin and Impaired Geotaxis in Drosophila surviving Sepsis: A Novel Model of Recovery from Sepsis

A. Murat Kaynar, MD, MPH[1], Veli Bakalov, MD[1], Silvia Martinez, MD[1], Alyssa Gregory, PhD[1], Steven Shapiro, MD[1], Derek Angus, MD[1]

[1]University of Pittsburgh, Pittsburgh, Pennsylvania

CS/Metab 25 (87) • Isoflurane Induces Substrate-Dependent Transient Mitochondrial PTP Opening

Bhawana Agarwal, PhD[1], Ranjan K. Dash, PhD[1], Zeijko J. Bosnjak, PhD[1], David F. Stowe, PhD[1], Lawrence A. Turner, MD[1], Amadou K. S. Camara, PhD[1]

[1]Medical College of Wisconsin, Milwaukee, Wisconsin

Poster Presentations Schedule

Moderated Poster Discussion: Clinical and Basic Pain
Moderators: Roy Levitt, MD and Jianguo Cheng, MD, PhD

Clin Basic Pain 36 (6) • The Global Burden of Chronic Pain: A Systematic Review and Meta-Analysis

Tracy P. Jackson, MD[1], Matthew Shotwell, PhD[1], Kelly McQueen, MD[1]

[1]Vanderbilt University, Nashville, Tennessee

Clin Basic Pain 37 (29) • The Pharmacokinetics and Anti-Hyperalgesic Efficacy of the mGlu5 Antagonist Fenobam in Healthy Volunteers

Michael Montana, MD, PhD[1], Karen Frey, BA[1], Tina Doshi, MD[1], James M. Wages, MD[1], Robert W. Gereau, PhD[1], Laura F. Cavallone, MD[1]

[1]Washington University, St. Louis, Missouri

Clin Basic Pain 38 (38) • Quantitative Cry Acoustics for Measurement of Pain in Neonates

Carrie Menser, MD[1], Stephen Bruehl, PhD[1], Dan France, PhD[1], Nathalie Maitre, MD, PhD[1], Don M. Wilkes, PhD[1], Olena Chorna, MS[1]

[1]Vanderbilt University, Nashville, Tennessee

Clin Basic Pain 39 (46) • Inconsistency in Reporting Pain Intensity Scores and Functional Activity Levels in Patients with Chronic Low Back Pain

Nobojsa Nick Knezevic, MD, PhD[1], Ivana Knezevic, MD[1], Kenneth D. Candido, MD[1]

[1]Advocate Illinois Masonic Medical Center, Chicago, Illinois

Clin Basic Pain 40 (47) • Mesenchymal Stem Cell Transplantation Reduces Chronic Neuropathic Pain and Opioid-induced Hyperalgesia in Rats

Jianguo Cheng, MD, PhD[1], Jun Shen, MD[1], Jing Yang, MD, PhD[1], Zhen Hua, MD, PhD[1], Kathleen Cheng[1], Liping Liu, MD, PhD[1]

[1]Cleveland Clinic, Cleveland, Ohio

Clin Basic Pain 41 (51) • Structure-Based Screening of Human Glycine Receptor Potentiators as Novel Analgesics for the Treatment of Chronic Pain

Yan Xu, PhD[1], Marta M. Wells, BS[1], David D. Mowrey, PhD[1], Tommy S. Tillman, PhD[1], Pei Tang, PhD[1]

[1]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Clin Basic Pain 42 (58) • Does Genetic Susceptibility to Persistent Post-op Pain (Thermal Hyperalgesia) Correlate with Other Phenotypes in the Mouse Phenome Database (MPD)?

Eugene S. Fu, MD[1], Houda Boucekkine, BS[1], Sarah Wishnek, PhD[1], Eden R. Martin, PhD[1], Roy C. Levitt, MD[1]

[1]University of Miami, Miami, Florida

Poster Presentations Schedule

Moderated Poster Discussion: Clinical Management
Moderators: Charles Emala, MS, MD

Clin Manag 43 (2) • Predicting Operating Room Scheduling Error via Automated Anesthesia Information Management System (AIMS)

Ahmed F. Attaallah, MD, PhD[1], Osama Elzamzamy, MD[1], Jeremiah L. Jeffers, MD[1], Pavithra Ranganathan, MD[1], Amy L. Phelps, PhD[2], Manuel C. Vallejo, MD, DMD[1]

[1]West Virginia University, Morgantown, West Virginia; [2]Duguesne University, Pittsburgh, Pennsylvania

Clin Manag 44 (15) • Electronically Mediated Time-Out Reduces the Incidence of Wrong Surgery: An Intervention Observation Study

Brian Rothman, MD[1], Warren S. Sandberg, MD, PhD[1]

[1]Vanderbilt University Medical Center, Nashville, Tennessee

Clin Manag 45 (23) • Implementation of a Novel Data Collection Tool in a Low and Middle-Income Country

Bantayehu Sileshi, MD[1], Mark Newton, MD[1], Mary Munhai, KRNA[2], Jon Scherdin, MA[1], Warren S. Sandberg, MD, PhD[1], Matthew McEvoy, MD[1]

[1]Vanderbilt University, Nashville, Tennessee, [2]AIC Kijabe Hospital, Kijabe, Kenya

Clin Manag 46 (63) • The Anesthesiologist as Operating Room Manager: Essential Part of the Comprehensive Care Model

Steven Dale Boggs, MD, MBA[1], Elizabeth A. Frost, MBChB, DRCOG[1], Jessica Deinleib, MD, PhD[2]

[1]Icahn School of Medicine at Mount Sinau, New York, New York, [2]Yale School of Medicine, New Haven, Connecticut

Poster Presentations Schedule

Moderated Poster Discussion: Toxicity and Cognitive Dysfunction
Moderators: Zhongcong Xie, MD, PhD and Thomas Floyd, MD

Tox Cogn Dysfx 54 (4) • Carbon Monoxide Modulates Cytochrome Oxidase Activity and Oxidative Stress in the Developing Murine Brain During Isoflurane Exposure

Richard Levy, MD, FAAP[1], Ying Cheng, MS[2]

[1]Columbia University Medical Center, New York, New York; [2]Children's National Medical Center, Washington DC. See Page 53 for complete abstract.

JUNIOR FACULTY RESEARCH AWARD

Tox Cogn Dysfx 55 (28) • Isoflurane Disrupts the Development of Dendrites in the Mouse Hippocampus via Activation of the mTOR Pathway

Cyrus D. Mintz, MD, PhD[1], Danye Jiang, BS[1], Yun K. Ryu, PhD[2], Sanghee Lim, MS[1], Minhye Kwak, MS[1]

[1]Johns Hopkins Hospital, Baltimore, Maryland; [2]Columbia University, New York, New York. See Page 40 for complete abstract.

Tox Cogn Dysfx 56 (54) • Astrocyte Specific Knockout of Hypoxia-Inducible Factor Impairs Hippocampal Learning after Mild Hypoxia

Cindy V. Leiton, PhD[1], Ying Wang, PhD[1], Elyssa Chen, PhD[1], Kristy Conn, DVM[1], Joher Sheikh, BS[1], Thomas Floyd, MD[1]

[1]Stony Brook University, Stony Brook, New York. See Page 54 for complete abstract.

Tox Cogn Dysfx 57 (66) • Maresin 1 Prevents Neuroinflammation in a Mouse Model of Postoperative Cognitive Decline

Niccolo Terrando, BSc (hons), DIC, PhD[1], Ting Yang, MD, PhD[1], Andrei Chagin, PhD[1], Katerina Akassoglou, PhD[2]

[1]Duke University, Durham, North Carolina, [2]Gladstone Institute of Neurology, UCSF, San Francisco, California. See Page 55 for complete abstract.

Tox Cogn Dysfx 58 (56) • Low-Dose Isoflurane Induces Profound Cognitive Dysfunction in Rats

Jonathan D. Kenny[1], Norman E. Taylor, MD, PhD[1], Emery N. Brown, MD, PhD[1], Ken Solt, MD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts

Tox Cogn Dysfx 59 (60) • Neuronal Marker Growth in the Rat Thalamus During Development Is Impeded by Anesthesia Exposure(s)

Rany Makaryus, MD[1], Tian Feng, BS[1], Hedok Lee, PhD[1], Mei Yu, BS[1]

[1]Stony Brook Medicine, Stony Brook, New York

Tox Cogn Dysfx 60 (76) • A Single Exposure to Isoflurane in Neonatal Mice Impairs Hippocampal Neuronal Development

Christy Gray, MD, PhD[1], Orion Furmanski, PhD[1], Cyrus Mintz, MD, PhD[1], Roger Johns, MD, PhD[1]

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland

Tox Cogn Dysfx 61 (22) • Sevoflurane Impairs Hippocampal Neuritic Extension and Increases Dendritic Spine Head F-Actin Concentration

Jeffrey H. Zimering, BA[1,2], Yuanlin, MD, MS[2], Yiying Zhang, MD, MS[2], Zhongcong Xie, MD, PhD[2]

[1]University of Rochester, Rochester, New York; [2]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Poster Presentations Schedule

Moderated Poster Discussion: Clinical Interventions and Outcomes
Moderators: Wei Chao, MD, PhD and Peter Goldstein, MD

Clin Int OC 66 (34) • Reducing Serious Intraoperative Peripheral Intravenous Catheter Infiltrations

Paul J. St. Jacques, MD[1], Michael H. Chi, MD[1], Jonathan P. Wanderer, MD, MPhil[1], Brian S. Rothman, MD[1], Michael S. Higgins, MD, MPH[1]

[1]Vanderbilt University School of Medicine, Nashville, Tennessee

Clin Int OC 67 (45) • Randomized Pilot Trial of Tubes to Prevent Ventilator-Associated Pneumonia

Miriam M. Treggiari, MD, PhD, MPH[1], N. David Yanez, PhD[1], Michael Aziz, MD[1], Steven Deem, MD[2]

[1]Oregon Health & Science University, Portland, Oregon; [2]Swedish Medical Center, Seattle, Washington

Clin Int OC 68 (71) • Markers of Immune Suppression Following Severe Burn Injury

Christopher P. Henson, DO[1], Liming Luan, PhD[1], Edward R. Sherwood, MD, PhD[1]

[1]Vanderbilt University, Nashville, Tennessee

Clin Int OC 69 (78) • Blood Volumes Discarded With Surgical Sponges

Gerhardt Konig, MD[1], Andrew Hosford, BSc[2], Siddarth Satish, BSc[2], Jonathan H. Waters, MD[1]

[1]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, 2Gauss Surgical, Los Altos, California

Clin Int OC 77 80) • Agreement Between Central Laboratory and Blood Gas Laboratory Sodium Concentrations - Do They Correlate for Therapeutic Decision Making?

Michael L. Ault, MD, FCCP, FCCM[1], Louanne M. Carabini, MD[1], Ntesi A. Asimi, MD[1], Eric M. Liotta, MD[1], Dhanesh K. Gupta, MD[1]

[1]Northwestern University Feinberg School of Medicine, Chicago, Illinois

Clin Int OC 78 (85) • The Extent of Cephalad Spread of Sensory Anesthesia Following a 5 ml Lidocaine 1.5% Test Dose is Inversely Associated With 1 and 24 Hour Local Consumption After Uterine Artery Embolization

Joseph Wickard, MD[1], Antoun Nader, MD[1]

[1]Northwestern University Feinberg School of Medicine, Chicago, Illinois

Poster Sessions

OC 2 (65)

Lack of Association Between Routine ACEI Use and Acute Renal Injury After Non-Cardiac Surgery in Patients Given Hydroxyethyl Starch Solutions

Omar Dyara, DO[1], Ehab Farg, MD[1], Maged Argalious, MD[1], Andrea Kurz, MD[1], Praveen Chahar, MD[1]

[1]Cleveland Clinic Foundation, Cleveland, Ohio

Background: Hydroxyethyl starch (HES) solutions are commonly used for volume resuscitation. However, recent studies suggest HES solutions can be associated with a significant risk of increased mortality and acute kidney injury (AKI). Angiotensin-converting enzyme inhibitors (ACEI) are frequently used as anti-hypertensive agents and to slow progression of nephropathy in patients diagnosed with diabetes. We thus evaluated the extent to which ACEI use is associated with reduced risk of AKI in patients given perioperative HES solutions. Secondarily, we considered whether the relationship depended on patients' baseline diabetic status.

Methods: Data was collected on 120, 406 patients having non-cardiac, non-urological, and non-transplant surgery at the Cleveland Clinic between January 2005 and September 2012 from the Cleveland Clinic Perioperative Health Documentation System. Patients at the Clinic are told to avoid taking ACEIs on the day of surgery, but we do not know what fraction follow this instruction; nor do we know when ACEIs are restarted. Exclusions were patients with preoperative chronic kidney disease (glomerular filtration rate of < 60 ml/min/1.73 m2), patients without major diagnostic or therapeutic surgery, patients with no pre- or postoperative serum creatinine recorded, and patients with missing covariate variables. Kidney function was measured by AKIN criteria. As per Walsh et al [1], we extended the normal 48-hour creatinine window used by the Acute Kidney Injury Network classification to seven days to better characterize the postoperative period. Urine output was not considered. Propensity matching was used to identify otherwise comparable groups of patients who were and were not given ACEIs. Matched variables included demographic characteristics, comorbidities, and baseline characteristics.

Results: Among the 120,406 surgical patients, there were 22,495 surgeries during which patients were given HES, including 2,242 patients (10%) who were taking ACEI and 20,253 (90%) who did not. 1,932 ACEI users (86% of the total ACEI users) were matched successfully with 1,932 patients who did not use ACEIs, for a total of 3,864 patients. Among the matched patients, there was not a significant association between ACEI use and odds of experiencing acute kidney injury (Wald test P = 0.29). The adjusted proportional odds ratio [95% confidence interval] comparing the ACEI group to the non-ACEI group was 1.13 [0.90, 1.41]. There was no significant interaction between the presence of diabetes and ACEI use (Wald test P = 0.31; a significance criterion of 0.1); that is, the odds ratios of developing more progressive stages of AKI did not differ significantly for diabetic and non-diabetic patients.

Conclusion: Aside from its retrospective approach, the primary limitation of our analysis is uncertainty whether ACEIs were continued on the day of surgery. In non-cardiac surgical patients given HES, the risk of developing AKI was similar in those taking ACEIs and those who did not in both diabetics and non-diabetics. Routine ACEI thus does not appear to provide perioperative renal protection.

Poster Sessions

OC 3 (73)

Improved Modeling of Post-operative Acute Kidney Injury Using Latent Variable Mixture Models: Overcoming the Null-Bias of Serum Creatinine Change

Loren E. Smith, MD, PhD[1], Derek K. Smith, DDS[1], Frederic T. Billings IV, MD, MSc[1]

[1]*Vanderbilt University, Nashville, Tennessee*

Introduction: Acute kidney injury (AKI) following cardiac surgery is most often diagnosed by measuring changes in serum creatinine (ΔSCr). Nephron damage can occur, however, without corresponding ΔSCr due to renal functional reserve. Therefore different mathematical relationships between AKI and ΔSCr exist in subsets of patients who have and have not exhausted their renal functional reserve. Current models of AKI fail to account for this confounding effect of renal functional reserve on ΔSCr. To address this limitation, a latent variable mixture model was built to account for these patient subsets, with the goal of producing a better model of AKI, but one still based on SCr measurements, which are readily available in clinical practice. By overcoming the null bias of ΔSCr, such a model would also better identify AKI-associated risk factors than current linear regression models.

Methods: In a prospective 544-subject study of cardiac surgery associated AKI, a latent variable mixture model and a linear regression model were fit to the observed ΔSCr, adjusted for pre-operative past medical history and baseline renal function +/- intraoperative AKI risk factors associated with the severity of surgery, hemodynamics, and resuscitation. All covariates were selected a priori. Baseline SCr was defined as the most recent SCr prior to surgery, and ΔSCr as the maximum ΔSCr in the 48 hours following surgery. Model fit was compared via calibration plots, bootstrap validation, and Akaike information criteria (AIC).

Results: The linear regression model under-predicted post-operative ΔSCr compared to the latent variable mixture model (Figure). The linear regression model's AIC was 456.8, while the latent variable mixture model's AIC was 175.4. Since even small differences in AIC are considered evidence of differential model fit, and lower AIC values indicate better model fit, these AIC values suggests the mixture model fit is superior. Indeed, relative likelihood calculations based on AIC suggest that the mixture model is 1x10^61 times more probable to provide superior fit compared to the traditional model. Incorporation of intraoperative risk factors into the latent variable mixture model further reduced the AIC from 175.4 to 145.2, despite an inherent AIC penalty for increased model covariates. This results in a 1x10^7 increased probability of improved model fit, strongly supporting the importance of the intraoperative course in the development of post-operative AKI.

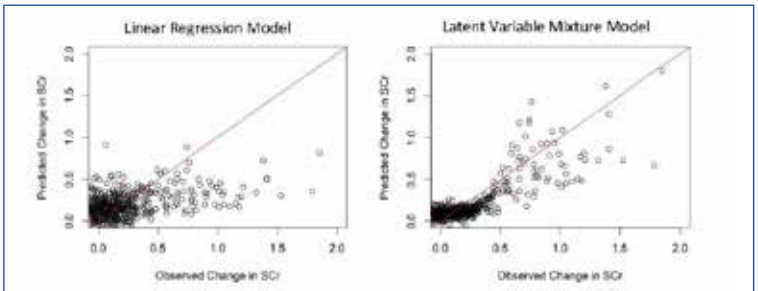

Figure Calibration Plots show that the predicted ΔSCr corresponds much closer to the observed ΔSCr for each subject using the latent variable mixture model compared to the linear regression model.

Conclusion: Latent variable mixture modeling significantly improves the estimation of perioperative AKI after cardiac surgery compared to traditional modeling and demonstrates the importance of the intraoperative course to AKI development. The mixture model's ability to overcome the confounding effect of renal functional reserve on ΔSCr likely accounts for the model's improved prediction of AKI. Future work will validate and calibrate the model in additional cohorts and will assess the ability of the model to predict long-term outcomes that are also associated with ΔSCr such as estimated glomerular filtration rate decline and progression to chronic kidney disease.

Poster Sessions

OC 9 (74)
Length of Stay and Readmission for Cardiac Surgery

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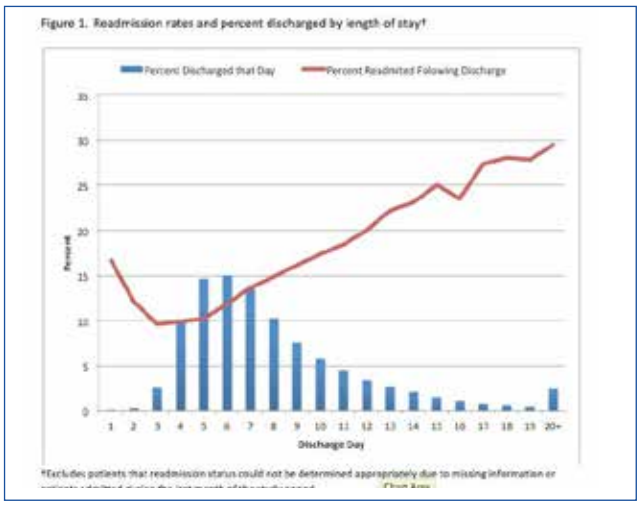
Introduction: Variability of length of stay (LOS) and associated factors have not been fully explored in an uncomplicated cardiac surgery population. Therefore, we sought to understand determinants of increased length of stay (LOS) and its variability after uncomplicated cardiac surgery.

Methods: Analyzing the State Inpatient Databases, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality database, we retrospectively reviewed six mutually exclusive groups of invasive cardiac surgery from 2007-2011 in California, Florida and New York. These groups include: isolated aortic valve surgeries [AVR]; mitral valve surgeries [MVR]; AVR and MVR [AVR/MVR]; AVR with coronary artery bypass grafting (CABG) [AVR/CABG]; MVR with CABG [MVR/CABG]; and AVR and MVR with CABG [AVR/MVR/CABG]. LOS and comorbidities were identified. Multivariable regression analysis (MVA) was used to determine factors associated with LOS greater than the median. Furthermore, we used unique identifiers to determine 30-day readmission rates. Records with an indication of postoperative complications or death were excluded.

Results and Major Findings: 139,175 discharges met study inclusion criteria: 68.2% CABG, 13.3% AVR, 7.4% MVR, 1.3% AVR/MVR, 7.2% AVR/CABG, 2.1% MVR/CABG, and 0.4% AVR/MVR/CABG. Overall median age was 66, 70.5% were male, 71.1% were white, 52.2% Medicare, and median modified Deyo Index2 was zero. Median LOS for the cohort was 7 days (Q1: 5, Q3: 10). By MVA predictors of prolonged LOS included surgical type [AVR/MVR/CABG (OR 2.59, 2.15-3.12) and AVR/MVR (OR 1.80, 1.63-2.00), when compared to CABG]; female gender (OR 1.33, 1.29-1.36); age >75 (OR 1.55, 1.45-1.65), and payer [Medicaid (OR 1.23, 1.18-1.27), Medicaid (OR 2.14, 2.04-2.24), when compared to private insurance]. Comorbities such as CHF (OR 2.13, 1.97-2.29), COPD (OR 1.19, 1.13-1.26), and renal disease (OR 1.84, 1.74-1.94) also predicted increased LOS. AVR (OR 0.62, 0.60-0.65) and MVR (OR 0.77, 0.74-0.81) had a lower OR of prolonged LOS. Despite uncomplicated postoperative courses LOS had significant variability, and the overall rate of 30-day readmissions was 14.8%. The percentage of patients discharged on each postoperative day shows wide variation with a peak at 6 days (Figure 1). 30-day readmission rates were lowest for discharges on days 3-5 (Figure 1).



Discussion: : LOS following uncomplicated cardiac surgeries is associated with various factors including age, gender, payer, co-morbidities, and extent of procedure performed. It is reasonable to take these factors into account when developing approaches to help decrease LOS. Further research is necessary to assess factors in the minimally invasive cardiac population, and to validate these findings.

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Poster Sessions

OC 10 (8)
Unplanned Rehospitalizations within 30 days of Hospital Discharge for Survivors of Critical Illness

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Rationale: Preventing hospital readmissions for serious chronic illnesses is a focus of national health care quality initiatives. Although 8 million people are admitted yearly to intensive care units (ICUs), rates of hospital readmission, or rehospitalization, after critical illness are unknown.

Methods: We performed a retrospective cohort study of intensive care unit (ICU) patients using the New York Statewide Planning and Research Cooperative System (SPARCS) for 2008-2010. We determined the cumulative incidence of unplanned rehospitalization at 30 days from hospital discharge for all ICU patients and after stratification by receipt of mechanical ventilation, by type of patient (medical versus surgical) and by age. We used competing risk regression models to identify predictors of rehospitalization at 30 days.

Results: There were 492,653 ICU patients who survived to hospital discharge, of which 79,960 (16.2%) were rehospitalized within 30 days. The cumulative incidence of unplanned rehospitalization was higher for patients receiving mechanical ventilation (29.4% for ventilation with tracheostomy versus 15.3% for none, $p < 0.001$) and older patients (21.1% for age ≥ 80 versus 12.4% for age < 60 at 30 days, $p < 0.001$). Medical and surgical patients had similar rates of rehospitalization (15.9% for medical versus 16.5% for surgical at 30 days, $p < 0.001$). Among rehospitalizations, over a quarter (28.6%) were readmitted to an ICU. Unadjusted mortality during rehospitalization was 7.6% for all patients and 15.4% for those requiring ICU care. Length of the index hospital stay (hazard ratio (HR) 1.97, 95% confidence interval (CI) 1.91 – 2.03, $p < 0.001$), being discharged to a skilled nursing facility (HR 1.54, 95% CI 1.51 – 1.57, $p < 0.001$) and having 4 or more Elixhauser comorbidities (HR 1.40 95% CI 1.35 – 1.45, $p < 0.001$) were the patient characteristics associated with the greatest hazard of rehospitalization at 30 days.

Conclusion: Approximately 16% of ICU patients are rehospitalized within 30 days of discharge. Patients with longer length of stay, patients discharged to a skilled nursing facility and patients with a high comorbidity burden were at the highest risk of rehospitalization at 30 days.

Poster Sessions

OC 11 (10)
Medical Follow-Up in the Year After Surgery and Subsequent Survival Among a National Cohort of Surgical Patients

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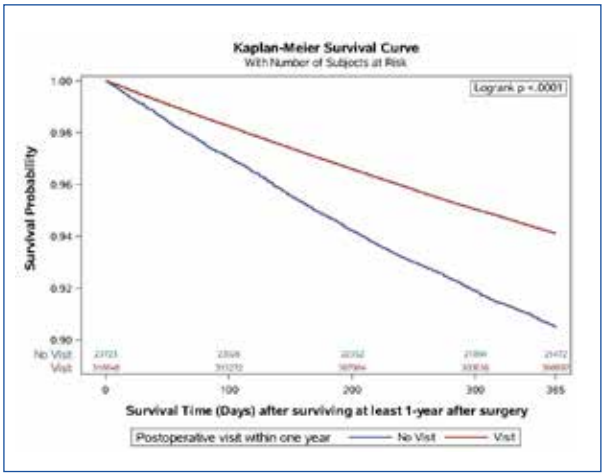
Background: Integration of surgical episodes into preventive medical follow-up has been proposed, but data describing the association among surgical care, non-surgical follow-up care, and long-term outcomes are lacking. We analyzed whether non-surgical follow-up during the first postoperative year was associated with reductions in all-cause mortality during postoperative year two.

Methods: With IRB approval, we created an EHR-based national historical cohort of adults who received surgical care at any Veterans healthcare facility between September 2006 and August 2011. The exposure of interest was whether or not the patient had at least one non-surgical clinic encounter within the VA in the 365 days following surgery. To minimize confounding due to perioperative morbidity and mortality, only patients who survived for a full 365-day period after surgery were included in the analysis. For those patients alive at the end of this exposure period, the outcome of interest was death occurring within the subsequent 365 day period (i.e. a total of two years following each index surgery). Unadjusted survival and adjusted Cox proportional hazard ratios were calculated to determine whether non-surgical clinic follow-up during the first postoperative year would be associated with a reduction in subsequent all-cause mortality during postoperative year two.



Results: A total of 385,790 patients were included in the original surgical cohort. Of these, 342,563 survived the 365 day postsurgical exposure period and were thus included in the survival analysis. Among the 342,563 patients included in the unadjusted analysis, 318,840 had a non-surgical ambulatory care follow-up visit in the year following surgery, and of these, only 5.9% died during the subsequent postsurgical year. This compares to 9.5% mortality among the 23,723 patients who did not have an ambulatory care follow-up visit (Log-rank p for difference <0.0001; See Figure 1). Thus, those with a follow-up visit experienced a 62% lower risk of death. After adjustment for confounders using a Cox Proportional-Hazards Regression Analysis, this effect was maintained. Patients who received non-surgical ambulatory follow-up care in the year after surgery had a 58.9% hazard of mortality in year 2 as compared to those who did not receive such care (HR 0.589, 95% CI 0.561-0.618). A nearly identical survival benefit continued to be observed when ASA Physical Status score was replaced with the Charlson Comorbidity Index (HR 0.569, 95% CI: 0.544-0.595, p<0.0001). A Cox frailty model to account for facility effects also demonstrated similar results.

Conclusion: The lack of non-surgical follow-up in postoperative year one was associated with increased all-cause mortality in postoperative year two. While the notion that observations and assessments made by anesthesiologists should be integrated into the larger care of the patient is not new, the present findings provide an evidentiary foundation suggestive of the public health opportunity that anesthesiologists have through promoting non-surgical follow-up care. Care coordination interventions aimed at integrating the surgical care episode into subsequent outpatient preventive medical care have the potential to improve long-term postoperative survival.

Edu 7 (19)

Assessing the Assessment: Psychometric Analysis of Scoring Instruments for the Assessment of Anesthesia Non-Technical Skills

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Introduction/Background: The optimal management of critical events requires health care teams to employ non-technical skills (NTS) such as teamwork, communication, decision making and vigilance. The most popular scale specifically designed to assess anesthesia providers' NTS is the Anesthesia Non-Technical Skills (ANTS). (1) The ANTS, while yielding valid skills scores, requires extensive background knowledge and training in behavioral theory and terminology, something that experienced clinicians and simulation instructors frequently lack. (2, 3) The Behaviorally Anchored Rating Scale (BARS) tool is a simplified measure of NTS that may be an alternative to ANTS. (4) We sought to assess the intra-rater reliability of the ANTS and BARS tools when used by novice and expert raters and to quantify the associations between the two NTS measures.

Table 1. Intra-Rater reliability of the ANTS tool between Novice and Expert raters

	Task Management	Decision Making	Situational Awareness	Teamwork	ANTS Score
Novice (n=72)	0.79*	0.72*	0.70*	0.72*	0.84*
Expert (n=36)	0.64*	0.57**	0.34^	0.62*	0.57**
Overall (n=108)	0.74*	0.66*	0.58*	0.68*	0.73*

Table 2. Intra-Rater reliability of the BARS tool between Novice and Expert raters

	Vigilance	Decision Making	Communication	Holistic Score	BARS Score
Novice (n=72)	0.64*	0.75*	0.78*	0.76*	0.81*
Expert (n=36)	0.65*	0.79*	0.67*	0.80*	0.79*
Overall (n=108)	0.63*	0.75*	0.74*	0.76*	0.79*

*P<.0001, **p<.001, ^p<0.05

Methods: Six raters (4 novice and 2 expert) reviewed and scored recordings of anesthesia trainees managing simulated pediatric critical events (hypoxemia, ventricular fibrillation (VF), supraventricular tachycardia (SVT)) using ANTS and BARS. Both groups of raters received training in the use of the ANTS and BARS tool prior to rating the recordings. The novice raters, all of whom were medical students, received additional education and training including an introduction to anesthesia crisis resource management, human factors and non-technical skills. The raters scored each simulated event using ANTS and BARS twice. Statistical analysis: To determine the intra-rater reliability of ANTS and BARS scores, Pearson correlation coefficients were calculated separately for the novice and expert raters. To investigate the association between ANTS and BARS scores, Pearson correlations were calculated. This was done by scenario and overall and was based on the raters' initial ratings.

Results: Based on the total score, the intra-rater reliability of the ANTS was r=0.73 (expert, r=0.67; novice, r=0.84) while that of the BARS was r=0.80 (expert, r=0.79; novice, r=0.81). The correlation between the ANTS and BARS total scores was r=0.74 (Hypoxemia, r=0.75; SVT, r=0.79; VF, r=0.65). Intra-rater reliability of novices and experts on each of the rating system sub-elements are shown in Table 1 (ANTS) and Table 2 (BARS). The correlation between the ANTS and BARS total scores was r=0.74 (Hypoxemia, r=0.75; SVT, r=0.79; VF, r=0.65).

Conclusion: Overall, the intra-rater reliabilities of both the ANTS and BARS were reasonably high. For both measures, intra-rater reliability was higher with the medical student raters, suggesting that properly trained novices can reliably assess the non-technical skills of anesthesia providers. Based on initial ratings, BARS scores explained approximately 55% of the variance of ANTS scores, suggesting that both tools are measuring similar constructs. The BARS is simpler tool and requires much less training than ANTS. Before recommending the BARS, additional studies are recommended to: a) identify and quantify other potential sources of measurement error; and b) gather additional evidence to support the tool's validity.

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Poster Sessions

Edu 8 (26)

Evaluating Peer-to-Peer Performance of Anesthesiology Critical Care Fellows in a Busy Multifaceted Fellowship Using Data Envelopment Analysis: A Case Study

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Introduction: Factors that contribute to the success of individual fellows within a critical care fellowship have not been well studied.1 Most programs currently place significant emphasis on summative evaluations to assess whether fellows are meeting ACGME milestones.2 We wanted to explore what aspects of the educational program and work characteristics contribute the most to an individual fellow's success as determined by year end Multidisciplinary Critical Care Knowledge Assessment Program (MCCKAP) scores and summative evaluations. We used data envelopment analysis to evaluate the academic performance of our fellows compared to their peers.(3)

Methods: Data Envelopment analysis or DEA is a non-parametric, operations research technique that uses linear programming to evaluate a unit based on its relative usage of resources (inputs) in producing the outcome or performance (outputs). Retrospective data from the 2013-14 was used to formulate the data set. Objective assessment of a fellow's overall performance required developing a composite score for each fellow based on multiple inputs. The inputs included the didactic sessions attended, the ratio of procedures performed to the clinical duty works hours, the percentage attempts of an elective "question of the day" program, and the outputs were the 3 digit MCCKAP score and quarterly evaluations of fellows.

Results: DEA output is an efficiency score for critical care fellow, ranging from 0 to 1, with a score of 1 implying a most efficient unit. Of the 7 fellows, 3 had a score of 1, 2 scored very close to 1 (0.98), 1 had a score of 0.78 and 1 had a score of 0.49. This score correlated well with the formal evaluations of fellows by attending physicians. Fellows with DEA < 1.0 (implying an inefficient unit) – did so because they used higher level of resources than their peers to produce a much lower performance (on MCCKAP and final evaluations).

Discussion: The DEA output (the efficiency scores) can be used to project the level of outputs that lower performing individuals should have achieved based on their level of effort. Alternatively, to forecast the level of effort needed to achieve the same output as their best performing peers. Data from the current group of critical care fellows will be included in the new data set and analysis rerun at the end of the 2014-15 academic year.

Conclusion: DEA is a feasible method of objectively evaluating peer performance in a critical care fellowship and can potentially be a powerful tool to guide individual performance during the fellowship.

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Poster Sessions

Edu 15 (42)
Evaluation of a Neonatal Resuscitation Teaching Curriculum in a Low-Resource Environment

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Introduction: In 2003 Liberia ended a cycle of civil war that spanned 2 decades and destroyed 95% of its health care facilities1. Since 2003 the health status in Liberia has been progressively improving until the recent 2014 Ebola epidemic overwhelmed an already strained system. The pre-ebola 2014 United Stations Human Development Report ranked Liberia as 175 out of 187 countries with a life expectancy of 60.6 years. The infant mortality rate was 73 per 1000 live births in 2009 and the under-five mortality rate was 75 per 1000 in 2012. By comparison, the United States has an HDI of 5/187, a life expectancy of 78.9 years, an infant mortality rate of 6 per 1000, and an under-five mortality rate of 7 per 1000 live births2,3,4,5. At the G8 meeting in Ontario in 2010, the G8 pledged 5 billion dollars in an agreement that calls to cut under-five mortality rates by two-thirds, indicating a shift in interests by advanced economies in helping countries such as Liberia improve health status. Consistent with the goal of decreasing infant mortality, a curriculum was developed for neonatal resuscitation for low-resource environments.

Methods: Following an exploratory site visit, a team of American Heart Association (AHA) certified medical personnel taught a two-day neonatal resuscitation curriculum designed for low-resource environments at a major referral hospital in Liberia in March 2014. The curriculum included lectures and simulations with manikins and medical equipment. Participants completed pre and post course surveys assessing knowledge and comfort level with performing resuscitation. Questions on comfort were rated on a Likert scale of 1 to 5. Knowledge was assessed with multiple choice questions. Analysis of demographics versus scores was done using Stata 12 (College Station, Texas) with a significance level of $p<0.05$.

Results: There were 75 participants total, with 56 individuals who completed both the pre course and post course surveys. The median participant age was 35 years old, ranging between 26 to 62 years old. Occupations included technicians (10.7%), nurses (55.3%), and physicians (21.4%). The aggregated median pretest score was 25% and the median posttest score was 88%. On average, each participant improved 51% on their posttest. Evaluation of posttest scores with linear regression concluded pretest score, prior NRP education, age, and occupation did not have a significant effect on the posttest scores. Gender was the only significant factor in determining posttest score. Females comprised 60% of the participants and were more likely to score higher on the posttest than males. However, when looking at gender, it was not affected by occupation, age, or prior NRP experience. Doing well on the pretest, age, gender, occupation, and prior NRP training did not have an effect on the post test score.

A paired t-test comparing pretest and posttest scores predicted a 51% increase in scores ($p<0.00001$). The median provider comfort level score pretest was 4 and posttest was 5. An ordered logistic regression analysis concluded that prior NRP education, age, gender, occupation, and posttest scores had a nonsignificant effect on performing NRP comfort level after the curriculum. A Wilcox rank test showed an expected difference in provider comfort level before and after the curriculum ($p<0.00001$).

Conclusion: Participant test scores improved by 51% after this neonatal resuscitation curriculum designed for low-resource environments. A curriculum that is lecture and simulation based may be an effective way of teaching health care providers in these environments as part of an effort to increase the country's health care capacity.

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Poster Sessions

Edu 16 (57)
A PACU Handover Training Initiative – The Curriculum Design

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Introduction: Failures of communication have been associated with poor quality care. Care transitions involving inter-professional handovers appear to be particularly vulnerable to communication failures. We developed a simulation-based intervention to improve actual handovers between anesthesia providers (AP) and nurses (RN) in an adult (VUH) and a pediatric (VCH) Post-Anesthesia Care Unit (PACU). The intervention included an electronic Handover tool at the bedside prior to every handover, observations of actual PACU handovers, and monthly unit performance feedback.

Methods: After IRB approval, this study was conducted over 16 months. The curriculum focused on communication, interpersonal skills and strategies to manage common obstacles to effective handovers. AP and PACU RN completed web-based didactics, then participated in 2-hr simulation sessions using standardized patients and clinicians, mannequin simulators and facilitated video debriefing. Each training session involved 4 trainees, 2 AP (AP1 & AP2) and 2 PACU RN (RN1 & RN2). Following an introduction, the 4 trainees in pairs (AP1 with RN1 & AP2 with RN2) performed a routine handover in the simulated PACU as a "pre-test". After the training session, the trainees performed a "post-test" simulated PACU handover (AP1 with RN2 and AP2 with RN1). All trainees evaluated the course using a 0 to 9 scale. Six months later, a 1-hr refresher course was offered to VUH clinicians. Prior to training, another handover assessment (Refresher) was performed as described above. All sessions were videotaped. Observed clinicians also provided self-evaluations (5-point scale) of their own handovers. After the study, a trained observer, blinded to handover type (Pre, Post, or Refresher), rated the simulated PACU handover videos, in random order, using a structured handover evaluation tool of 8 sub-scales measuring components of handover performance and a global score (all 1-5 scales).

Table 1. Blinded Ratings of Simulated Handovers

Comparison of Global Ratings				
Training Type		**Pre-Test** Mean(SD)	**Post-Test** Mean(SD)	**Signif** (p-value)
VUH Initial (Pre- vs. Post)		3.07(0.65)	3.13(0.43)	0.55
VCH Initial (Pre- vs. Post)		3.11(0.61)	3.02(0.46)	0.31
VUH Initial Pre-test and Post-Test vs. VUH Refresher		3.06(0.57) 3.31(0.52)	3.07(0.64)	**0.05** / 0.08
Handover Component Ratings – Pre and Post Training B *(not all comparison are shown)*				
Handover Component	**Handover**	**Pre-Test** Mean(SD)	**Post-Test** Mean(SD)	**Signif** (p-value)
Readiness for Report	VUH Pre vs. Post	2.88(1.41)	3.51(1.05)	**0.01**
	VUH Initial	2.88(1.41)		**0.01**
	VUH Refresher	3.49(1.10)		
Introduction	VUH Pre vs. Post	2.45(1.06)	2.29(1.16)	0.61
	VUH Initial		2.29(1.16)	0.13
	VUH Refresher	2.72(1.38)		
Content	VUH Pre vs. Post	2.02(0.29)	1.97(0.18)	0.26
	VUH Initial		1.95(0.21)	0.06
	VUH Refresher	2.11(0.56)		
Comprehension	VUH Pre vs. Post	3.28(0.45)	3.41(0.53)	0.15
	VUH Initial		3.43(0.53)	0.16
	VUH Refresher	3.29(0.53)		
Engagement	VUH Pre vs. Post	4.48(0.62)	4.52(0.70)	0.76
	VUH Initial		4.51(0.69)	0.59
	VUH Refresher	4.57 (0.59)		
Coordination	VUH Pre vs. Post	3.55(0.54)	3.71(0.49)	0.13
	VUH Initial	3.55(0.53)		**0.05**
	VUH Refresher	3.75(0.51)		
Clarity and Organization	VUH Pre vs. Post	3.03(0.64)	3.12(0.49)	0.40
	VUH Initial	3.03(0.64)	3.10(0.53)	0.06 / 0.14
	VUH Refresher	3.27(0.67)		

Results: A total of 452 clinicians (211 APs & 241 RNs) were trained. 429 course evaluations were received from 126 APs (60%) & 160 RNs (66%). The courses received excellent evaluations, with ratings for VUH and VCH clinicians of 7.7±1.2 and 8.1±0.7, respectively (mean±SD). 981 handover self-evaluations were received from 226 APs & 118 RNs. Providers' self-evaluation of handover effectiveness improved significantly after training, albeit to a greater extent in RNs than APs. APs scored their handover effectiveness and the "responsiveness" of the RN higher than did RNs in the same PACU. After training, all providers reported feeling under less time pressure during handovers. 294 simulated handovers were videotaped. The Pre-test and Post-test handover ratings were not significantly different (Table 1) suggesting no obvious immediate improvement in the quality of routine handovers after an intensive 2-hour simulation-based training session. In contrast, for adult PACU providers, the Refresher handovers were rated higher (6 months later) than the initial two handovers. Significant improvements were noted in 'Readiness for Report' and 'Coordination.'

Discussion: The simulation-based curriculum was very well received by experienced clinicians and favorably affected real-world clinician perceptions of handover interactions and effectiveness. Although there was no immediate improvement in the global scores of routine simulated handovers following the training, improved ratings on the 'Readiness for Report' item suggest some learning occurred. The simulated handover prior to the VUH refresher course was scored as significantly better than those before and after the initial training session. We postulate that this improvement was a consequence of other elements of this multimodal intervention, including the ability to practice the skills learned in simulation during actual handovers. Data showing significantly improved ratings of actual handovers throughout the study support this hypothesis (Anesth Analg, in press).

CS/Metab 18 (30)
Regulation of Neutrophil Mobilization and Recruitment by the TLR4 agonist Monophosphoryl Lipid A: Cellular and Molecular Mechanisms

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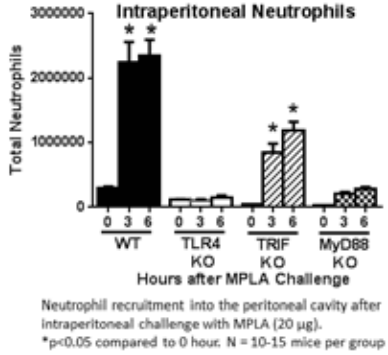
Background: The Toll-Like Receptor 4 (TLR4) agonist monophosphoryl lipid A (MPLA) is currently used as an adjuvant in FDA-approved vaccines (1) Previous studies report that the immunoadjuvant effects of MPLA are mediated through activation of the TRIF-dependent signaling pathway (2) Our studies show that MPLA will prime the innate immune system to enhance non-specific immunity against bacterial infections, an effect that is dependent on augmented neutrophil recruitment (3) However, the signaling mechanisms by which MPLA enhances neutrophil mobilization and recruitment are unknown. Our aim was to identify the role of TLR4-, TRIF-, and MyD88-dependent signaling in facilitating neutrophil mobilization and recruitment upon MPLA administration.

Methods: Activation of the MyD88- and TRIF-dependent signaling pathways in bone marrow-derived macrophages in vitro and intraperitoneal leukocytes in vivo was determined by assessment of IκB kinase (IκK) and IRF-3 phosphorylation, respectively, using Western blotting. To assess neutrophil recruitment and mobilization, neutrophil numbers in blood and peritoneal cavity were measured after intraperitoneal MPLA (20 µg) challenge in TLR4, TRIF, and MyD88 knockout (KO) mice and corresponding wild type controls. Concentrations of growth factor and chemokines that regulate neutrophil expansion (G-CSF) and recruitment (KC, MIP-2) were measured in plasma and peritoneal lavage fluid using multiplex immunoassays at the same time points.



Neutrophil recruitment into the peritoneal cavity after intraperitoneal challenge with MPLA (20 µg). *p<0.05 compared to 0 hour. N = 10-15 mice per group

Results: MPLA potently induced phosphorylation of IκK and IRF-3 in bone marrow-derived macrophages and intraperitoneal leukocytes, respectively. Wild type (WT) mice showed a tripling of blood neutrophils and ~10-fold increase in intraperitoneal neutrophils (<0.3 million to 2.3 million, see figure) at 3 hours after MPLA administration, an effect that was absent in TLR4-deficient C57BL/ScN mice. In MyD88 KO mice, blood neutrophil numbers increased post-MPLA injection to levels that were similar to that observed in wild type mice, whereas MPLA-induced recruitment of neutrophils into the peritoneal cavity was ablated. TRIF KO mice showed delayed mobilization of neutrophils into blood, but ultimately the peak blood neutrophil numbers in TRIF KO mice were similar to wild type mice. Recruitment of neutrophils into the peritoneal cavity was attenuated in TRIF KO mice compared to wild type controls. MPLA induced a significant increase of G-CSF (6620 ± 230 pg/ml) in plasma at 6 hours after MPLA but was a weak inducer of IL-6 (112 ± 26 pg/ml). MPLA stimulated an increase of MIP-2 and KC in plasma and peritoneal cavity. Production of G-CSF, MIP-2 and KC were nearly ablated in MyD88 KO mice and were attenuated in TRIF KO mice after MPLA challenge.

Conclusion: MPLA potently induces activation of both MyD88- and TRIF-dependent signaling pathways and is a strong inducer of neutrophil mobilization and recruitment. MPLA-induced neutrophil mobilization from bone marrow into blood is partially mediated by activation of TRIF-dependent signaling and is independent of MyD88 whereas neutrophil recruitment to the site of MPLA administration is primarily mediated by activation of the MyD88 pathway. MPLA is a potent stimulus for production of G-CSF, MIP-2 and KC, which are regulated primarily through activation of the MyD88 pathway. These findings advance knowledge of the molecular mechanisms that regulate the antimicrobial effects of MPLA.

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Poster Sessions

CS/Metab 19 (32)
Melanopsin Mediates Light-Dependent Relaxation In Blood Vessels [1]

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Introduction and General Purpose of the Study: "Photorelaxation", the reversible relaxation of blood vessels to light, was initially described by Furchgott et al. in 1955 [2]. It appears to be cGMP-dependent and endothelial-independent but the role of nitric oxide (NO) in photorelaxation has been controversial [3-8], with some studies showing that NOS inhibition with L-NAME not only fails to inhibit the response [3], but in some cases enhances and prolongs it [4]. Given the controversy we postulated an entirely novel mechanism: That photorelaxation is mediated by transduction through photosensitive receptors in blood vessels; photoreceptors that are part of the family of Non-image-forming (NIF) opsins.

Methods: Vasoreactivity: Photorelaxation of blood vessels was assessed via force-tension myography. Light was delivered via cold light lamp (40,000-190,000 LUX), light diodes (red [620-750 nm], green [495-570 nm] or blue [380-495 nm]), or a monochromator with varying wavelength.

Laser Doppler Flowmetry: A laser-Doppler flow probe was placed on the proximal ventral surface of the tail. Relative changes in red blood cell flux were monitored with a Perimed PeriFlux System 5000 laser-Doppler Flowmeter.

RTPCR: To demonstrate the expression of melanopsin (Opn4), G protein-coupled receptor kinase (GRK2), phosphodiesterase (PDE)5A and PDE6G, RTPCR was performed using mRNA isolated from mouse aortas.

Membrane potential (Em) Measurements: Endothelium-denuded segments of murine thoracic aorta were pinned in place, lumen side down in a recoding chamber. Intracellular recordings were performed in current clamp (3.0–4.0 kHz sampling rate) mode and recorded on a chart recorder (TA240; Gould Instrument Systems).

Results and Major Findings: 1) In ex-vivo force tension myography experiments, light induces intensity dependent vasorelaxation in mouse aorta demonstrating dose-dependent effects of cold white light on Opn4+/+ mouse aorta and absence of photorelaxation in aortas from Opn4-/- mice or Opn4+/+ aortas pre-incubated with Opn4 inhibitor [9].

2) Photorelaxation response is wavelength specific: we observed no vasorelaxation in Opn4+/+ aorta to red (620-750 nm) and green (495-570 nm) spectra but maximum vasorelaxation was observed to blue (380-495 nm) spectrum light.

3) Force Tension myography and intracellular patch clamp experiments on endothelial intact and denuded vessels in the presence and absence of pharmacologic inhibitors demonstrated that photorelaxation signal transduction is endothelium and eNOS-independent but involves sGC, PDE6, and vessel hyperpolarization.

4) Mouse aorta demonstrates desensitization, i.e diminished vasodilatory responses to iso-intensity repeat light stimulation. A complete attenuation of desensitization / enhanced vasodilatory responses to same iso-intensity repeat light stimulation is observed following inhibition or knockdown of GRK2 in Opn4++ mouse aorta

5) Determining the in vivo physiological consequences, we used Laser Doppler Flowmetry, red blood cell flux was measured as the tail was exposed to blue light for 10 min followed by a 10 min dark period. There was a significant increase in tail blood flow in Opn4+/+ mice with exposure to blue light, which was reversed in dark. This phenomenon was not observed in Opn4-/- mice (Fig A,B).

Conclusion: Opn4 receptors are present in blood vessels, and mediate wavelength specific, light-dependent vascular relaxation. This photorelaxation signal transduction involves cGMP and PDE6, but

continued on page 78

not PKG. Furthermore it is regulated by GRK2, and involves vascular hyperpolarization. This receptor pathway could be targeted for wavelength-specific light-based therapy in the treatment of diseases that involve altered vasoreactivity.

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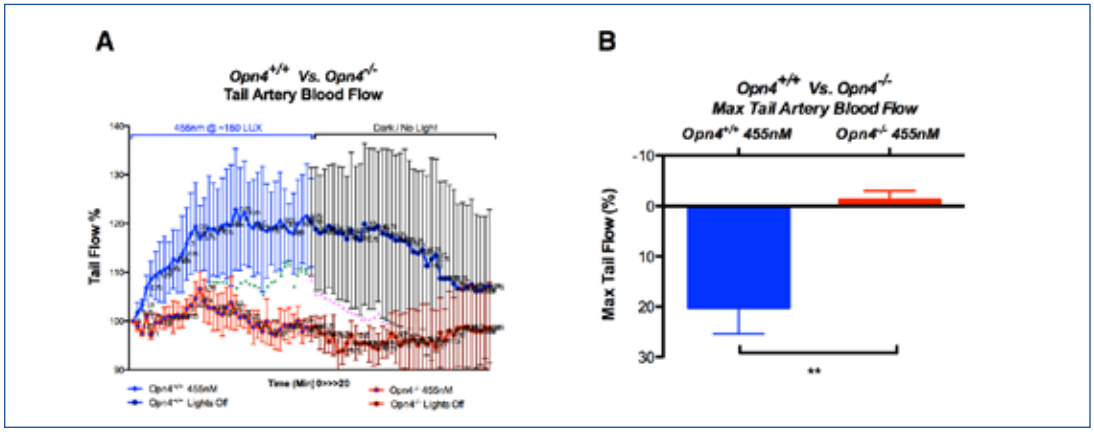

Poster Sessions

CS/Metab 26 (36)
A Novel Mechanism for Cardioprotection by Intralipid

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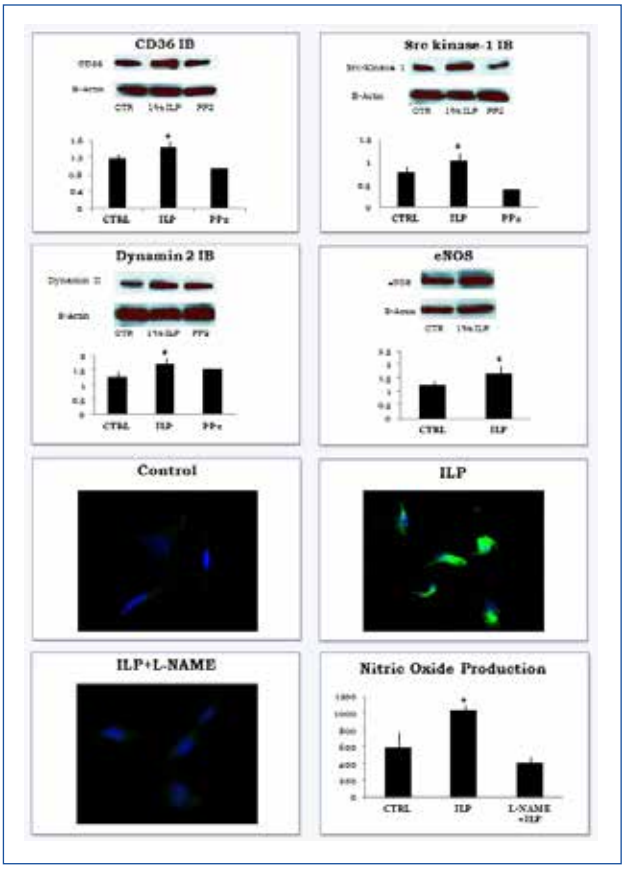
Background: Intralipid™ (ILP) is a fat emulsion shown to be cardioprotective against myocardial ischemia-reperfusion (IR) injury in rodents. While recovery from myocardial IR is impaired in fatty acid translocase (CD36)-null mice, addition of a selective CD36 ligand offers cardioprotection (1). Additionally, eNOS-derived nitric oxide (NO) plays an important role in pro-survival pathways following myocardial IR (2). We hypothesize that uptake of ILP occurs via CD36 in caveolae, small flask-shaped plasma membrane invaginations that play a role in endocytosis and signal transduction. Src kinase-1 then phosphorylates dynamin 2 which cleaves the CD36 caveolae. Following uptake, ILP increases eNOS-derived NO which mediates protection against oxidative stress.



Methods: Protein expression was measured in T3 - T6 human umbilical vein endothelial cells (HUVECs) following a post-conditioning protocol in which IR was simulated by 0.2 mM hydrogen peroxide (H2O2) for 30 min followed by 1% ILP for 2 h. Experimental groups included H2O2 only (CTRL), 1% ILP, and 1% ILP with the src-kinase inhibitor PP2. After harvesting and isolation, protein was loaded onto a SDS polyacrylamide gel, electro-transferred to nitrocellulose paper, blocked with 10% nonfat dry milk and incubated overnight with anti-CD36, src kinase-1, dynamin 2, and eNOS antibodies. Equal protein loading onto each gel lane was confirmed with β-actin. NO production was quantified through confocal fluorescence utilizing 50 mcM 4,5-diaminofluorescein diacetate (DAF-2 DA) in CTRL, 1% ILP, and 1% ILP + 1 mcM of the NOS inhibitor Nβ-Nitro-L-arginine methyl ester hydrochloride (L-NAME) groups.

Results: ILP led to a 24% increase in CD36 expression, a 33% increase in src-kinase, a 34% increase in dynamin 2, and a 36% increase in eNOS. Addition of PP2 to ILP resulted in a 36% decrease in CD36 expression, a 61% decrease in src-kinase, and no change in dynamin 2 compared to CTRL. Furthermore, ILP led to a 77% increase in NO, whereas addition of L-NAME to ILP led to a 30% decrease compared to CTRL.

Conclusion: Present findings suggest that ILP enters HUVECs via endocytosis by the CD36 fatty acid translocase. Src kinase-1 phosphorylates dynamin 2 which then pulls the complex into the cell. Subsequent phosphorylation of eNOS increases NO production to mediate myocardial protection against oxidative stress during IR.

Acknowledgements: Supported by the Department of Veterans Affairs (CARA-026-10F), FAER (MSARF), and NHLBI (T35).

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Poster Sessions

CS/Metab 28 (68)

Characterization of Cytochrome P450 Reductase Mutants that Control Its Activity with Cytochrome P450 50

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Introduction: Humans possess 57 different cyts P450. Approximately one half of the human cyts P450 metabolize the vast majority of drugs employed by aβnesthesiologists. As a result, those enzymes regulate the duration of action, efficacy and toxicity of drugs encountered in the practice of anesthesia. The different microsomal cyts P450 receive electrons from a single redox partner, cyt P450 reductase (CYPOR). The reductase, which has two flavin cofactors, accepts two electrons from NADPH, which passes them along to FAD. FAD then transfers one electron at a time to FMN. The 2- electron-reduced FMN is the ultimate electron donor to cyt P450. The flavin cofactors, FMN and FAD, exist in three oxidation states – oxidized, 1-electron- reduced (semiquinone) and 2-electron-reduced (hydroquinone). It is only the FMN hydroquinone that reduces cyts P450. To understand the biochemical and structural basis of the ability of FMN to reduce cyt P450, we have deleted amino acids in a loop near the FMN that have been proposed to regulate electron transfer from FMN to cyt P450.

Methods: Two mutations, ΔGlycine141 and ΔGlycine143, were constructed, by site-directed mutagenesis, then expressed in E. coli and purified. The mutations were located in a flexible loop, whose conformation varies with the redox state of the FMN. The loop does not contact the flavin ring in the oxidized form but rotates to an "up" position to react with the protonated Nitrogen 5 of the one-electron- reduced flavin.

Results and Discussion: When the loop, which forms a hydrogen-bond with the reduced and protonated N5H of the FMN in the wild type reductase, was shortened by one residue, ΔG141, a marked diminution in the ability of mutant reductase to transfer electrons to cyt P450 were observed. The ΔG141 mutant was unable to reduce cyt P450 because the redox potentials of the 1- and 2-electron-reduced FMN had been reversed and the reduction of cyt P450 was no longer thermodynamically feasible. Unlike water, the redox potentials of chemical entities by convention only run uphill from negative to positive.

The ΔG141 mutant altered the redox potential of the flavin ring by preventing protonation and hence charge neutralization of the flavin. The atomic detailed crystal structure of the mutant reductase revealed that deleting G141 rigidified and shortened the flexible loop in contact with the protonated N5 (N5H) of the 1-and 2-electron-reduced FMN in the wild type reductase. As a result, the shorter, rigid loop inhibited protonation of the N5 in the 1-electron-reduced FMN.

Crystallography revealed that deletion of G143 also gave rise to a mutant with a shortened, flexible loop that, nevertheless, could slowly reduce cyt P450. The loop did not contact the flavin in either the oxidized or reduced form. The ΔG143 mutant's redox potentials were both appropriate (negative enough) for cyt P450 reduction. However, the G143 deletion variant protein also donated its electrons very rapidly to oxygen. In essence, oxygen was outcompeting cyt P450 for the electrons from the FMN. That the FMN N5H did form a hydrogen bond at least transiently with either the loop or a solvent water molecule was inferred from its activity with cyt P450 and its redox potentials.

Poster Sessions

CS/Metab 29 (72)
General Anesthetic-Mediated Effects on Autophagy Determine Cell Survival

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Background: General anesthetic (GAs) mediate both neuroprotection and neurotoxicity via their effects on the intracellular Ca2+ homeostasis and apoptosis. Little is known about the effects of anesthetics on autophapgy, which affects cell survival by either inhibiting or promoting apoptosis. Since Inositol trisphosphate receptor (InsP3R) activity plays an important role in the regulation of autophagy, GAs may control cell survival fate by affecting autophagy via differential activation of InsP3Rs.

Methods: Tissue cultures, (wild type chicken B lymphocytes (DT40-WT) or with InsP3R isoforms knocked out (DT40-TKO); SH-SY5Y human neuroblastoma cells; wild type pheochromocytoma cells (PC12-WT) or with an Alzheimer's presenlin-1 mutation (PC12-L286V)), were treated with isoflurane or propofol. Cell viability determined by the MTT assay. Autophagy activity determined by LC3-II, Beclin-1, AMPK and mTOR levels with IHC or Western blot. Autophagy flux monitored by LC3-II levels in the presence or absence of Bafilomycin (Baf A1), levels of p62 and lysosome protein LAMP1. Apoptosis determined by DNA fragmentation (TUNEL). Mitochondrial stress measured by cytosolic ATP levels and mitochondrial membrane potential changes with TME immunostaining. Animal studies, wild type (WT) or transgenic Opt-Het mice, with decreased levels of type 1 InsP3Rs, were treated with 1.2% isoflurane for 2 h a day for 5 continuous days. Western blot brain cortex assays measured autophagy (LC3-II, AMPK) and apoptosis (Caspase-3).

Results: In SH-SY5Y cells, propofol increased the autophagy biomarker LC3-II, Beclin-1 expression, phosphorylated AMPK and inhibited the activity of mTOR, suggesting that propofol stimulated autophagy by activation of InsP3Rs in the mTOR-dependent pathway (Fig. 1). A prolonged exposure to propofol (24h) impaired the autophagy flux as it did not further increase LC3-II levels in the presence of Baf A1, decreased degradation of P62, increased LAMP1 expression, loss of mitochondrial membrane potential and decreased cytosolic ATP. In consistent, propofol treatment (24h) induced cell damage, which was inhibited by adequate stimulation of autophagy with rapamycin or lithium but not the autophagy inhibitor (3-MA). The autophagy promoter, rapamycin, also induced cell death, suggesting excessive autophagy may become neurotoxic (Fig. 1). Cell death induced by propofol was ameliorated by xestospongin C, indicating InsP3R activation. In contrast, a short exposure to propofol (2.5 or 4 h) increased p62 degradation without loss of mitochondrial membrane potential, decreased cytosolic ATP or induction of apoptosis, Isoflurane significantly increased autophagy activity in DT40-WT only but not TKO cells. In PC12 cells, isoflurane significantly increased autolysosomes in PS1-286 but not PS1-WT cells and was inhibited by xestospongin C, indicating isoflurane impaired the turnover of autolysosomes in InsP3R dependent pathway. In animals, isoflurane significantly increased LC3-II in the postnatal day 7 (P7) WT brain but not in the Opt-Het or the adult brain (P60) of either genotype, suggesting impairment of autophagy flux and increased sensitivity to anesthetics in the developing brain. Isoflurane only induced apoptosis at P7 in the WT, suggesting that impairment of autophagy flux may be a novel mechanism for anesthetic toxicity in the developing brain.

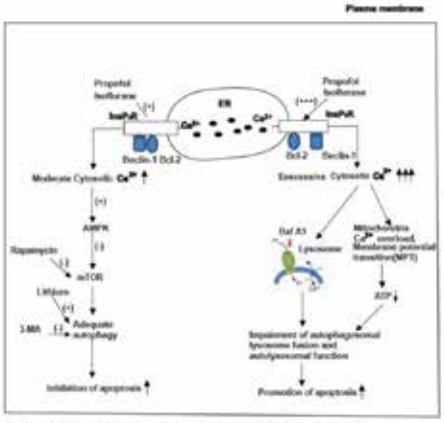

Figure 1. Dual effects of general anesthetics on autophagy and associated apoptosis. The $InsP_3R$ provides a platform for the Bcl-2 and Beclin-1 complex, and the release of Beclin-1 from Bcl-2 increases activation of the $InsP_3R$. Moderate elevation of the cytosolic Ca^{2+} by GA-mediated activation of $InsP_3Rs$ for a short duration may increase autophagy activity adequately via the AMPK and mTOR dependent pathway, thus inhibiting apoptosis. Lithium and rapamycin increase autophagy activity but 3-MA is a general inhibitor of autophagy. On the other hand, an abnormal elevation of the cytosolic Ca^{2+} by excessive activation of the $InsP_3R$ for prolonged durations, as well as the GA-mediated decrease or depletion of the endoplasmic reticulum Ca^{2+} and the abnormal increase of the mitochondria Ca^{2+} concentration, may impair autophagy flux via the following mechanisms: 1) Impaired fusion between autophagosomes and lysosomes to form the autolysosome; 2) Decreased H^+ and increased pH inside the lysosome or autolysosome and thus impairing function of lysosomal enzymes; 3) Overload of mitochondria with Ca^{2+} decreases ATP production and impairs lysosome or autolysosome function. Impaired autophagy flux eventually promotes apoptosis.

Conclusion: GAs stimulate autophagy in the mTOR-dependent pathway, providing neuroprotection when used at low concentrations for short exposures. However, at high concentrations for prolonged duration, GAs impair the autophagy flux, producing neurotoxicity, especially in the developing brain. The GA-mediated effects on apoptosis and autophagy may be closely integrated, both via activation of InsP3R.

Poster Sessions

Clin Neuro 33 (5)
Role of Surgery Requiring Anesthesia in Postoperative Cognitive Impairment

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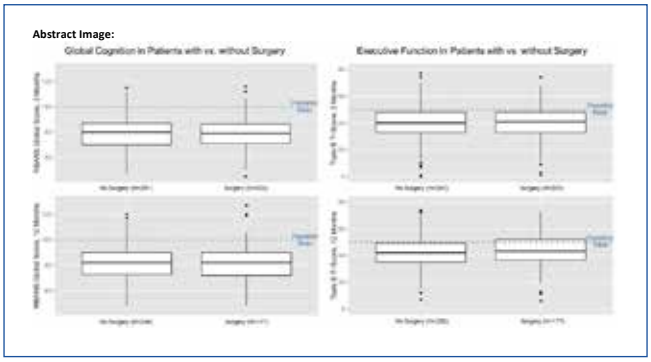
Introduction: Emerging data question whether postoperative cognitive dysfunction is attributable to surgery and anesthesia. (1-5) We tested whether surgery requiring anesthesia is an independent risk factor for long-term cognitive impairment.

Methods: This multicenter prospective cohort study enrolled patients within 72 hours of respiratory failure or shock. Demographic and hospital data, including surgery requiring anesthesia, were collected from admission to 30 days after enrollment. At 3 and 12 months post-discharge, we assessed global cognition with Repeatable Battery for the Assessment of Neuropsychological Status (RBANS: mean population adjusted score of 100±15; lower scores indicate worse cognition) and executive function with Trail Making Test, Part B (Trails B: mean population adjusted score of 50±10; lower scores indicate worse function). Linear regression was used to study the associations of surgery requiring anesthesia with outcomes in 2 separate models: 1) after adjusting for only baseline covariates (age, Charlson comorbidity index, education years, Informant Questionnaire on Cognitive Decline in the Elderly score, and Framingham stroke risk score) and 2) with the addition of in-hospital covariates (coma and delirium duration, severe sepsis duration, hypoxemia intervals, Sequential Organ Failure Assessment score, and doses of analgesics, sedatives, and antipsychotics). A subset of patients with detailed anesthetic records was additionally analyzed to study the association of surgical and anesthesia characteristics on outcomes.



Results: Of the 1,041 patients enrolled, the median age was 62, APACHE II score was 24, and 402 (39%) had surgery requiring general anesthesia. After accounting for death (n=329) and loss to follow-up or withdrawal (n=177), 534 patients had testing at 3 and/or 12 months, 219 (41%) of whom had surgery. Median RBANS global cognition scores were similar at 3 and 12 months in patients who had surgery vs. those who did not (79 vs. 80; 82 vs. 82), approximately 1.5 standard deviations below population mean. Median Trails B executive function scores were also similar in those who had surgery vs. those who did not (41 vs. 40; 43 vs. 42), approximately 1 standard deviation below population mean. Surgery requiring anesthesia was not associated with cognitive or executive dysfunction at 3 or 12 months in models incorporating baseline covariates with and without in-hospital covariates (all $p>0.15$). Increasing age, lower education years, and longer delirium duration were associated with worse 3 and 12-month cognitive function (all $p<0.02$), and longer delirium duration was associated with worse 3 and 12-month executive function ($p<0.01$). Neither emergent surgery, number of surgeries, nor anesthesia duration was associated with cognitive or executive dysfunction in the subset of 233 patients.

Conclusion: In critically ill patients, neither surgery requiring anesthesia nor specific operative characteristics increased risk for long-term cognition or executive function deficits. Such deficits were common and associated with baseline patient characteristics and in-hospital delirium.

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Poster Sessions

Clin Neuro 34 (55)
Validity of Neuromonitoring in Aneurysm Surgery

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Introduction: Intracranial aneurysm clipping is associated with significant mortality and morbidity, primarily related to ischemia in the vascular territory of the aneurysm. Surgical clipping of aneurysms is preferred in cases where the morphology of the aneurysm does not permit endovascular coiling. Over the last 5-10 years intraoperative monitoring of motor evoked potential (MEP), sensory evoked potential (SSEP) and EEG (collectively referred to as neuromonitoring) is being advocated to identify any ischemic insult intraoperatively which could potentially result in a poor outcome. The premise behind neuromonitoring is any ischemic insult will lead to an alert in the monitors, which with appropriate corrective measures could be resolved, thus preventing ischemic damage. Our aim in this study was to retrospectively evaluate the validity of intraoperative neuromonitoring during aneurysm surgery.

Methods: After approval from Yale University IRB electronics records of 72 patients who were monitored with MEP, SSEP & EEG during surgical clipping of aneurysm was studied. Pre & postoperative outcome (immediate & at 6 weeks follow up) was recorded. Intraoperative changes in MEP, SSEP & EEG (alerts), as determined by the electrophysiologist and any intervention carried out by the anesthesiologist and the surgeon was identified for all the cases. The intraoperative neuromonitoring alerts were correlated with the postoperative outcome. The sensitivity, positive and negative predictive value of neuromonitoring alerts was calculated.

Results: Of the 72 patients 70 had clipping and 2 underwent endovascular coiling. The patient population was a mixed group of unruptured and ruptured aneurysms. There were 14 males and 58 females (M: F 1:4). Most of the aneurysms were in the anterior and middle cerebral territory. Out of the 72 patients 61 had a good outcome (85.9% - minimal or no neurological deficit) while 11 had some deficits. Among the patients with good outcome 19 had neuromonitoring alert, which resolved with appropriate intervention and the outcome was good. Of the 11 patients with deficits 3 had alerts and 8 patients had no alert. Altogether 22 patients who had some alert in neuromonitoring (14 in EEG, 8 in MEP and 6 in SSEP). The alerts were:

- In the EEG - decrease in amplitude and frequency, burst suppression.

- In MEP - decrease in amplitude of the motor action potential

- In SSEP - 50% decrease in amplitude and /or 10% increase in latency.

Of these 22 patients in19 cases the neuromonitoring alerts resolved after some intervention and these patients recovered with minimal or no deficit. In the remaining 3 the changes did not recover and patients had significant deficits postoperatively. These were the 3 patients who were in Hunting & Hess grade 3 or higher prior to surgery. Among the 50 patients with no changes in EEG, MEP or SSEP, 8 had neurological deficit at 6 weeks follow up. Among these 50 patients there were 16 who had a Hunting & Hess grade 3 or higher prior to surgery. Collectively the sensitivity of neuromonitoring was 70.3%. The positive predictive value was 86.3% and the negative predictive value was 84%.

Conclusion: In the entire group with the institution of intraoperative neuromonitoring 85.9% patients had a good outcome. While the individual monitors by themselves were not sensitive enough when all the three monitors are applied the sensitivity of detection of intraoperative ischemia improves to 70%.

Poster Sessions

Clin Neuro 35 (59)
Effects of Anesthesia, Surgery, and APOE4 on Brain Atrophy in Older Adults

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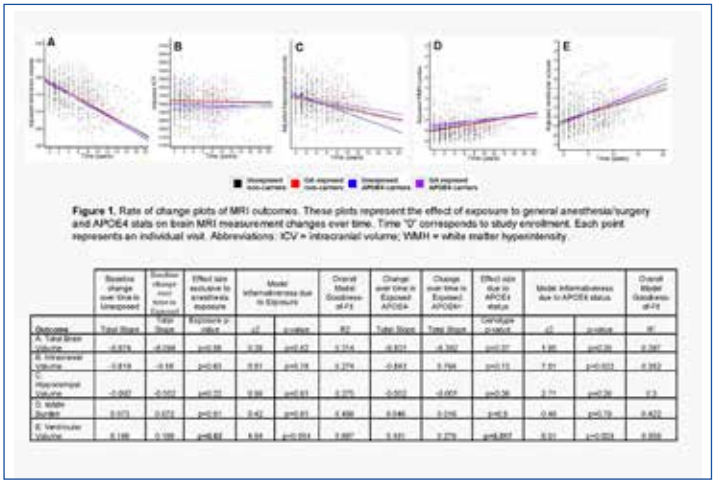
Introduction: The diagnosis of postoperative cognitive dysfunction (POCD) requires perioperative neurocognitive testing, and there are no standard criteria for the diagnosis or assessment of POCD. To meet the need for objective measures of postoperative neurocognitive injury, there has been an increasing interest in the identification of biomarkers. Brain tissue atrophy rates have been used as a marker of Alzheimer's disease progression, and serial MRI techniques primarily focus on volumetric analysis of the hippocampus, whole brain, and ventricles.1 A recent study reported that surgical patients had increased rates of atrophy for cortical gray matter and hippocampus and lateral ventricle enlargement as compared to non-surgical controls.2 We hypothesized that exposure to surgery and general anesthesia (GA) in older adults would lead to a more accelerated rate of brain atrophy that is more rapid in those with an apolipoprotein E β4 (APOE4) allele.



Methods: Using a retrospective cohort design, we performed an analysis of two longstanding natural history studies of cognitive aging. We used mixed-effects statistical models to assess the relationships between exposure to surgery and general anesthesia, APOE genotype, and longitudinal change of brain tissue atrophy. Brain structural MRI measurements included hippocampal volume, white matter hyperintensity burden, and ventricular volume which were all normalized according to total intracranial volume. Principal assessment evaluated cross-sectional change over time, and we controlled for potential confounders including age, education level, gender, and Cumulative Illness Rating.

Results: Out of a total of 527 participants, 182 participants had a combined total of 331 surgeries under general anesthesia after enrollment in the study. The mean follow-up after study enrollment was 7 years (SD 4.6). There was no difference between the two groups in sex distribution, mean years of education, presence of an APOE4 allele, or Cumulative Illness Rating Scale. On average, exposed participants were 3.9 years younger than unexposed participants. Participants exposed to surgery/GA during the study period experienced a more rapid rate of ventricular enlargement over time compared to the unexposed group (p=0.03, Figure 1E). There were no differences in the other brain volumes between groups (Figure 1A-D). Next, the exposed participants were subdivided into two groups based on whether they had at least one copy of the APOE4 allele. Among participants exposed to surgery/GA, the APOE4+ group experienced a more dramatic rate of increase in ventricular volume over time compared to the exposed APOE4- group (p=0.017). The rates of change in the other measured brain volumes did not differ based on APOE4 status.

Conclusion: Older adults with an exposure to surgery/GA had a more rapid rate of ventricular enlargement when compared to those who did not undergo surgery/GA. Further, among all participants with a history of surgery/GA, the APOE4+ group had an increased rate of ventricular enlargement than the APOE4- group.

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Poster Sessions

Basic Neuro Sci 47 (39)

The Importance of Body Posture for Waste Removal via the Brain-Wide Glymphatic Pathway

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The 'glymphatic' pathway has been shown to expedite clearance of interstitial waste including soluble amyloid beta and tau from the brain. Intriguingly, glymphatic transport is controlled by the brain's arousal level because during sleep or anesthesia, the brain's interstitial space volume expand to facilitate convective influx of cerebrospinal fluid (CSF), which interchanges with interstitial fluid (ISF), resulting in enhanced (compared to awake state) transport of metabolic waste toward para-venous conduits connecting to lymphatics on the neck. Humans and as well as animals exhibit different body postures during the awake and sleep states. Therefore, not only the level of consciousness, but also body posture might affect glymphatic transport efficiency. Here we use dynamic contrast enhanced MRI in combination with administration of paramagnetic contrast into the CSF to examine the effect of body posture on glymphatic transport in the anesthetized rat's brain. Brain-wide glymphatic influx as well as clearance was most efficient in the lateral position when compared to supine or prone positions. In the prone position, where the rat's head was in the most upright position (mimicking posture during the awake state), glymphatic transport was the least efficient. The prone position was also characterized by pronounced CSF efflux along larger caliber cervical vessels. We propose that the most popular sleep posture (lateral) have evolved to optimize glymphatic activity during sleep and that posture must be considered in anesthesia/surgical procedures as well as for diagnostic imaging procedures developed in the near future to assess glymphatic transport efficacy in humans.

Poster Sessions

Basic Neuro Sci 48 (40)

Peroxiredoxin-1 is a Novel Danger Signal Involved in Neurotoxic Microglial Activation After Experimental Cardiac Arrest

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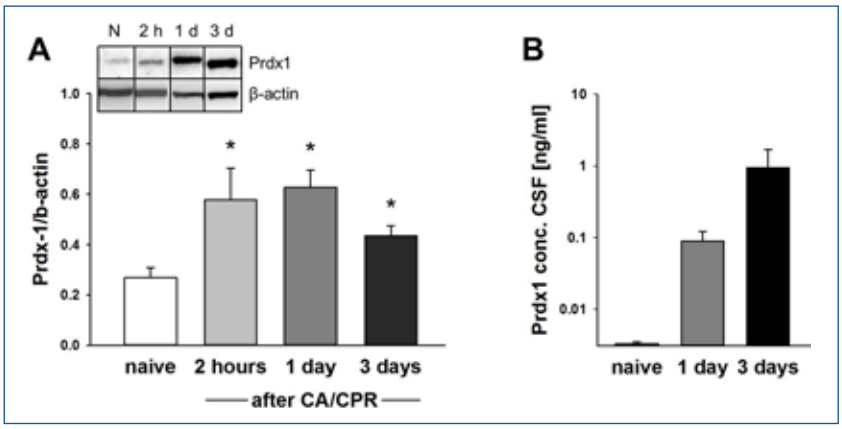
Background: Cardiac arrest (CA) is a common manifestation of ischemic heart disease. While advances in cardiopulmonary resuscitation (CPR) and critical care have improved survival after cardiac arrest, survivors frequently suffer brain injury that leads to long-term cognitive dysfunction. Cardiac arrest causes inflammation and activation of microglia, the brain resident immune cells, which precedes neuronal death in ischemia-sensitive brain regions [1]. We hypothesized that microglia are activated to a neurotoxic phenotype after cardiac arrest and exacerbate neuronal death, and that a danger signal released by injured neurons drives this activation.

Methods: In vivo: CA was induced in anesthetized and intubated male adult C57BL/6 mice by injection of potassium chloride. CPR was begun after 10 min of CA. Hippocampal tissue was harvested and cerebrospinal fluid (CSF) collected 1 or 3 days after CA/CPR for quantification of antioxidant protein Peroxiredoxin-1 (Prx1) by immunoblot (tissue) or ELISA (CSF). Recombinant Prx1 was injected into the hippocampus of additional mice and microglial activation assessed by immunohistochemistry using Iba1 antibody 1 day later. In vitro: Primary cultured mouse neurons were exposed to oxygen-glucose deprivation (OGD) to simulate ischemia, and cell death assessed 1 day later. Neurotoxicity of primary mouse microglia was assessed by measuring neuronal death in microglia-neuronal co-cultures after OGD. Microglial release of cytokines was quantified by ELISA. Group differences were evaluated using ANOVA or Student's t-test, as appropriate. Results are mean±SEM.



Results: Prx1 protein was upregulated in mouse hippocampus within 2 hrs after CA/CPR (Fig. 1A) and released into the CSF, where it became detectable within the first day after CA/CPR (Fig. 1B). Similarly, cultured neurons released Prx1 into the medium after OGD. This neuron-conditioned medium (NCM) induced a pro-inflammatory phenotype in cultured microglia, characterized by release of TNF-β (104 ± 31 pg/100.000 cells vs 0.8 ± 0.4 untreated) and IL-β (11.4 ± 6.5 vs 0 ± 0 untreated). Similar inflammation was induced when microglia were treated with recombinant Prx1 (TNFβ 1482 ± 798, IL-1β 8.0 ± 5), while depletion of Prx1 from neuron-conditioned medium by immunoprecipitation abolished the cytokine release. Microglia activated by NCM or recombinant Prx1 significantly increased neuronal cell death after OGD, compared to untreated microglia (NCM 37 ± 6% death, Prx1 34 ± 3%, untreated 25 ± 5%, $P<0.05$). Finally, injection of recombinant Prx1 into the hippocampus caused morphologic activation of microglia that mimicked activation after cardiac arrest.

Conclusion: We identified Prx1 as a novel danger molecule that is released by ischemia-injured neurons and activates microglia to a pro-inflammatory and neurotoxic phenotype, which exacerbates neuronal death. As Prx1 release after CA/CPR precedes microglial activation, it provides a promising new target for interventions aimed at reducing brain injury and subsequent dysfunction after CA/CPR by blocking inflammation and microglial neurotoxicity.

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Poster Sessions

Basic Neuro Sci 49 (41)
The Parabrachial Nucleus Mediates Respiratory Rate Depression from Intravenous Remifentanil

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Introduction: Despite much clinical interest in strategies to reduce the risk of opioid-induced respiratory depression, the brainstem locations mediating this dangerous side effect remain incompletely defined. We have previously shown in an in vivo decerebrate rabbit model that the preBötzinger Complex (preBC), which is considered part of the central respiratory pattern generator, mediates some opioid effects on respiratory phase timing, however, the pronounced opioid-induced bradypnea cannot be reversed in the preBC (1). In the in vivo canine preparation, respiratory rate depression can be at least partially reversed in a subarea of the parabrachial nucleus (PBN) in the pons (2). The current study sought to identify this region in adult rabbits and to determine whether opioid-effects on this region similarly impact inspiratory and expiratory phase duration.

Methods: The study was approved by the local Animal Care Committee and conformed to NIH standards. Adult New Zealand White rabbits were anesthetized, tracheotomized, ventilated and decerebrated. An occipital craniotomy and cerebellectomy allowed access to the pons for recording and drug microinjection. Phrenic nerve recordings provided respiratory rate, inspiratory (Ti) and expiratory (Te) duration and peak phrenic amplitude (PPA, neural tidal volume). A subarea of the parabrachial nucleus responsible for respiratory rate control ("tachypneic area") was identified by the tachypneic response to localized injection of β-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA, 50 µM, 70 nl).

Protocol 1: The mu-opioid receptor agonist [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) was injected bilaterally into the "tachypneic area" at pharmacological concentrations (100 µM, 700nl) to determine the effect of direct opioid receptor stimulation in this area and the injection volume required to achieve maximal effect. Bilateral injection of the opioid antagonist naloxone (1mM, 840nl) was used to reverse the effect.

Protocol 2: To identify whether the "tachypneic area" also mediated respiratory depression at clinical tissue levels of opioids (~20 nM) (3) the mu-opioid agonist remifentanil was infused intravenously (~0.5 mcg/kg/min) until respiratory rate and peak phrenic amplitude were depressed by approximately 50%. Naloxone (1mM, 840 nl) was then bilaterally injected into the "tachypneic area" in an attempt to reverse respiratory depression.

Results: Protocol 1: In eleven animals, DAMGO injection into the "tachypneic area" of the PBN resulted in a decrease in respiratory rate from 23±13 bpm to 12±7 bpm ($p<0.001$). This resulted from an increase in Ti by 1.1±1.7 sec ($p=0.04$) and an increase in Te by 3.1±3.7 sec ($p=0.007$). These changes were reversed by local naloxone.

Protocol 2: In a separate set of animals, intravenous remifentanil depressed respiratory rate from 26±11 bpm to 14±7 bpm ($p<0.001$, $n=11$). This was due to an increase in Te by 2.6±2.3 sec ($p<0.001$) while Ti was unchanged ($p=0.50$). Local naloxone injection into the "tachypneic area" partially reversed this effect by 6±6 bpm ($p=0.02$), which was due to a decrease in Te by 2.2±2.4 sec ($p=0.002$). The data for Ti and Te were fitted into a hypothetical model assessing the medullary and pontine contributions to respiratory phase timing as far as they are affected by systemic opioids. The model predicts that Te duration strongly depends on pontine inputs while Ti duration receives comparable inputs from pons and medulla.

Conclusion: The results suggest that a circumscribed subarea of the PBN is strongly involved in opioid-induced respiratory rate depression and that this role is likely due to its prominent contribution to expiratory phase duration.

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Poster Sessions

Basic Neuro Sci 50 (53)

The Role of Increased Branched-Chain Amino Acids in the Blood on Brain Extracellular Fluid Glutamate Concentrations in Naive Rats

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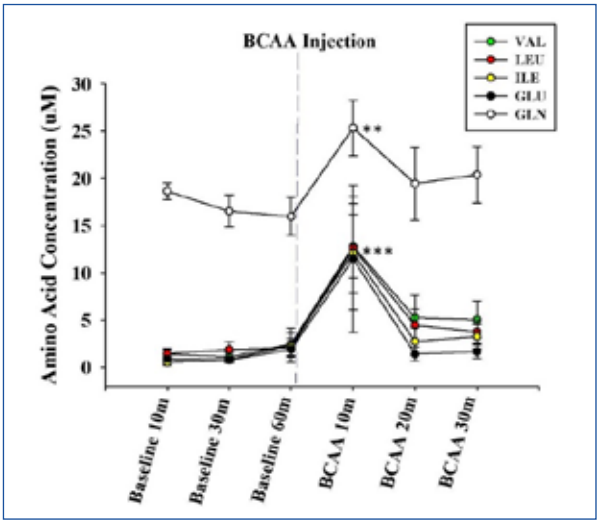
Introduction and General Purpose of the Study: The branched chain amino acids (BCAAs) valine, leucine, and isoleucine are essential amino acids that are diet-derived. Recent studies have demonstrated that BCAAs may play an important role in neurotransmission. Although BCAAs are known to play an important role in several metabolic pathways throughout the body, the role of BCAAs on brain metabolism and seizure regulation is poorly understood. Preliminary in-vivo brain microdialysis studies from our laboratory have shown that in humans with mesial temporal lobe epilepsy (MTLE), basal concentrations of glutamate and BCAAs are elevated in the extracellular fluid (ECF) of the epileptogenic hippocampus. Just prior to seizure onset glutamate and all BCAAs increase in the ECF and remain elevated for several hours after termination of the seizure. It is unknown why BCAAs are elevated in the hippocampal ECF of patients with MTLE, and whether they contribute to the observed increased glutamate concentrations. The objective of this study was to determine whether increased concentrations of blood BCAAs leads to increased concentrations of BCAAs, glutamate, and glutamine in the ECF of the brain in naive rats.



Methods: In four rats, a microdialysis guide cannula was surgically implanted in the left dentate gyrus, and a central venous catheter was surgically inserted in the right internal jugular vein. A microdialysis probe was inserted under brief isoflurane anesthesia, and flow was established through the probe by infusing 2 µL/min of artificial cerebral spinal fluid (aCSF). After baseline dialysate samples were collected for one hour, a 4% isotonic BCAA solution was injected (0.8cc/100g weight) intravenously, followed by a 30-minute intravenous infusion (0.8cc/100g weight). The EZ: FAAST Free Amino Acid analysis kit and ultra-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS) was used for quantification of BCAAs, glutamate, and glutamine. Statistical comparisons between baseline and post-injection amino acids were done with Repeated Measures ANOVA.

Results and Major Findings: The results are shown in Figure 1. Compared with average baseline brain ECF concentrations, IV injection of BCAAs resulted in a transient increase in the brain ECF concentrations of valine (1.65 ± 0.78 to 12.8 ± 3.3, $p<0.0005$), leucine (1.77 ± 0.73 to 12.60 ± 4.70, $p<0.0005$), and isoleucine (1.26 ± 1.05 to 12.10 ± 5.99, $p<0.005$). There were no significant differences between the 3 BCAAs after injection. IV injection of BCAAs also resulted in a transient increase in the brain ECF concentrations of glutamate (1.19 ± 0.45 to 11.5 ± 7.8, $p<0.0005$) and glutamine (17.05 ± 1.56 to 25.34 ± 2.95, $p<0.005$).

Conclusion: This study demonstrated that increases in blood BCAA concentrations results in increased brain concentrations of BCAAs, glutamate, and glutamine in naïve rats. This study gives important insight into how changes in blood chemistry impact brain concentrations of glutamate, which may subsequently result in secondary brain damage. Although the role of BCAAs in seizure formation is unknown, these results suggest that BCAAs may play an important role in neurochemical modulation.

Poster Sessions

Basic Neuro Sci 51 (77)
O-GlcNac Glycosylation in Schwann Cells for Myelin Maintenance and Axon Survival

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Peripheral neuropathies (PN) are a heterogeneous group of disorders characterized by peripheral nerve abnormalities and the most common hereditary disease as a group. With an incidence of up to 8% in elderly populations, they are a cause of substantial morbidity and a significant economic and societal burden. The etiology for these diseases is varied, ranging from genetic mutations to vascular and metabolic irregularities. Schwann cells (SCs), the main glial cells in the peripheral nervous system (PNS), are intimately associated with all peripheral nerve axons – either myelinating individual axons or forming Remak bundles with multiple axons. Such tight interaction between schwann cells and axons is essential for the function and survival of the peripheral nerves (Corfas et al., 2004).

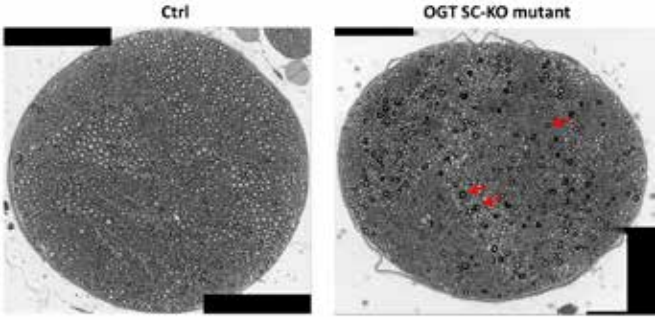

Figure 1. Tomaculous neuropathy in OGT SC-KO mice. The representative image of semi-thin section of sciatic nerve indicates numerous thick myelinated fibers (tomacula, red arrows) in 3month-old OGT SC-KO mice.

Growing number of studies have indicated a metabolic interaction between schwann cells and axons in the PNS, and its implication in the pathogenesis of peripheral neuropathies. We hypothesize the O-GlcNAc transferase (OGT) in schwann cells as a potential player for such metabolic interaction. OGT mediates O-linked glycosylation on serine/threonine residues on proteins with N-Acetylglucosamine (hereafter called O-GlcNacylation) (Hart et al., 2011). O-GlcNacylation is a unique form of post-translational modification in many ways. Most importantly, O-GlcNacylation is a faithful readout of the cellular glucose level as the glucose feeds the synthesis of the O-GlcNacylation substrate UDP-O-GlcNac through the hexosamine biosynthetic pathway. In addition, nuclear and cytosolic O-GlcNacylation is known to interact with other forms of intracellular post-translational modification. Those characteristics of O-GlcNacylation are in line with the proposed roles of OGT from other studies in metabolic homeostasis and signaling and the implications of OGT in human disorders including diabetics, tumorigenesis, and neurodegenerative diseases. However, the role of OGT and O-GlcNacylation in schwann cells and a potential implication in peripheral neuropathies have yet to be explored.

To study the role of O-GlcNacylation in schwann cells, therefore, we generated mice lacking OGT specifically in schwann cells using the Cre/loxP recombination system (hence called OGT SC-KO mice). Importantly, we found the phenotypes of the OGT SC-KO mice recapitulating many features of peripheral neuropathies. First, the OGT SC-KO mice performed poorly on various behaviors, motor and sensory tests, and display hindlimb clasping, a characteristic phenotype of peripheral neuropathy. Sensory and motor nerve conductions in OGT SC-KO mice were slower and diminished compared to the control mice, implicating abnormal nerve physiology originated from defects in both neurons/axons and schwann cells. Morphometric analysis on sciatic nerve sections indicated abnormally hypermyelinated nerves (tomaculous neuropathy) and accompanying progressive loss of large diameter axons in OGT SC-KO mice (see figure 1).

In conclusion, in this study we found post-translational O-GlcNac glycosylation by O-GlcNac transferase (OGT) in schwann cell is critical in maintaining myelination and axonal survival. Therefore, this study supports the idea of a metabolic interaction between schwann cell and axon in the peripheral nervous system, and provide with a basis of future therapeutic targeting on schwann cell metabolism in treating peripheral neuropathies.

Basic Neuro Sci 52 (79)

Transcriptional Profiling of K+ Channel Expression Patterns (in Mice) Identifies Kcnh8 as Potential Key Regulator of Circadian Rhythms

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Circadian rhythms, responsible for the coordination of many physiologic functions, are determined by a master clock, the neurons of the suprachiasmatic nucleus (SCN) [1]. To keep time, SCN neurons utilize a transcription/translation feedback loop (molecular oscillator) that oscillates with a near 24-hour period. The transcription factors and much of the related molecular machinery that constitute the molecular oscillator have been identified and mutations leading to sleep and circadian disturbance have been discovered [2]. Despite the strides made, a fundamental feature of SCN neurons, the rhythmic changes in electrical activity, remains poorly understood. SCN neurons depolarize and fire rhythmically during the day, then hyperpolarize and fire infrequently at night [3]. The spontaneous daily variations in the excitability of SCN neurons requires changes in resting K+ currents, although the channels responsible are unknown [4]. Circadian changes in the expression levels of several K+ channel genes have been described but cannot account for changes in the excitability of SCN neurons. This study sought to identify candidate K+ channels that could underlie the circadian changes in SCN neuron excitability.

Multiple functionally and molecularly distinct types of K+ channels have been identified including: voltage-gated (Kv), Ca2+-activated (KCa), two-pore domain (K2P) channels and others, several of which could underlie the observed daily changes in the excitability of SCN neurons [5]. Examination of ion channel gene expression patterns in the SCN is technically challenging due to the low transcript number and the small size of the SCN (~10,000 neurons in each of the bilateral nuclei). To overcome these challenges, the temporal expression patterns of 90 ion channel-related genes were examined simultaneously using Taqman PCR probes configured in a low density array (TLDA). Target genes were selected based on known SCN (or other neuron) expression and the potential of a channel to affect daily oscillations in membrane potential and firing rate [6]. SCN from 12 week old mice (6 animals per time point) were collected from animals entrained to a 12 hour light: 12 hour dark cycle and then held in constant darkness for 48-72 hours prior to sacrifice. Animals were sacrificed, the brains removed and 300μm coronal sections were cut. Reverse transcription and use of the TLDAs were done according to the manufacturer's (Applied Biosystems) directions. Results were analyzed using the ΔΔCT method. Rhythmic (Per2) and non-rhythmic (HPRT, PolR1, and GADH) genes were used as controls.

This study delineated the temporal circadian expression for many K+ channel genes. Importantly, Kcnh8 (Kv21.1), was among the very few genes examined that showed a clear circadian temporal expression pattern: indeed, the pattern observed would be expected to result in daily changes in the resting membrane potentials and the firing rates of SCN neurons. Kcnh8 (Kv12.1) message expression level doubles during the relative night. Kv12.1 is a voltage-gated K+ channel (Kv) subunit that produces K+ channels that are open and generates a hyperpolarizing current at subthreshold potentials, a current that would lower membrane potential and suppress firing [7].

In summary, Kcnh8 (Kv12.1) has the correct temporal expression profile and Kv12.1 mediated currents have the key properties that could generate the rhythmic changes in SCN neuron excitability identifying Kv12.1 as a potential critical component of the machinery for generating circadian rhythms.

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Poster Sessions

Basic Neuro Sci 53 (82)

A Predictable Sequence Of Brain Stem Network Reactivation in Rodents Anesthetized with Either Propofol or Isoflurane

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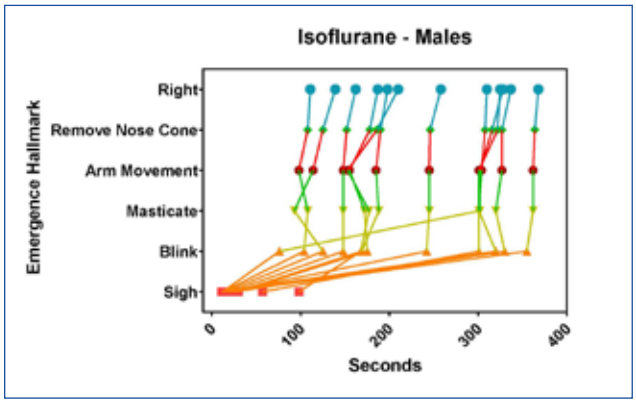
Introduction: Arousal networks in the brain stem are not only critical to maintaining vigilance while awake, but also important in modulating emergence from general anesthesia [1]. Most brain stem nuclei are phylogenetically preserved in form and function. For example, the reticular formation (medulla) contains the pre-Botzinger complex which is involved in regulating breathing in both humans and rodents [2]. While, the pons contains the nuclei of cranial nerves (CN) 3, 4, 6, and 7 which mediate blinking as well as the trigeminal nucleus (CN 5) which mediates facial sensation and chewing. In this study, the authors explored the variability in the re-animation sequence through the use of an animal model of general anesthesia without surgery.



Methods: Using in-bred adult male rats (Sprague-Dawley) anesthetized with either inhaled isoflurane (60 minutes) or injected propofol (200 mg/kg, intraperitoneal, i.p.), the authors measured the latency for specific behavioral reflexes to be observed after the cessation of anesthetic agent administration. To control for any potential painful or stressful effects of the i.p. injection, isoflurane animals were administered an equivalent volume of intralipid before inhaled induction. After loss of righting reflex, animals in each group were placed supine on a heated pad and monitored for heart rate, pulse oximetry, respiratory rate, and temperature. Each anesthetic regimen involved administration of > 90% oxygen via nose cone. The latency to recover characteristic behavioral reflexes was measured. End emergence was determined by a sustained recovery of righting reflex (unable to be re-positioned supine). Although the respiratory rate was initially slower for a portion of the propofol anesthetic, pilot data revealed no differences in blood pressure, PaCO2, or arterial pH between the two anesthetic regimens (measured via intraccardiac puncture) suggesting equivalent minute ventilations among the two groups.

Results: Despite a larger variability in the time required to reach observed behavioral endpoints after i.p. propofol administration, the sequence of reanimation was generally conserved across the two different anesthetic regimens. Most animals regained key reflexes in a caudal to rostral progression before righting. The propofol group, progressed (in order) from forelimb movement, sighing, blinking, mastication, rejection of nose cone, and finally righting. Although the isoflurane emergence was faster, the progression was in nearly the same sequence with the exception that forelimb movement occurred after return of the pontine reflexes. We attribute the difference in forelimb movement to the known effects of volatile anesthetics on the spinal cord [3]. The intra-subject variability in sequence varied little, e.g., the first animal to sigh was typically the first animal to blink (and eventually right themselves).

Discussion: As compared to general anesthesia with isoflurane, injection of propofol demonstrates an expected susceptibility to myoclonus, longer emergence, and more variability in the latency of measured neurologic reflexes in our model. However, despite obvious pharmacokinetic and pharmacodynamic differences between the two anesthetics, the re-activation of brain stem nuclei signaling imminent emergence appears in a strikingly similar and predictable sequence. We take these results to mean that, emergence from general anesthesia occurs in an orderly and progressive fashion in a roughly caudal to rostral sequence [4] on the order of seconds to minutes. Careful observation of the neurologic hallmarks of this re-animation sequence can alert the anesthesiologist to potential deviations of this trajectory which may herald non-preferred recovery characteristics.

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Poster Sessions

Organ Inj 80 (12)

Hyperoxic Resuscitation Improves Survival but Worsens Neurologic Outcome in a Rat Polytrauma Model of Traumatic Brain Injury Plus Hemorrhagic Shock

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Introduction: Many victims of traumatic brain injury (TBI) experience additional injuries, including those resulting in hemorrhagic shock (HS). Hemorrhage, with attendant hypotension and reduced delivery of oxygen to the brain, places the TBI victim at significant risk for exacerbation of the primary brain injury. Thus, use of inspired or ventilatory oxygen might overcome reduced oxygen delivery, improve neurologic outcome, and reduce injury to other vital organs. However, both preclinical and clinical studies suggest that hyperoxic resuscitation following TBI and ischemic brain injury can worsen outcome (1,2), based on increased brain inflammation (3), oxidative modification of proteins (4), and impaired aerobic cerebral energy metabolism (5). Nevertheless, one study using a mouse polytrauma model indicated a slight improvement in hippocampal neuronal survival following hyperoxic compared to normoxic resuscitation (6). This study tested the hypothesis that inspiration of 100% oxygen during resuscitation following TBI and HS improves survival, reduces brain lesion volume, and improves neurologic outcome compared to what occurs in the absence of supplemental oxygen.

Methods: The polytrauma model used adult male Sprague-Dawley rats subjected to controlled cortical impact (CCI)-induced TBI followed by 30 min of shock (mean arterial pressure = 38-40 mm Hg) induced by blood withdrawal. The shock phase was followed by a one hr "pre-hospital" Hextend fluid resuscitation phase and then a one hr "hospital phase" when shed blood was re-infused. Rats were randomized on the day of surgery to 3 groups with 10 per group: sham, polytrauma normoxic, and polytrauma hyperoxic. Normoxic animals inspired room air and hyperoxic animals inspired 100% oxygen during both resuscitation phases. Neurobehavioral tests were conducted weekly until the rats were perfused with fixative at 30 days post injury. Brain sections were stained with Fluoro Jade B and used for quantification of total cortical lesion volumes.

Results: Survival was significantly greater ($p<0.05$) following hyperoxic (83%) compared to normoxic resuscitation (56%). All mortalities were associated with lung injury and occurred within the first 4 days. Composite neuroscores obtained at 2-4 weeks following normoxic resuscitation were not different than those of shams, whereas those of hyperoxic animals were significantly lower than those of shams ($p<0.05$). Balance beam foot faults measured at 2 weeks post-injury were much greater following hyperoxic resuscitation compared to normoxic resuscitation and to those of shams ($p<0.01$). There was no significant difference in cortical lesion volumes between the normoxic and hyperoxic polytrauma groups.

Conclusion: The survival of rats following CCI plus HS was greater following hyperoxic resuscitation. In contrast, neurologic outcomes were better following normoxic resuscitation. While hyperoxia during resuscitation appears beneficial for shock sensitive organs, e.g., the lung, it appears detrimental to the brain following polytrauma, possibly due to synergistic oxidative stress.

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Poster Sessions

Organ Inj 81 (37)

Even Protective Ventilation Can Cause Acute Lung Injury in a Mouse Model of Chronic Obstructive Pulmonary Disease

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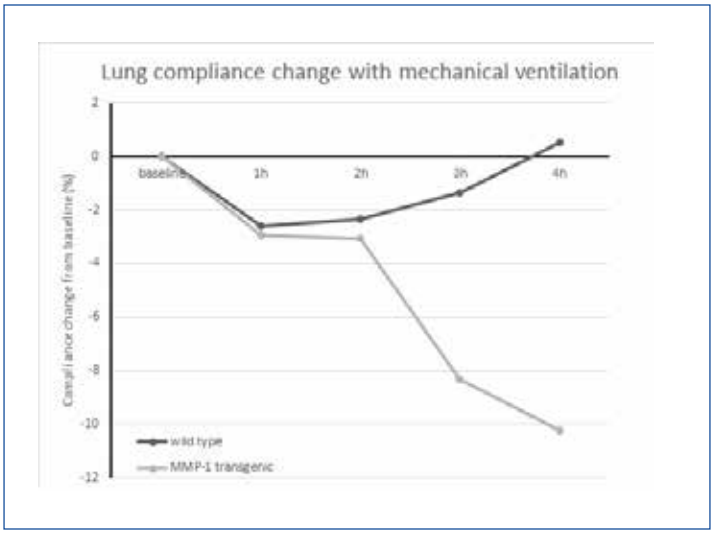
Rationale: Since recognized in the ARDSNet trial, lung protective ventilation using low tidal volumes has become a mainstay of ventilator management in critically ill patients. This protective ventilation, experimentally and in practice, has been shown to significantly reduce the incidence of ventilator associated lung injury (VALI) and improve outcomes in patients with normal or acutely injured lungs. Less well studied is the appropriate ventilatory strategy for patients suffering from chronic lung disease, especially chronic obstructive pulmonary disease (COPD). Amongst patients admitted to the ICU for an acute exacerbation of COPD, 25% are likely to die during that hospitalization. Invasive ventilation has been shown to be a risk factor for death in these patients suggesting that some degree of VALI may be occurring and worsening outcomes. Investigations in to the occurrence and nature of VALI in lungs already damaged from COPD could yield new ventilation protocols for patients with COPD that could lead to overall reductions in morbidity and mortality from the disease.



Methods: Mice transgenic for lung-specific expression of human matrix metalloproteinase-1 (MMP-1, known to develop emphysematous changes similar to those in humans with emphysema) were compared with wild type animals. Animals were anesthetized and tracheotomized and either immediately sacrificed or exposed to 4 hours low tidal volume (7ml/kg) ventilation and then sacrificed. For ventilated mice, compliance and resistance measurements were completed hourly. Following sacrifice, some animals were subjected to bronchoalveolar lavage. The pulmonary circulation was cleared of red blood cells, and lungs were preserved either for molecular or histologic study.

Results: Assessing acute lung injury via both in vivo and post-mortem methods, "protective" ventilation was found to cause significant lung injury in MMP-1 transgenic mice. Over the course of 4 hours of ventilation, pulmonary compliance gradually decreased, such that after 4 hours of ventilation, lung compliance decreased by more than 10% (Fig.). Age-matched controls show essentially no change in compliance after 4 hours of ventilation. Ventilated MMP-1 transgenic mice also exhibited a marked increase in brochoalveolar lavage protein over non-ventilated mutants (74%) than did age-matched ventilated controls over non-ventilated controls (43%), reflecting greater lung injury in the transgenic animals.

Conclusion: Acute lung injury has been found to occur employing what is thought to be "protective" ventilation even after a short amount of time in a mouse model of COPD. With further study, these results may suggest the need to reevaluate ventilation protocols in patients with COPD or other chronic lung diseases.

Poster Sessions

Clin Int OC 70 (9)
Nitrous Oxide for Treatment-Resistant Major Depression: a Proof-of-Concept Trial

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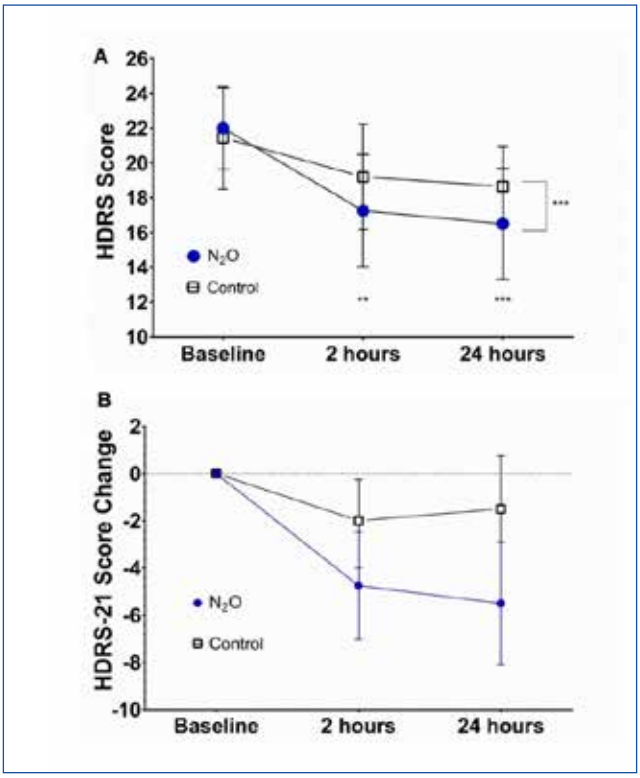
Background: Recently, NMDA receptor antagonists, such as ketamine, have been shown to provide rapid antidepressant effects in patients with treatment-resistant depression (TRD). Because nitrous oxide, an inhalational general anesthetic, is also an NMDA receptor antagonist, we hypothesized that nitrous oxide may be a rapidly acting treatment for TRD.

Methods: In this proof-of-principle, blinded, randomized placebo-controlled crossover trial 20 TRD patients received a 1-hour inhalation of up to 50% nitrous oxide/50% oxygen or 50% nitrogen/50% oxygen (placebo control) in random order. Primary endpoint was the change on the 21-point Hamilton Depression Rating Scale (HRDS-21) 24 hours after treatment.



Results: Mean duration of nitrous oxide treatment was 55.6 ± 2.5 (SD) minutes at a median inspiratory nitrous oxide concentration of 44% (37 – 45%, median, IQR). In two patients nitrous oxide treatment was briefly interrupted and in three discontinued. Depressive symptoms improved significantly at 2 hours and 24 hours after receiving nitrous oxide compared to placebo (mean difference in HDRS-21 score at 2 hours: -4.8 points, 95% CI -1.8 to – 7.8 points, p= 0.002; at 24 hours: -5.5 points, 95% CI -2.5 to -8.5 points, p<0.001; comparison between nitrous oxide and placebo: p<0.001). Four patients (20%) had treatment response (reduction ≥50% on HRDS) and three patients (15%) a full remission (HRDS ≤ 7 points) after nitrous oxide compared to one patient (5%) and none after placebo (odds ratio [OR] for response 4.0, 95% CI 0.45 – 35.79; OR for remission 3.0, 95% CI 0.31 – 28.8, respectively. No serious adverse events occurred and all adverse events were brief and of mild to moderate severity.

Conclusion: This proof-of-concept trial demonstrated that nitrous oxide has rapid and marked antidepressant effects in patients with treatment-resistant depression.

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Poster Sessions

Clin Int OC 71 (13)

Peripheral Venous Waveform Analysis for Detecting Acute Intraoperative Blood Loss

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Introduction and General Purpose of the Study: Subclinical and ongoing blood loss is difficult to detect. Standard vital sign monitoring, including heart rate and blood pressure, fails to detect hemorrhage prior to end-organ damage.1Arterial-based methods such as pulse pressure variation, stroke volume variation, and plethysmographic wave respiratory variation can only predict fluid responsiveness but do not directly measure volume status.2Recent data has supported that peripheral venous analysis can quantify simulated hypovolemia in healthy volunteers undergoing lower body negative pressure.3 We therefore hypothesize that peripheral intravenous waveform analysis (PIVA) via a standard intravenous catheter can be used to detect perioperative hemorrhage.

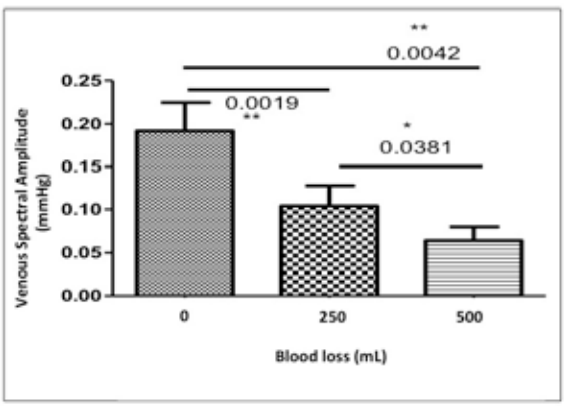

Figure 1. Peripheral venous waveform analysis (PIVA) detects subclinical blood loss in patients undergoing coronary artery bypass surgery (n=17).

Methods: In compliance with our Institutional Review Board, we enrolled 17 patients with normal ventricular function presenting for elective coronary artery bypass surgery. Following induction of general anesthesia, central venous, pulmonary artery, and intra-arterial catheters were inserted as per standard anesthesia protocol. A standard pressure transducer was attached directly to a peripheral intravenous catheter and connected to LabChart (ADINstruments, Colorado) for peripheral venous waveform recordings and Fourier transform analysis. Prior to incision, up to 10 mL/kg of autologous blood was collected and stored over a 10-minute period. Amplitude of the first spectral harmonic of the venous waveform was recorded at baseline, 250mL, and 500mL of blood loss.

Results and Major Findings: We found significant and quantifiable correlation between subclinical (<5% total blood volume) hemorrhage and PIVA (Figure 1). PIVA detected hemorrhage earlier than standard vital signs, pulmonary artery pressure, and central venous pressure. Further, PIVA was independent of heart-lung interactions during mechanical ventilation, a requirement for pulse pressure and stroke volume variation to detect hypovolemia (data not shown).

Conclusion: This pilot study shows that PIVA appears to be superior to standard and invasive monitors for detecting subclinical blood loss. In addition, PIVA analysis does not depend upon effects of mechanical ventilation on heart-lung interactions, filling a critical void for monitoring spontaneously breathing patients. We are continuing our research to detect hemorrhage in spontaneously breathing patients in order to prove this theory. Extensions of PIVA applications include pediatrics, obstetrics, military, civilian trauma, global health, and critical care arenas.

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Clin Int OC 72 (14)

Spinal Anesthesia for Lumbar Spine Surgery: Overall Drug Utilization and the Need for Hemodynamic Support

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Introduction and General Purpose: Both general and neuraxial anesthetics have been used for lumbar spine surgery, with general anesthesia being more common. Despite published clinical research dating back to 1959 (1), there have been relatively few articles related to the use of spinal anesthesia for spine surgery. While some authors have found spinal anesthesia to offer some benefits such as shorter anesthesia and operative times,(2,3) others have found that general anesthesia is preferable (4). In our institution we have routinely used spinal anesthetics for certain lumbar spine procedures. Anecdotally we observed that spinal anesthesia (SA) generally worked well, caused less hypotension requiring vasopressor use, and far fewer medications were administered when compared to general anesthesia (GA). We hypothesized that a review of our data would confirm our observations. To test this hypothesis we completed a retrospective, case-control study to compare patients who received SA to those who received GA.

Methods: Patients undergoing 1-2 level lumbar spine procedures including decompression, formaniotomy, or microdiscectomy by a single surgeon during the years 2008 and 2014 were analyzed. The patients were selected for SA or GA after a discussion with the surgical and anesthesia teams as well as the patient. The variables recorded for the study included the patient characteristics of age, sex, BMI, and ASA physical status classification. The characteristics of the anesthetics included vasopressor use and total number of medications administered.

Results: ASA classification was similar between the two groups ($p = 0.35$). SA was used more frequently than GA in older patients than (mean age 66 years vs. 61 years, $p < 0.001$) and females ($p < 0.04$). BMI was not statistically significant in this study ($p = 0.129$). The frequency of vasopressor use was significantly less in the SA group for phenylephrine boluses ($p = 0.004$), phenylephrine infusions ($p = 0.01$) and ephedrine boluses ($p < 0.001$). The number of medications used per case was significantly reduced in the SA group (mean 10.47 vs. 5.73, $p < 0.001$).

Anesthetic Parameters

Variable	Spinal	General	p Value
Ephedrine bolus (%)	21	46	< 0.001
Phenylephrine bolus (%)	28	36	0.004
Phenylephrine infusion (%)	48	61	0.01
Medications (#)	5.7	10.4	<0.001

Conclusion: This study demonstrates the reduced need for vasopressor support when using SA for spine surgery, suggesting a more hemodynamically stable anesthetic. In addition, total drug use was reduced by approximately 50%, thereby reducing the risk for medication error and potential for adverse drug reactions.

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Poster Sessions

Clin Int OC 73 (16)
Myocardial Injury after Electroconvulsive Therapy: A Prospective Cohort Study

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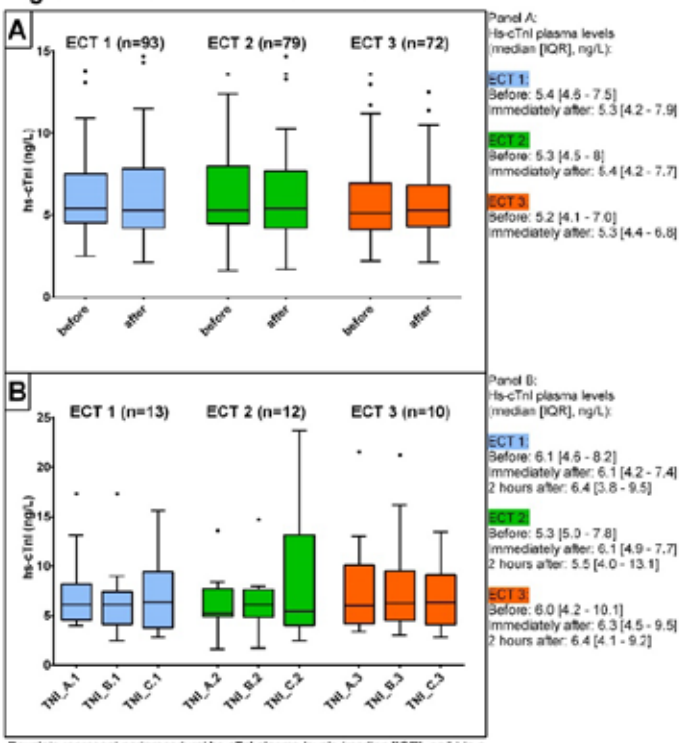
Introduction and General Purpose of the Study: Electroconvulsive therapy (ECT) - an effective treatment for severe psychiatric illness - can lead to cardiovascular adverse events. It is unclear whether ECT is associated with myocardial injury.

Methods: This was a prospective cohort study to determine myocardial injury using high sensitivity cardiac troponin I (hs-cTnI) (Abbott Architect STAT©) before and immediately after ECT in a series of up to 3 treatments. In a subgroup of patients, additional blood samples were obtained 2 hours after ECT. ECG changes and clinical signs of myocardial ischemia were also obtained. Hs-cTnI above the sex-specific 99th percentile of the upper reference limit was defined as abnormal. Myocardial injury was defined as abnormal hs-cTnI novel after ECT. Myocardial infarction was defined as myocardial injury plus ECG changes and/or clinical signs of ischemia.

Figure 1. Hs-cTnI before and after ECT



Boxplots represent periprocedural hs-cTnI plasma levels (median [IQR], ng/L) in a series of 3 treatments. Panel A shows data of all patients (Friedman's ANOVA: n=72; P=0.4). Panel B shows data of the subgroup with an additional blood sample obtained 2 hours after ECT (Friedman's ANOVA: n=10; P=0.6).
ECT = electroconvulsive therapy, hs-cTnI = high sensitivity cardiac troponin I

Results and Major Findings: The analysis included 100 adults. Hs-cTnI was abnormal before ECT in 6 patients (6%) and after ECT in 12 patients (12%). The composite incidence of myocardial injury and/or infarction after ECT was 6% (n=6 of 94) comprising an incidence of 4% of myocardial injury (n=4 of 94) and an incidence of 2% of myocardial infarction (n= 2 of 94). The median [IQR] of hs-cTnI did neither change immediately nor 2 hours after ECT (Figure 1).

Conclusion: ECT led to myocardial injury in 4% of patients and to myocardial infarction in 2% of patients.

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Poster Sessions

Clin Int OC 74 (25)
Choice of Intravenous Crystalloid Therapy and Major In-Hospital Outcomes among Adult Patients Undergoing Cardiac Surgery

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Introduction and General Purpose of the Study: Adults undergoing Cardiac Surgery (CS) receive intravenous (IV) crystalloids and/or colloids routinely - both during and after the procedure. Several studies have compared these two fluid types. 1-2 However the safety of balanced versus non-balanced crystalloid solutions has not been well studied. Important clinical and health economic outcomes may differ, as balanced crystalloids may be associated with a lower incidence of hyperchloremic metabolic acidosis. Despite this, many clinicians choose isotonic saline as the first-line IV crystalloid for resuscitation. We tested the hypothesis that major in-hospital outcomes differed among patients that received balanced versus non-balanced crystalloids during and up to 72 hours after the index CS procedure.

Methods: After approval from the Duke University Medical Center IRB, we identified a large patient cohort using the de-identified electronic medical record repository (Healthfacts®) from Cerner Inc., Kansas City, MO. Patients were included if they underwent one of several selected CS procedures; received at least 500mL of crystalloid within 1 day after surgery; were treated at a hospital performing at least 100 cardiac surgical procedures per year (on average); and survived for at least one day after surgery between January 2009 and March 2013. Patients with a length-of-stay (LOS)>30 days, undergoing multiple CS procedures on different days, receiving >1L of any fluid on the day prior to surgery, or those treated at hospitals performing <=100 procedures per year were excluded. Patients were classified either as recipients of balanced solutions (Lactated Ringer's solution, Plasmalyte®, Normosol® etc.) or not (mainly isotonic saline 0.9%). Other IV fluids were categorized and adjusted for in analyses (including hydroxyethyl starch, albumin, hypertonic saline, 5% dextrose with saline, etc.). The primary outcome was mortality at any time within 90-days following surgery (either during the index hospitalization or upon readmission). Additional major adverse outcomes studied included: renal events (new dialysis, an elevation in creatinine); cardiac or vascular events (re-vascularization, MI, stroke, heart failure, arrhythmias); respiratory failure; infectious, gastrointestinal, or neurologic complications.

Results and Major Findings: Univariate analyses of patient and hospital demographics, comorbidities, acute physiology score, types of CS, and fluid volumes were performed. In multivariate propensity-score adjusted analyses accounting for demographics, admission source, payer, census region, hospital characteristics, Elixhauser comorbidities during hospitalization, and the acute physiology score, we compared 5641 patients treated with 0.9% saline matched 1:1 with 5641 patients treated with balanced crystalloids. Almost all measurable characteristics were comparable and variables that were not (despite greedy matching): acute physiology score, bed size, admission source, payer, census region, and differences in the volumes of fluids were adjusted for in additional logistic regression analyses. Figure 1 shows significant baseline differences in the probability of receipt of balanced versus non-balanced crystalloids. After matching, patient groups were largely comparable. The odds of mortality 90-days following the receipt of balanced crystalloids (rather than 0.9% saline during and after CS) were 0.67 (0.53 – 0.86, 95% CI). Overall improved outcomes were associated with the receipt of balanced rather than non-balanced crystalloids.

Conclusion: In robust propensity-score matched multivariate analyses, the receipt of intravenous balanced crystalloid solutions during and up to 72 hours after Cardiac Surgery was associated with reduced in-hospital mortality, and decreased morbidity (renal and respiratory failure). The use of isotonic saline was significantly more common in larger hospitals (bed size >500), in teaching hospitals, and in the Northeast, while balanced crystalloids were used more commonly in the

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South and Midwest. Observations are consistent with several recent reports3-6 and may have broad public health implications.

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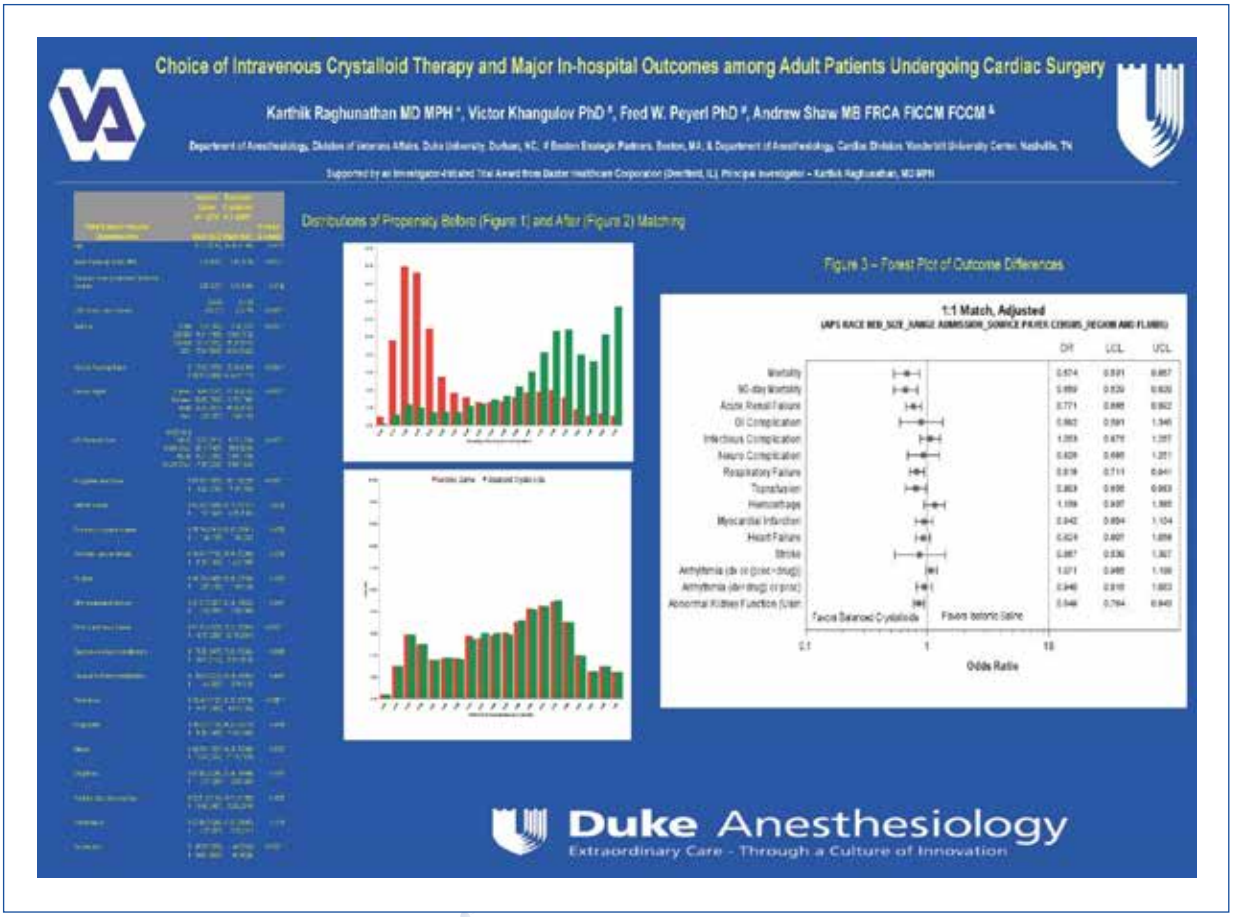

Poster Sessions

Clin Int OC 75 (31)
Alarm Limits for Intraoperative Drug Infusions: A Report from the Multicenter Perioperative Outcomes Group (MPOG)

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Introduction: Continuous infusions are commonly used by anesthesiology providers during surgical procedures. Most infusion pumps now have libraries of drug-specific alarm settings. These alarm libraries are generally created through a subjective process involving user feedback and by querying the pumps for events that bypass the alarm settings.1,2 In general, alarm settings should be predictable for the rate at which the alarm is triggered and meaningful for the situation in which they are used; if not, through the process of alarm fatigue, alarms are ignored or no longer noticed.3 In this paper we explore calculating the 90th, 95th, or other quantile level of infusion rate used in the operating room for use as alarm settings, thus creating predictable and selectable rates of alarming.

Methods: We extracted infusion rate data for six major hospitals using intraoperative records provided by MPOG (Multicenter Perioperative Outcomes Group)4 for adult surgery. We selected seven common infusions for study: three anesthetics--propofol, remifentanil, and dexmedetomidine, and 4 vasoactive medications--norepinephrine, phenylephrine, esmolol and nitroglycerin. Each data entry for an infusion during a procedure was included in the data set. We created an overall usage histogram for each infusion that weighted the contribution from each institution equally. We calculated the median, 90th, 95th and other quantile levels for each infusion.

Results: The median infusion rates for the anesthetic agents propofol, remifentanil, and dexmedetomidine were 75 mcg/kg/min, 0.11 mcg/kg/min, and .5 mcg/kg/h, respectively. The median rates for the vasoactive medications norepinephrine, phenylephrine, esmolol, and nitroglycerin were 0.05 mcg/kg/min, 30 mcg/min, 50 mcg/kg/min, and 0.3 mcg/kg/min, respectively. Complete results are shown in the accompanying table. As an example, the 80th, 90th, and 95th percentile infusion rates for propofol were 125 mcg/kg/min, 150 mcg/kg/min, and 180 mcg/kg/min, respectively. Upper limit alarm settings for propofol would be selected from one of its upper-end quantiles for infusion rate.

Table Median and other Percentile Limits for Common Anesthesia Infusions

Infusion	percentiles					
Anesthetics	median	80th	85th	90th	95th	99th
Propofol (mcg/kg/min)	75	125	150	150	180	250
Remifentanil (mcg/kg/min)	0.11	0.25	0.25	0.35	0.5	0.75
Dexmedetomidine (mcg/kg/h)	0.5	0.7	0.8	1.0	1.0	2.0
Vasoactive Agents						
Norepinephrine (mcg/kg/min)	.05	.11	0.13	0.18	0.25	0.5
Phenylephrine (mcg/min)	30	50	60	70	95	180
Esmolol (mcg/kg/min)	50	100	150	175	200	300
Nitroglycerin (mcg/kg/min)	0.3	0.8	1.0	1.2	2.9	>3.0

Conclusion: We have demonstrated a method for creating alarm settings for intraoperative infusions using usage profiles from pooled electronic medical record data. The advantages of this method include being empirically based on actual usage data and the transparency of the simple statistical methods. Alarm settings based on quantile usage rates will be triggered at a predictable rate; i.e., the 95th quantile will be exceeded on average during one in twenty infusion rate entries. Alarm settings with selectable and predictable frequencies for triggering may prove useful in minimizing alarm fatigue.

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Poster Sessions

Clin Int OC 76 (33)
Identifying Patients at Risk for Escalation of Care after Rapid Response Activation

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Introduction: Rapid Response Teams (RRTs) have been effective in reducing the number of cardiopulmonary arrests in adult hospitals by up to 50% yet have been ineffective in decreasing overall hospital mortality (1,2). One hypothesis to explain these disparate findings is that RRT activation triggers are non-specific and may be occurring too late, especially in the subset of patients who require escalation of care to a monitored unit or the ICU. Our own institutional data, for example, shows that patients who require an escalation of care after a rapid response activation have four times higher mortality than the overall hospital mortality. We therefore sought to determine patient characteristics that determine the need for escalation of care following an RRT activation, to help earlier detection of these patients.

Methods: In this retrospective study, we reviewed the Vanderbilt University Hospital RRT database that has detailed prospectively collected data with respect to RRT activations. Our dependent (outcome) variable of interest was escalation of level of care, defined as transfer of patients to the ICU or a telemetry unit from the floor, or to the ICU from a telemetry unit. Our independent predictor variables of interest were patient demographic information (age and gender), admission service (medical vs. surgical), RRT trigger (agitation/delirium, blood pressure change, heart rate change, oxygenation change, respiratory rate change, labored breathing or general concern), RRT activator (patient/family/friend/nurse/physician or other employee), RRT responding team (Surgical ICU, Medical ICU, Cardiovascular ICU or Neurological ICU) and number of RRT activations. We used multivariable logistic regression to identify risk factors for level-of-care escalation.

Table: Independent Risk Factors Associated with Transfer to Higher Level of Care

	Odds Ratio	95% CI	p value
Gender	0.86	0.70-1.06	0.165
Age	1.00	0.99-1.00	0.731
Service (surgery vs. medicine)	1.76	1.41-2.21	<0.001
Caller (ref =family/friend/patient)			
RN	3.38	0.93-12.19	0.063
MD	16.68	3.75-65.54	<0.001
Rapid Response Trigger			
Delirium	2.15	0.79-5.87	0.133
Change in blood pressure	1.08	0.60-1.92	0.789
Change in heart rate	1.20	0.68-2.13	0.527
Change in oxygenation status	2.22	1.26-3.90	0.005
Increased respiratory rate	1.48	0.69-3.15	0.308
Chest pain	0.55	0.28-1.11	0.097
Change in level of consciousness	1.34	0.74-2.40	0.321
General concern about patient	0.63	0.32-1.22	0.176
Hemorrhage	1.33	0.56-3.17	0.51
Labored breathing	3.72	1.90-7.25	<0.001

Results: We assessed data on a total of 2,193 RRT activations between 2009 and 2014. The median age of our patients was 61 years, 49% were males, 68% were on the medical service, 93% were activated by the bedside nurse, and in 86% of cases it was the first RRT call. Major triggers for the RRT calls were changes in oxygenation (21%), heart rate (18%), blood pressure (17%) or mental status (15%). Forty percent (879/2193) of the RRT activations led to care escalation. In the multivariate analysis, factors associated with an escalation of care included change in oxygenation [Odds Ratio (OR) 2.22, 95% Confidence Interval (CI) 1.26-3.90, p=0.005], labored breathing (OR 3.72, CI 1.90–7.25, p<0.001), being on a surgical service (OR1.76, CI 1.41–2.21, p<0.001) and having a RRT activated by an MD (OR 16.68, CI 3.75-65.54, p<0.001). See Table 1.

Conclusion: Analysis of our single institution RRT experience revealed that surgical patients, and respiratory abnormalities as triggers for RRT activation, were associated with care escalation to the ICU. This information will allow us to identify patients at risk for escalation of care and develop more sensitive triggers to identify these patients earlier, prior to the need for care escalation.

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Poster Sessions

Clin Int OC 79 (86)

The Effect of High-Dose Cholecalciferol Supplementation on Perioperative Vitamin D Status in Colorectal Surgery Patients: A Randomized, Placebo-Controlled, Pilot Trial

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Introduction: Low vitamin D status is associated with undesirable perioperative outcomes such as healthcare-associated infections [1], cardiovascular events [2], and in-hospital mortality [2,3]. Since very little is known about strategies to optimize perioperative vitamin D status [4], our goal was to conduct a randomized, placebo-controlled trial to determine the effect of high-dose cholecalciferol (vitamin D3) supplementation on perioperative vitamin D status in patients scheduled for elective colorectal surgery.

Methods: The protocol was registered on ClinicalTrials.gov (NCT01689779). We planned to recruit a total of 80 patients with an interim analysis once 60 patients completed the study. Patients scheduled for elective colorectal surgery received either a single oral dose of cholecalciferol (100,000 IU) or matched placebo, 5-7 days before surgery. Blood samples were assessed at baseline, on the day of surgery (DOS), on postoperative day (POD) 1, and during follow-up on POD 12-14 (POSTOP) for: 1) 25-hydroxyvitamin D (25OHD); 2) albumin and vitamin D binding protein to calculate bioavailable 25OHD (b25OHD); and 3) high-sensitivity C-reactive protein (hsCRP). T-tests were used to compare mean 25OHD, b25OHD, and hsCRP levels between the placebo and cholecalciferol groups at each time point. % change in biomarkers relative to baseline on DOS, POD1, and POSTOP were compared between groups using two-way repeated-measures ANOVA tests.

Results: Demographic and clinical information related to the placebo (n=32) and cholecalciferol (n=28) groups at interim analysis is shown in Table 1. Both 25OHD and b25OHD were similar between groups at baseline, while only b25OHD was similar between groups on POD1. 25OHD and b25OHD levels were different between groups at all other time points. hsCRP levels did not differ between groups at any time point. Repeated-measures ANOVA testing demonstrated a difference in the % change in 25OHD and b25OHD levels between groups (F=16.7; p=0.001 and F=7.7; p=0.007, respectively) and over time (F=66.5; p<0.001 and F=3.2; p=0.04, respectively). % change in hsCRP levels was not different between groups (F=0.01, p=0.9) but was different over time (F=15, p<0.001). None of the patients experienced adverse effects related to cholecalciferol supplementation. The trial was closed following the interim analysis due to the significant improvement in vitamin D status in the cholecalciferol group compared to the placebo group. Further enrollment was not expected to materially change these results.

Table 1: Baseline characteristics of the study cohort (n=60)

	Placebo N=32	Cholecalciferol N=28	P-value
Age (years)	61 ± 13	56 ± 13	0.14
Sex (%)			
Female	63	50	0.04
Male	37	50	
BMI (kg/m^2)	29 ± 6	29 ± 6	1.00
ASA physical status	2.3 ± 0.5	2.2 ± 0.4	0.99
Type of surgery (%)			0.77
Laparoscopic-assisted	66	64	
Open abdominal	34	36	
Vitamin D supplementation* (%)			0.48
No	59	54	
Yes	41	46	
25OHD (ng/mL)			
Baseline	29 ± 11	28 ± 12	0.74
DOS	27 ± 11	36 ± 12	0.004
POD1	23 ± 9	31 ± 11	0.004
POSTOP	28 ± 13	39 ± 13	0.002
b25OHD (ng/mL)			
Baseline	3.7 ± 2.5	3.7 ± 2.3	0.99
DOS	3.7 ± 2.2	4.8 ± 2.6	0.08
POD1	3.4 ± 2.2	4.9 ± 2.4	0.01
POSTOP	3.3 ± 2.3	5.1 ± 2.9	0.01
hsCRP (mg/L)			
Baseline	10 ± 26	9 ± 18	0.86
DOS	7 ± 10	7 ± 12	0.99
POD1	103 ± 55	90 ± 57	0.38
POSTOP	41 ± 55	33 ± 42	0.53

BMI = Body mass index; ASA = American Society of Anesthesiologists. 25OHD = 25-hydroxyvitamin D; b25OHD = bioavailable 25-hydroxyvitamin D; hsCRP = high-sensitivity C-reactive protein; DOS = day of surgery; POD1 = postoperative day 1; POSTOP = post-operative day 12-14. (*) Supplementation ranged from 400 IU to 2000 IU. Means were compared using T-tests and proportions were compared using chi-squared testing.

Conclusions: In our cohort of patients, a single dose of 100,000 IU cholecalciferol given 5-7 days before elective colorectal surgery was safe and resulted in significant improvement in perioperative vitamin D status. Future trials are needed to determine whether preoperative vitamin D status optimization can influence important clinical outcomes such as postoperative complications, length of stay, and mortality.

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OC 5 (11)

Surgical Risk Predictions Are Not Meaningfully Improved by Including the Intraoperative Course: An Analysis of the Risk Quantification Index, Present-On-Admission Risk Model, and Surgical Apgar Score

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Introduction and General Purpose of the Study: Estimating surgical risk is critical for perioperative decision making and risk-stratification. Current risk-adjustment measures do not integrate dynamic clinical parameters along with baseline patient characteristics, which may allow a more accurate prediction of surgical risk and appropriate allocation of postoperative clinical resources. Our goal was to determine if the preoperative Risk Quantification Index (1) (RQI) and Present-On-Admission Risk (2) (POARisk) model would be improved by including the intraoperative Surgical Apgar Score (3) (SAS).

Methods: We identified adult, non-cardiac surgical cases with postoperative hospital admission. The RQI and POARisk were calculated using published methodologies, and model performance was compared with and without the SAS. Relative quality was measured using Akaike information criterion and Bayesian information criterion. Calibration was compared by the Brier score. Discrimination was compared by the area under the receiver operating curves (AUROC) using a bootstrapping procedure to estimate confidence intervals.

Results and Major Findings: 47,214 cases were identified with data required to calculate the RQI. SAS alone was a statistically significant predictor of both 30-day mortality and in-hospital mortality in this cohort ($p<0.0001$), with an AUROC of 0.64. The RQI had excellent discrimination with an AUROC of 0.8278 (95% confidence interval 0.8276, 0.8281), which improved slightly to 0.8395 (0.8394, 0.8397) with the addition of the SAS. 116,132 cases were identified with data required to calculate the POARisk. The POARisk had excellent discrimination with an AUROC of 0.8583 (0.8583, 0.8584), which improved slightly to 0.8621 (0.8620, 0.8621) by including the SAS. Similarly, overall performance and relative quality also improved.

Conclusion: While there was a minor improvement in discrimination, the RQI and POARisk preoperative risk models were not meaningfully improved by adding intraoperative risk using the SAS. Interesting, this suggests that risk stratification is not improved by combining dynamic clinical parameters from the patient's intraoperative course with procedural risk estimate models. This further suggests that postoperative resources can be appropriately allocated using only information available prior to surgery.

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Poster Sessions

OC 6 (18)

Interaction Effects of Acute Kidney Injury, Acute Respiratory Failure, and Sepsis on 30-day Postoperative Mortality in Patients Undergoing High-Risk Intra-abdominal General Surgical Procedures

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Background: Acute kidney injury (AKI), acute respiratory failure (ARF), and sepsis are distinct but related inflammatory processes (1). We hypothesized that there are significant biological interactions between these three processes to synergistically increase the risk of short-term perioperative mortality in patients undergoing high-risk intraabdominal general surgery procedures.

Methods: After IRB exemption, we performed a retrospective, observational cohort study of data (2005-2011) from the American College of Surgeons National Surgical Quality Improvement Program, a high-quality surgical outcomes dataset. High-risk procedures were those with a risk of AKI, ARF, or sepsis that was greater than the average risk in all intraabdominal general surgery procedures. Patients with preoperative acute renal insufficiency, dialysis, pneumonia, mechanical ventilation, and sepsis were excluded. The complications of interest were: 1) AKI - increase in serum creatinine >2 mg/dl or postoperative dialysis; 2) ARF - postoperative reintubation or mechanical ventilation; and 3) sepsis - sepsis or septic shock. The effects of AKI, ARF, and sepsis on 30-day mortality were assessed using a Cox proportional hazards model. Additive interactions were assessed with the relative excess risk due to interaction.

Table 1. Characteristics of patients undergoing high-risk intraabdominal general surgery by acute kidney injury, sepsis, and acute respiratory failure status, American College of Surgeons-National Surgical Quality Improvement Program, 2005-2011.

	Acute Kidney Injury		Sepsis		Acute Respiratory Failure		None
Patients	**2,751**	**p**	**14,723**	**p**	**7,956**	**p**	**198,533**
Age (years)	66.1 (13.7)	***	62.0 (15.6)	***	67.5 (13.9)	***	59.5 (16.0)
Female	1,070 (38.9)	***	7,100 (48.3)	***	3,711 (46.7)	***	105,885 (53.4)
White	1,901 (69.1)	***	10,731 (72.9)	**	5,820 (73.2)	*	147,448 (74.3)
ASA Class							
1	17 (0.6)	***	172 (1.2)	***	42 (0.5)	***	6,730 (3.4)
2	566 (20.6)		4,059 (27.6)		1,242 (15.6)		92,207 (46.5)
3	1,738 (63.2)		8,834 (60.1)		5,022 (63.2)		90,903 (45.8)
4	413 (15.0)		1,597 (10.9)		1,575 (19.8)		8,390 (4.2)
5	14 (0.5)		48 (0.3)		59 (0.7)		91 (0.1)
Body Mass Index (kg/m^2)	29.8 (8.3)	***	28.0 (7.5)	***	28.3 (8.0)	***	27.7 (6.8)
Emergency	454 (16.5)	***	2,051 (13.9)	***	1,865 (23.4)	***	19,718 (9.9)
Diabetic	788 (28.6)	***	2,795 (19.0)	***	1,857 (23.3)	***	27,307 (13.8)
Dyspnea	484 (17.6)	***	2,082 (14.1)	***	1,576 (19.8)	***	17,110 (8.6)
Chronic Obstructive Pulmonary Disease	273 (9.9)	***	1,279 (8.7)	***	1,133 (14.2)	***	8,589 (4.3)
Congestive Heart Failure	80 (2.9)	***	223 (1.5)	***	242 (3.0)	***	1,072 (0.5)
Myocardial Infarction	45 (1.6)	***	153 (1.0)	***	132 (1.7)	***	838 (0.4)
Coronary Revascularization (PCI or CABG)	504 (18.3)	***	1,878 (12.8)	***	1,398 (17.6)	***	16,685 (8.4)
Angina	47 (1.7)	***	123 (0.8)	***	124 (1.6)	***	961 (0.5)
Hypertension	1,974 (71.8)	***	7,967 (54.1)	***	5,238 (65.8)	***	90,606 (45.6)
Peripheral Vascular Disease	80 (2.9)	***	325 (2.2)	***	319 (4.0)	***	2,348 (1.2)
Stroke (with or without neuro deficit)	272 (9.9)	***	1,182 (8.0)	***	906 (11.4)	***	10,091 (5.1)
Current Smoker	508 (18.5)		3,265 (22.2)	***	1,812 (22.8)	***	37,990 (19.1)
Functionally Dependent	382 (13.9)	***	1,991 (13.5)	***	1,595 (20.1)	***	9,779 (4.9)
Ascites	115 (4.2)	***	515 (3.5)	***	333 (4.2)	***	3,018 (1.5)
Chronic Steroid Use	188 (6.8)	**	1,186 (8.1)	***	594 (7.5)	***	10,437 (5.3)
Cancer	406 (14.8)	***	2,050 (14.0)	***	3,871 (48.7)	**	93,596 (47.2)
Bleeding disorders	289 (10.5)	***	1,175 (8.0)	***	896 (11.3)	***	9,000 (4.5)
Transfusions > 4 Units 72 hours prior to surgery	80 (2.9)	***	244 (1.7)	***	242 (3.0)	***	1,622 (0.8)
Hematocrit (%)	35.7 (6.0)	***	36.5 (5.9)	***	35.8 (6.3)	***	37.9 (5.5)
Estimated Glomerular Filtration Rate (ml/min/1.73m^2)							
<30	271 (9.9)	***	440 (3.0)	***	431 (5.4)	***	2,828 (1.4)
30-60	814 (29.6)		2,627 (17.8)		2,051 (25.8)		27,820 (14.0)
60-90	922 (33.5)		5,405 (36.7)		2,998 (37.7)		77,020 (38.8)
>90	653 (23.7)		5,615 (38.1)		2,229 (28.0)		75,906 (38.2)
Missing	91 (3.3)		636 (4.3)		247 (3.1)		14,959 (7.5)

ASA, American Society of Anesthesiologists; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft. Continuous variables expressed as mean (standard deviation). Categorical variables expressed as counts (%).
***P<0.0001 vs. None group
**P<0.01 vs. None group
*P<0.05 vs. None group

Results: Of 217,994 patients, AKI, ARF, and sepsis developed in 1.3%, 3.7%, and 6.8%, respectively. Those with complications had higher rates of comorbidities and risk factors compared to those not developing a complication (Table 1). The 30-day mortality risk with sepsis, ARF, and AKI were 11.4%, 24.1%, and 25.1%, respectively, compared to 0.8% without these complications. The adjusted hazard ratios and 95% confidence intervals for a single complication (vs. no complication) on mortality were 7.24 [6.46, 8.11], 10.8 [8.56, 13.6], and 14.2 [12.8, 15.7] for sepsis, AKI, and ARF, respectively. For two complications, the adjusted hazard ratios were 30.8 [28.0, 33.9], 42.6 [34.3, 52.9], and 65.2 [53.9, 78.8] for ARF/sepsis, AKI/sepsis, and ARF/AKI, respectively. Finally, the adjusted hazard ratio for all 3 complications was 105 [92.8, 118]. Positive additive interactions, indicating biological synergism, were found for each combination of 2 complications. The relative excess risk due to interaction for all 3 complications was not statistically significant.

Conclusion: In high-risk general surgery patients, the development of acute kidney injury, acute respiratory failure, or sepsis is independently associated with an increase in 30-day mortality. In addition, the development of 2 complications show significant positive interactions to further increase the risk of mortality than would be expected by the independent effects of each complication alone. Our findings suggest that preventing the development of an additional inflammatory complication after an initial complication has occurred may represent a window of opportunity for substantially reducing perioperative mortality.

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OC 12 (20)

Effects of Intra-Operative Positive End-Expiratory Pressure on the Postoperative Respiratory Complications in Patients Undergoing Craniotomy: A Retrospective Study

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Introduction: Post-operative pulmonary complications such as atelectasis and pneumonia commonly occur regardless of preoperative pulmonary functional status1. These complications are associated with risk of mortality, increased cost and length of hospital stay2-4. In order to minimize the complications, positive end-expiratory pressure (PEEP) is recommended to be used during anesthesia5-8. However, recent studies have demonstrated that PEEP can initiate/exacerbate inflammation and cause acute lung injury9-12. It is unclear whether intra-operative PEEP provides protection or causes harm to patients with healthy lungs13-16. Besides, one of the uncertainties from previous studies is the heterogeneity of the patient population and the surgical procedures. The purpose of this study is to determine the effect of PEEP applied intra-operatively on the incidence of post-operative respiratory complications in otherwise healthy patients requiring a craniotomy.

Methods: This retrospective observational study covered a 5-year period from January 1, 2008 to December 31, 2012. The data was obtained from electronic anesthesia and respiratory care databases at Massachusetts General Hospital. The patients were restricted to adults undergoing elective craniotomies without existing respiratory disease (Figure 1). A total of 2437 patients were included in the final analysis. The patients were divided into two groups according to application of intra-operative PEEP < 5 cmH2O or ≥ 5 cmH2O. Our primary outcome was the incidence of post-operative re-intubation or non-invasive positive pressure ventilation (NIV) due to respiratory complications. The secondary outcomes were the incidences of post-operative pneumonia and length of hospital and ICU stay.

Results and Major Findings: There were no significant differences between groups in age, smoking history, or anesthesia duration (Table 1). However, there were significant differences in gender, BMI, ASA classification, PIP, VT, end-tidal CO2, peripheral oxygen saturation, fluid balance, and estimated blood loss ($p < 0.05$). For patients requiring re-intubation, the ventilation duration and causes are listed in Table 2. There was no significant difference in the incidence of re-intubation (OR = 0.965, p = 0.999) (Figure 2) or post-operative pneumonia (OR = 1.225, p = 0.523) (Figure 3). The incidence of re-intubation was associated with current smoking history (p = 0.04) and post-operative pneumonia (p = 0.006) (Table 3).

Conclusion: PEEP applied intra-operatively to patients with healthy lungs who underwent elective craniotomies neither causes harm nor provides benefit in terms of incidence of re-intubation, incidence of post-operative pneumonia, length of hospital stay or ICU stay. Active smoking and post-operative pneumonia are associated with re-intubation.

Keywords: Positive end-expiratory pressure (PEEP), mechanical ventilation, acute lung injury, general anesthesia, pneumonia.

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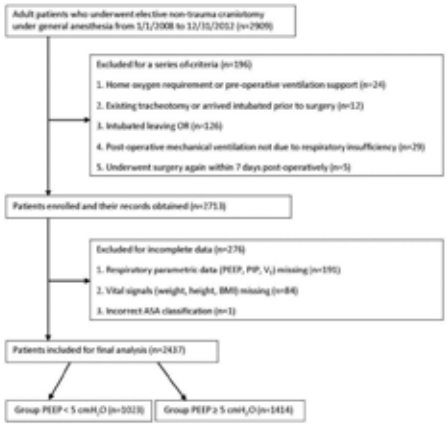

Figure 1. Flow chart of patient selection

Table 1. Demographic information and intra-operative care of patients receiving intra-operative PEEP< or ≥ 5 cmH_2O

	PEEP < 5 cmH_2O (n=1023)	PEEP ≥ 5 cmH_2O (n=1414)	*p* value
Age (years old)	53 (42, 64)	53 (44, 64)	0.715
Gender (Male/Female)	362/661	605/809	0.000
Weight (kg)	72 (61, 84)	81 (69, 95)	0.000
Height (cm)	168 (160, 175)	170 (160, 178)	0.000
BMI (kg/m^2)	25.4 (22.8, 29.2)	28.0 (24.6, 32.6)	0.000
ASA class (I/II/III/IV)	40/627/335/21	40/862/498/14	0.049
Smoke status (current/quit/no/ data-missing)	202/340/466/15	307/470/624/13	0.405
Anesthesia Duration (minutes)	281 (215, 396.5)	293 (225, 405.5)	0.250
PIP (cmH_2O)	18 (16, 21)	21 (18, 24)	0.000
VT (ml)	498 (456.5, 562)	524 (472, 595)	0.000
VT/AIBW (ml/kg)	7.00 (6.27, 7.79)	6.56 (5.83, 7.39)	0.000
VT/IBW (ml/kg)	8.40 (7.55, 9.38)	8.56 (7.69, 9.63)	0.003
$ETCO_2$ (mmHg)	31 (28, 33)	31 (29, 33)	0.003
SpO_2 (%)	99 (98, 100)	99 (98, 100)	0.000
FeO_2 (%)	28 (23, 43)	28 (22, 42)	0.097
FiO_2 (%)	32 (28, 47)	32 (27, 46)	0.377
Fluid Balance (ml)	551 (-135, 1311)	590 (-67, 1302)	0.030
Fluid Balance/Time (ml/hour)	105 (-28, 254)	42 (-63, 84)	0.001
EBL (ml)	250 (150, 400)	250 (150, 400)	0.002
Blood & FFP Transfusion (unit)	0 (0, 0)	0 (0, 0)	0.311
5% Albumin (ml)	0 (0, 0)	0 (0, 0)	0.275
Re-intubation	3	4	0.999
Post-operation pneumonia	16	27	0.523
ICU stay(day)	1 (1, 2)	1 (1, 2)	0.516
Hospital stay(day)	4 (3, 7)	4 (3, 7)	0.065

Data are presented as median and IQR. IQR = inter-quartile range. BMI = body mass index: (weight [kg]) / (height [m])^2, ASA = American Society of Anesthesiologists, PIP = peak inspiratory pressure, PEEP = positive end-expiratory pressure, RR = respiratory rate, MV = minute volume, VT = tidal volume, AIBW = actual body weight, IBW = ideal body weight, $ETCO_2$ = end-tidal carbon dioxide pressure, SpO_2 = peripheral oxygen saturation, FeO_2 = fraction of end-tidal oxygen, FiO_2 =fraction of inspired oxygen; EBL = estimated blood loss.

Table 2 Duration and causes of re-intubation

Patient No.	Duration (day)	Causes
Patient 1	6	Left lower lobe pneumonia
Patient 2	2	Sudden tachypnea and tachycardia
Patient 3	1	Breathing weak in left lung
Patient 4	7	Multifocal pneumonia, atelectasis and laryngeal edema,
Patient 5	1	PaO_2/FiO_2 = 93/0.38
Patient 6	1	Atelectasis in right mid lower lung
Patient 7	4	Aspiration, tachypnea, COPD, asthma, acute respiratory failure

PaO_2 = partial pressure of oxygen in arterial blood; FiO_2 = fraction of inspired oxygen; COPD = chronic obstructive pulmonary disease.

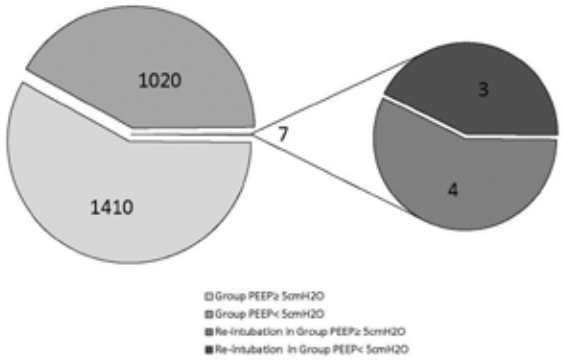

Figure 2. Patients who required re-intubation

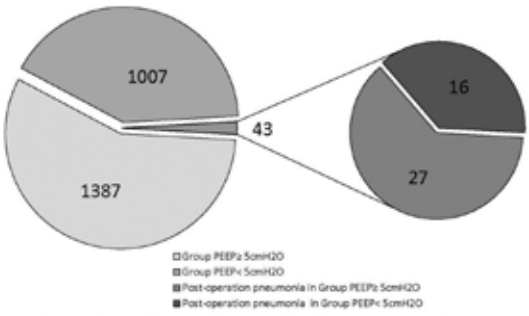

Figure 3. Patients who acquired post-operation pneumonia

Table 3. Risk factors for requiring post-operative re-intubation

	Stratified	Re-intubation/Non-re-intubation (%)	Odds Ratio (95% CI)	*p* value
Age (years)	≥ 65 < 65	3/563(0.550) 4/1867(0.214)	2.487 (0.555, 11.146)	0.433
Age (years)	≥ 60 < 60	3/824(0.595) 2 /1594(0.125)	4.767 (0.923, 24.622)	0.097
Gender (Male/Female)	M F	4/963(0.414) 3/1467(0.204)	2.031 (0.454, 9.085)	0.576
BMI (kg/m^2)	≥ 30 < 30	3/741(0.403) 4/1686(0.236)	1.708 (0.380, 7.682)	0.747
ASA class	≥ 3 < 3	3/863(0.374) 2/1547(0.117)	4.339 (0.879, 23.446)	0.113
Smoke status	Current Quitter No	4/707(0.780) 3/1877(0.138) 0/323(0.000)	5.669 (1.317, 22.471)	0.040
Anesthesia Duration (minutes)	≥ 300 < 300	4/1130(0.350) 3/1257(0.232)	1.511 (0.338, 6.767)	0.869
PIP (cmH_2O)	> 20 ≤ 20	3/1012(0.282) 4/1368(0.292)	0.966 (0.216, 4.324)	0.999
VT/IBW (ml/kg)	> 10 ≤ 10	2/1010(0.198) 5/2120(0.247)	1.982 (0.383, 10.253)	0.744
Fluid Balance (ml)	≥ 1000 < 1000	2/1640(0.732) 5/2160(0.250)	0.995 (0.436, 17.872)	0.172
EBL (ml)	≥ 1000 < 1000	3/941(0.855) 4/2360(0.256)	0.992 (0.894, 34.749)	0.243
Fluid Balance/ Time (ml/hour)	≥ 100 < 100	5/1125(0.598) 2/1179(0.169)	2.500 (0.456, 12.167)	0.499
Blood & FFP Transfusion (unit)	> 0 = 0	5/1126(0.885) 4/2310(0.258)	9.994 (0.432, 28.895)	0.283
5% Albumin (ml)	> 0 = 0	0/168 (0.000) 7/2228(0.300)		0.999
Pneumonia	Yes No	2 /43(0.056) 5/2589(0.002)	23.307(4.391, 123.645)	0.000

Data are presented as median and IQR.

Poster Sessions

OC 13 (21)
Intraoperative Normoxia, Oxidative Damage, and Organ Injury Following Cardiac Surgery

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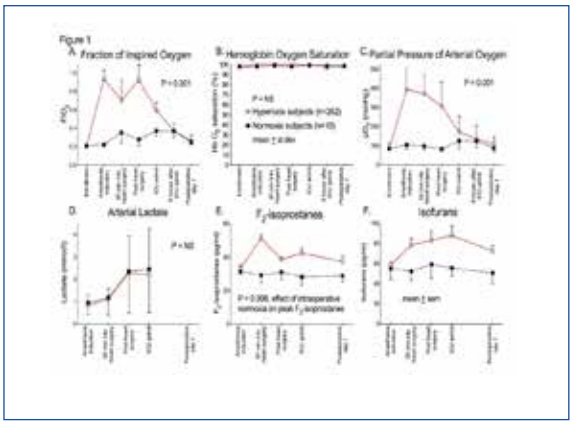
Introduction: Anesthesiologists often ventilate patients with concentrations of oxygen well above those required to saturate hemoglobin. In other clinical scenarios, hyperoxia is harmful, such as resuscitation from cardiac arrest where hyperoxia independently predicts brain injury.1 Hyperoxia increases oxidative damage in vitro and in experimental ischemia reperfusion, and in a prior study of cardiac surgery patients, increased intraoperative F2-isoprostanes, best markers for assessment of oxidative damage in vivo,2 independently predicted postoperative acute kidney injury (AKI).3 We hypothesize that normoxia during cardiac surgery decreases intraoperative oxidative damage and postoperative organ injury.

Methods: In a 486 subject cardiac surgery cohort, we assessed for patients administered normoxia, defined as a median arterial pO2 between 70-120 mmHg during surgery and matched those with patients administered hyperoxia, defined as a median pO2 >200 mmHg, based on risk factors for intraoperative oxidative stress. Fraction of inspired oxygen (FIO2), hemoglobin oxygen saturation (Hb O2 sat), and pO2 were measured to assess oxygen administration, F2-isoprostanes and isofurans in plasma to assess oxidative damage, and AKI, defined using AKIN criteria, delirium, defined as any positive CAM-ICU assessment in the ICU, and new-onset atrial fibrillation to compare postoperative morbidity between normoxia and hyperoxia groups.

Results: Ten subjects were administered normoxia throughout surgery. Risk factors for intraoperative oxidative stress, including cigarette smoking (incidence 15%), body mass index (median 27.7 kg/m2), age (66 years), use of CPB (70%), and baseline markers of oxidative stress were similar between these normoxia patients and 262 risk-matched controls administered hyperoxia. The FIO2 ($p<0.001$) and pO2 ($p<0.001$) were considerably less in normoxic patients, but Hb O2 sat and arterial lactate concentrations, safety markers of ischemia, were not different compared to hyperoxic patients (Figure). Specifically, the median intraoperative FIO2 and pO2 were 0.28 and 85 mmHg in normoxic subjects compared to 0.82 and 367 mmHg in hyperoxic subjects ($P<0.001$ for both). Peak F2-isoprostane concentrations were 42.7% less in the normoxic group ($P=0.008$), and neither F2-isoprostanes nor isofurans increased above baseline during the perioperative period in normoxic patients, while F2-isoprostanes rose 38% and isofurans 33% in hyperoxic patients (Figure). In addition, no normoxic subjects suffered from AKI (20.0% incidence in hyperoxic group, $P=0.04$) or delirium (23.8% in hyperoxic group, $P=0.02$), and 20% developed new-onset atrial fibrillation (28.8% in hyperoxic group, $P=0.53$).



Conclusion: Normoxia during cardiac surgery is associated with reduced intraoperative oxidative damage, and no subjects administered normoxia suffered from AKI or ICU delirium following surgery. A randomized clinical trial is warranted to determine if normoxia decreases intraoperative oxidative damage and postoperative morbidity, compared to the hyperoxia anesthesiologists typically provide.

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OC 14 (27)

Epidemiology of Critical Care Admissions in a Tertiary Hospital of Sub-Saharan Africa

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Background: The World Health Organization recommends that any facility providing surgical care should have an intensive care unit (ICU) (defined as an area providing more nursing care than the general wards, 24-hour monitoring, and the provision of oxygen), but many hospitals in sub-Saharan Africa are unable to meet this need.[1] ICU mortality in this region is high, ranging from 32.2-63.6%.[2-6] The purpose of this study was to describe the characteristics and outcomes of patients admitted to the ICU of a tertiary care center of Malawi, to better characterize the burden of disease and to identify risk factors for mortality.

Methods: This was a retrospective, cross-sectional study of all patients admitted to the ICU of Queen Elizabeth Central Hospital (QECH), a 1300-bed tertiary care center in Blantyre, Malawi, between September 1, 2013 and October 17, 2014. The ICU contains 4 ventilator-equipped beds, and is the only critical care unit serving the hospital. Patients were stratified by survival, and demographics, clinical characteristics, and outcome data were summarized.

Table 1. Characteristics of patients admitted to intensive care

	Total, n (%)	Died in ICU, n (%)	Missing data, n (%)	p
Total cohort, n (%)	390 (100)	90 (24)	0 (0)	--
Gender, n (%)			51 (13)	0.07
Female	171 (50)	47 (27)		
Male	168 (50)	32 (19)		
Age category, n (%)			20 (5)	0.108
Neonate (<1year)	35 (9)	13 (37)		
Pediatric (1-17yrs)	113 (31)	21 (19)		
18-29 years	100 (27)	25 (26)		
30-49 years	80 (22)	20 (25)		
>50 years	42 (11)	6 (14)		
Length of Stay in ICU, n (%)			33 (8)	<0.001
<1 day	42 (12)	24 (57)		
1 day	107 (30)	22 (21)		
2 days	67 (19)	6 (10)		
>3 days	141 (21)	30 (21)		
Discharge destination for survivors, n (%)			10 (3)	--
Ward	285 (75)	--		
High-Dependency ward	2 (0.5)	--		
Transfer to other hospital	3 (0.8)	--		
Diagnostic category on ICU admission			0 (0)	<0.001
Surgical, n (%)	281 (72)	44 (16)		
General	139 (49)	24 (18)		
Orthopaedic	34 (12)	3 (9)		
Neurologic	35 (13)	6 (17)		
Otolaryngology	35 (12)	0 (0)		
Cardiothoracic	24 (9)	4 (17)		
Ophthalmologic	2 (1)	1 (50)		
Gynecologic	5 (2)	1 (20)		
Burns	3 (1)	3 (100)		
Anesthesia	4 (1)	2 (50)		
Medical, n (%)	71 (18)	29 (41)		
Respiratory	28 (39)	9 (35)		
Neurology	20 (28)	9 (47)		
Infectious Disease	10 (14)	6 (60)		
Cardiovascular	3 (4)	2 (66)		
Renal	2 (3)	1 (50)		
Gastroenterology	2 (3)	1 (50)		
Other*	6 (8)	1 (17)		
Obstetrics, n (%)	38 (10)	17 (45)		
Admission diagnosis secondary to Trauma, n (%)	57 (15)	12 (21)	0 (0)	0.612
Admission with Sepsis, n (%)	27 (7)	16 (59)	0 (0)	<0.001
Utilization of Mechanical Ventilation, n (%)	242 (77)	72 (30)	76 (19)	<0.001
Utilization of Blood transfusion, n (%)	34 (9)	11 (32)	0 (0)	0.172

Results: There were 390 patients admitted during the study period. The median age was 22 (IQR 6-35), and 50% of patients were female. The majority of patients were admitted with surgical diagnoses (72%); the remaining patients were admitted with medical (18%) or obstetric (10%) diagnoses. Overall ICU mortality was high (24%), and mortality was highest in the first 24 hours of ICU stay (57%). Although fewer patients were admitted with medical or obstetric diagnoses, these patients had higher mortality than surgical patients (41% and 45%, respectively, versus 16%, p<0.001). Admission diagnoses with the highest mortality included burns (100%, n=3), cardiovascular disease (66%, n=3), infectious disease (60%, n=10), sepsis (59%, n=27), and anesthetic complications (50%, n=4). Anesthetic complications included high spinal (n=3) and malignant hyperthermia (n=1).

Conclusion: There is a shortage of data describing critical illness in low-income countries, particularly in sub-Saharan Africa. Surgical disease comprises the majority of ICU utilization in this region. Focused training programs are warranted to reduce anesthesia-related mortality. This data may guide strategies for improving critical care in the region.

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Poster Sessions

CS/Metab 23 (75)
Discovery of AMPA Receptor GluA4 Subunit Expression in Mouse and Human Epidermal Keratinocytes

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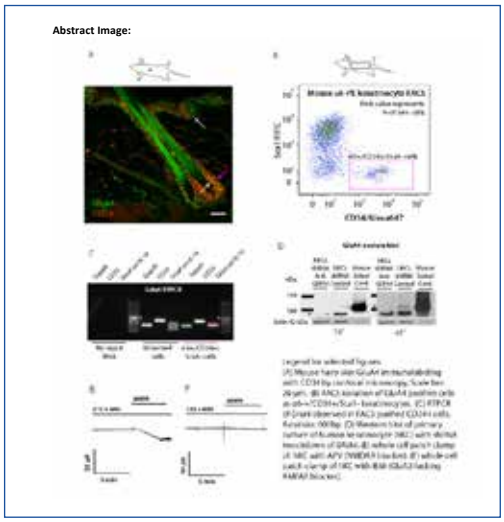
Introduction: Opioids are the mainstay of treatment for acute pain, but their utility in chronic pain is confounded by responses to chronic opioids including tolerance and sensitization. Our previous work in a murine chronic opioid paradigm demonstrated changes in α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid type ionotropic glutamate receptor (AMPAR) levels in the brain and spinal cord underlie some of these adaptations (1, 2). The same opioid paradigm also increased spontaneous firing of peripheral C-fibers (3), but mechanisms underlying this alteration are unknown, thus we explored AMPAR expression in the periphery.



Methods: AMPAR immunohistochemistry of skin preparations were done in glabrous hind paws and hairy dorsal skins of opioid naïve C57BL6 mice. RTPCR was done on FACS isolated CD34(+) mouse epidermal keratinocytes, and Gria4 RTPCR products were sequenced. GluA4-IL was also done in human neonatal foreskin (discarded from routine circumcisions) and cultured primary human epidermal keratinocytes (hKCs) from them. GRIA4 RTPCR was done with hKCs, and shRNA knockdown of GRIA4 was assayed by GluA4 western blot. Whole cell patch clamp recordings were taken from hKCs.

Results: Surprisingly, GluA4-IL was more evident in epidermal keratinocytes than peripheral nerve fibers, in glabrous and hairy skin of mice. Although GRIA4 RTPCR of skin biopsies was described (4), the cell-type expressing GRIA4 remained obscure. Meanwhile, GluA4 expression is described in melanocytes (5). To corroborate the GluA4-IL of keratinocytes, RTPCR of FACS isolated keratinocytes followed by sequencing confirmed Gria4 expression in CD34(+) stem cells (6). GluA4-IL of human skin and hKCs, and RTPCR of GRIA4 of hKCs all support human keratinocyte expression of GRIA4/GluA4. Notably, human keratinocyte GRIA4 may be a novel splice variant. shRNA of GRIA4 in hKCs also demonstrated loss of GluA4 bands. Finally, whole cell patch clamping of hKCs confirmed an AMPA-inducible current.

Conclusion: Our work describes the unexpected expression of GluA4 subunit of AMPAR in keratinocytes of mouse and human. Exteroception by skin is generally attributed to free nerve terminals of primary afferent neurons arborized in the epidermis (7), however keratinocytes are electrochemically excitable (8), and recent works revealed their importance in sensation through calcium mediated signaling involving TRP channel family members (9, 10). GluA2 lacking AMPARs are also calcium permeable ion channels (11), and based upon our observation of AMPA-inducible inward currents and GluA4 expression, we propose the keratinocyte GluA4 plays a role in nociceptive or pruritogenic transduction by keratinocytes. Another possibility is that CD34(+) hair follicle stem cells use glutamatergic signaling for calcium mediated wound healing responses to injury, as proliferation and differentiation of keratinocytes are calcium dependent processes (12).

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Poster Sessions

CS/Metab 24 (83)

Drosomycin and Impaired Geotaxis in Drosophila Surviving Sepsis: A Novel Model of Recovery from Sepsis

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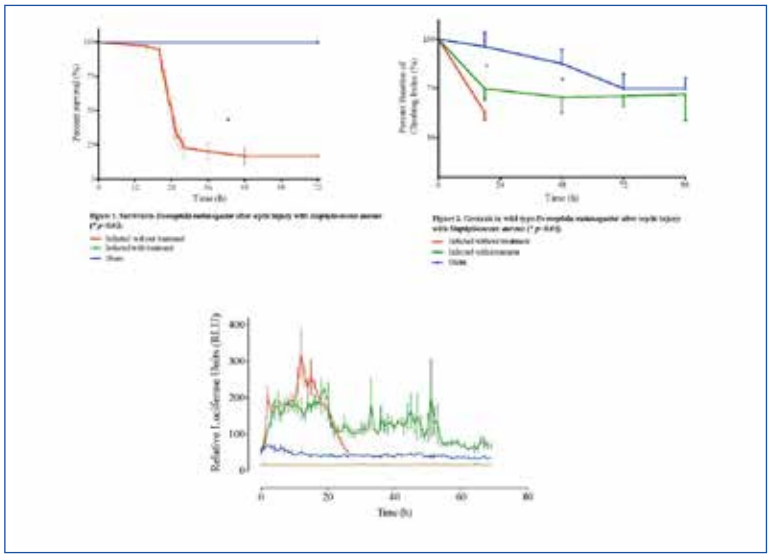
Objective: Surviving sepsis is complicated by multiple organ failure, increasing morbidity and mortality even after prolonged periods. Persistent inflammation has been implicated, however mechanisms are unknown and suitable pre-clinical models are lacking. We developed a novel Drosophila melanogaster model of recovery from sepsis to test whether sepsis-induced inflammatory changes are associated with functional and immune recovery.

Design: Prospective randomized invertebrate study.

Subjects: Wild type (WT), Drosomycin-GFP, Drosomycin-deficient, UAS-drs-RNAi/He-Gal4, and NF-βB-luc reporter, (4-5 d) male Drosophila melanogaster were used.



Intervention: Drosophila were infected with Staphylococcus aureus or pricked with aseptic needles as shams. Subsets of insects were treated with oral linezolid with a 2 h delay after the infection.

Measurements: Survival curves for WT, Drosomycin-deficient, and UAS-drs-RNAi/He-Gal4 flies were generated of each group (control, sham, infection, infection+antibiotics) over a 7-day course. Rapid Iterative Negative Geotaxis (RING) was assessed in all the groups as a surrogate for neuromuscular functional outcome up to 96 h following infection. The flies were harvested over the 7-day course to evaluate bacterial burden and inflammatory gene expression patterns, imaged for NF-κB activation and Drosomycin expression.

Results: Groups of 30 flies were repeated at least three times for each experimental condition. The results showed that when treated with antibiotics, flies had improved survival compared to untreated flies (99%, p=0.001). Among survivors of sepsis, geotaxis remained low for up to 3 days following sepsis as compared the sham and age-matched control flies. Decline in geotaxis correlated with persistent inflammation in the absence of any obvious infection as shown by persistent elevation of NF-κB. The expression of antimicrobial peptides (AMP) remained significantly elevated over the course of 7 days after sepsis, especially drosomycin (5.7 -fold, p= 0.0145) on day 7 compared to sham flies. Drosomycin was expressed in the fat body. Drosomycin-deficient and UAS-drs-RNAi/He-Gal4 flies had significantly more pronounced defect in geotaxis following recovery from sepsis ($p<0.05$).

Conclusion: We report a novel Drosophila model of recovery from severe sepsis and the associated neuromuscular dysfunction. Using Drosomycin knockdown flies, we propose a link between neuromuscular dysfunction and Drosomycin, one of the most expressed antimicrobial peptide in Drosophila melanogaster immune response, in Drosophila surviving sepsis.

Poster Sessions

CS/Metab 25 (87)
Isoflurane Induces Substrate-Dependent Transient Mitochondrial PTP Opening

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The volatile anesthetic isoflurane (ISO) may increase permeability of mitochondria to protect against mitochondrial induced cellular injury. Prolonged opening of the mitochondrial permeability transition pore (mPTP) inevitably causes mitochondrial and cellular demise, whereas transient mPTP opening may release accumulated Ca2+ from the matrix to avoid subsequent irreversible mPTP opening due to Ca2+ overload. To test if ISO alters mPTP opening, we isolated mitochondria from Wistar rat hearts to assess buffer Ca2+ uptake by Fura 4F. We found that: (a) ISO (1 mM) induced earlier mPTP opening by increasing Ca2+ uptake rate with succinate (SUC). (b) ISO did not alter mPTP opening but reduced Ca2+ uptake with pyruvate/malate. (c) 10 µM ryanodine or 10 nM imperatoxin A with SUC increased Ca2+ uptake and induced earlier mPTP opening; this suggests that ISO's effects on mPTP may be due to increased conductance via the putative mitochondrial ryanodine receptors (mRyR). We have patch-clamped single mRyRs in mitoplasts. Our data infer indirectly that SUC substrate - dependent transient mPTP opening may be due to enhanced RyR Ca2+ uptake. Transient Ca2+ release could be a mechanism underlying ISO-induced cardiac protection in ischemia- reperfusion injury.

Poster Sessions

Clin Basic Pain 36 (6)
The Global Burden of Chronic Pain: A Systematic Review and Meta-Analysis

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Introduction: The global burden of chronic pain is projected to be large and growing, in concert with non-communicable disease burden. Documentation of the chronic pain burden has not been consistent in the international literature, and little progress toward managing this growing crisis has been made. This first meta-analysis of the global pain literature in low-middle income countries (LMIC) reveals the prevalence as reported in the literature, as well as the many gaps in global pain knowledge.

Methods: The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for systematic review were used to search six databases representing the international literature. Seventy-nine articles were identified as relevant for meta-analysis.

Results: Our systematic literature review with meta-analysis found a 33% prevalence of any type of chronic pain in general populations when evaluating surveys performed in low and middle-income countries. Common subgroups of pain, including musculoskeletal pain, headache, low back pain, pelvic pain, temporomandibular pain, irritable bowel syndrome and fibromyalgia were globally reported. Workers and the elderly reported every type of chronic pain more frequently than other demographic groups.

Conclusion: Pain prevalence in LMIC is consistent with Global Burden of Disability data. This meta-analysis reveals the spectrum of chronic pain in LMIC, but has fallen short of revealing clear etiologies for the pain. The demonstration of the prevalence of chronic pain is essential as goals are set by the global health community to find solutions for acute and chronic pain.

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Table 1: Results of meta-analysis

Pain Type	N*	Pooled	N*	General	N*	Elderly	N*	Workers	Patients
LBP	35	0.28 (0.24, 0.33)	15	0.18 (0.14, 0.24)	9	0.31 (0.22, 0.41)	11	0.44 (0.33, 0.55)	82146
HA	21	0.44 (0.35, 0.54)	11	0.39 (0.27, 0.53)	6	0.49 (0.37, 0.60)	4	0.52 (0.16, 0.86)	34586
CDH	10	0.06 (0.04, 0.11)	6	0.05 (0.03, 0.07)	1	--	3	0.12 (0.08, 0.19)	19022
CM	7	0.09 (0.05, 0.15)	5	0.10 (0.05, 0.20)	1	--	1	--	17662
CTTH	7	0.04 (0.02, 0.07)	6	0.04 (0.02, 0.09)	1	--	0	--	15468
CPP	6	0.13 (0.08, 0.21)	5	0.11 (0.08, 0.16)	1	--	0	--	27158
TMD	2	0.07 (0.01, 0.31)	0	--	2	0.07 (0.01, 0.31)	0	--	6494
WSP	5	0.17 (0.11, 0.26)	3	0.14 (0.09, 0.22)	2	0.22 (0.09, 0.46)	0	--	8136
FMS	5	0.05 (0.03, 0.07)	3	0.04 (0.03, 0.07)	1	--	1	--	9214
JP	16	0.26 (0.18, 0.36)	7	0.14 (0.11, 0.18)	8	0.42 (0.26, 0.60)	1	--	49326
MSK	12	0.47 (0.35, 0.59)	5	--	4	0.39 (0.23, 0.57)	3	0.86 (0.85, 0.87)	38468
AP	5	0.08 (0.04, 0.18)	3	--	1	0.06 (0.01, 0.28)	1		10348
ANY	19	0.40 (0.31, 0.50)	11	0.33 (0.26, 0.40)	6	0.56 (0.36, 0.75)	2	0.35 (0.04, 0.88)	35665

LBP=low back pain, HA=headache, CDH=chronic daily headache, CTTH=chronic tension-type headache, CPP=chronic pelvic pain, TMD=temporomandibular disorder, WSP=widespread pain, FMS=fibromyalgia syndrome, JP=joint pain, MSK=musculoskeletal pain, AP=abdominal pain, ANY=any pain

Poster Sessions

Clin Basic Pain 37 (29)

The Pharmacokinetics and Anti-Hyperalgesic Efficacy of the mGlu5 Antagonist Fenobam in Healthy Volunteers

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Introduction and General Purpose of the Study: G-protein coupled metabotropic glutamate receptor 5 (mGlu5) is expressed throughout the pain neuraxis and has been demonstrated to play a role in the modulation of nociception in rodents. Fenobam [N-(3-chlorophenyl)-N'-(4,5-dihydro-1-methyl-4-oxo-1H-imidazole- 2-yl)urea] is a potent, selective, and noncompetitive allosteric modulator of mGlu5 that has been tested in human subjects as a therapy for anxiety and Fragile X mental retardation. Preclinical data suggest that fenobam is analgesic via an mGlu5 specific mechanism in rodents, and that analgesic tolerance and significant side effects do not develop with repeated dosing (Refs. 1,2). Given these characteristics, fenobam represents an ideal compound for proof of concept studies to test the analgesic efficacy of mGlu5 antagonists in human subjects.

The investigation presented here was designed to characterize the pharmacokinetics and side effects profile of three doses (50 mg, 100 mg, and 150 mg) of orally administered fenobam and test directly the hypothesis that fenobam will reduce the area of cutaneous hyperalgesia in a double-blinded, placebo-controlled, crossover-design model of central sensitization in healthy human volunteers. We also sought to assess the effects of mGlu5 modulation on working memory, cognitive performance, and mood and affect.

Methods: The pharmacokinetics and side effect profile of fenobam were examined with 32 healthy male and non-pregnant female, 18-50 year-old volunteers, who received either 50, 100, or 150 mg of oral fenobam or placebo in a double blinded fashion (ClinicalTrials.gov NCT01806415). Following drug or placebo administration blood samples were collected at multiple time points up to 600 minutes to assess fenobam plasma concentration. Complete blood counts and complete metabolic panels were also collected immediately before and 24 hours after drug administration. The effects of fenobam on central sensitization were assessed using a randomized, double-blinded, two-way, cross-over trial (ClinicalTrials.gov NCT01981395) with 32 additional volunteers who received either 150 mg fenobam or placebo and were then exposed to the heat/capsaicin model of cutaneous sensitization (Refs. 3,4,5,6), which combines heat stimulation with topical low dose capsaicin applied to the surface of the forearm to generate reversible pain and sensory changes associated with peripheral and central sensitization. During the cross-over study session subjects received the experimental treatment they had not received previously. Changes in mood/affect and cognitive function of subjects following fenobam administration were also evaluated using the Letter and Number Sequencing Assessment and the Abbreviated Positive and Negative Affect Scale and Brief State Anxiety Measure (Ref. 7).

Results and Major Findings: Fenobam reaches peak plasma concentration between 2 and 5 hours after oral administration with pronounced inter-individual differences. Side effects included mild headache, metallic taste, nausea, and mild fatigue. The reproducibility of cutaneous sensitization with the heat capsaicin model was verified and observations of the effects of fenobam on central sensitization, mood/affect, and cognitive function were performed.

Conclusion: Oral fenobam administration in human subjects demonstrates variable, but dose-dependent plasma concentrations without significant clinical side effects. The effects of fenobam on a human model of central sensitization were also tested in order to evaluate the analgesic efficacy of mGlu5 negative allosteric modulators in humans.

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Poster Sessions

Clin Basic Pain 38 (38)
Quantitative Cry Acoustics for Measurement of Pain in Neonates

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One of the greatest challenges to providing effective pain management in neonates remains the reliable identification of neonatal pain (1, 2). Pharmacological under treatment and overtreatment of pain both have potential adverse effects. Infant crying provides a potential source of valuable communication from infants about their experiences. However, published studies suggest that distinguishing cries resulting from painful versus non-painful stimuli is extremely difficult for the human ear (3, 4). This study sought to develop a reliable algorithm for objectively quantifying pain-related cry acoustics based on bedside recordings of infants undergoing routine painful procedures, and to validate this algorithm using brain Event-Related Potential (ERP) methodology as an objective index of neonatal somatosensory processing. We hypothesized that cry acoustics can reliably distinguish crying associated with painful stimuli such as a heel lance from cries in response to non-painful tactile stimuli.

To test our hypothesis, we conducted a prospective observational study of 54 healthy full-term newborns. We recorded and analyzed cries elicited in response to a series of standardized stimuli, including 50 very brief room temperature air puffs applied at randomly varying intervals, a 2-second cold air puff, and a heel lance clinically required for blood sampling. Acoustical recordings were obtained from each participant using a portable high-quality digital field recorder with a unidirectional external microphone. Acoustical recordings were edited using Audacity to remove any identifying information and background noises. Cry signals which were comprised of a mixture of voiced, unvoiced, and silent intervals were then analyzed in Matlab. Seventy nine acoustical features were extracted from the cry samples for analysis. These parameters were selected to adequately characterize glottal airflow, resonance of the vocal tract, amplitude and energy distribution of the cry signal, and patterns of phonation, hyperphonation, disphonation, and silence. Cortical somatosensory processing was also measured through ERP recordings simultaneously obtained during each stimulus.

Between-subject analyses of the acoustical parameters of painful heel lance cries vs. cold stimulus cries (total n=40) revealed 4 individual acoustical features that significantly discriminated between these stimuli ($p<0.05$). An additional 5 acoustical features showed similar non-significant trends ($p<0.10$). A linear classification algorithm including 10 acoustical features was derived in a random 60% subsample of cries using bootstrapping methods, accurately identifying the painful stimulus with sensitivity=0.87 and specificity=0.74. This algorithm replicated well in the remaining 40% of the sample. To further validate these findings, we will report on relationships between cry acoustic features, stimulus conditions, and ERP data reflecting cortical somatosensory processing of the stimuli. These results suggest it may be feasible to use cry acoustics to identify neonatal pain.

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Poster Sessions

Clin Basic Pain 39 (46)

Inconsistency in Reporting Pain Intensity Scores and Functional Activity Levels in Patients with Chronic Low Back Pain

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Introduction: Pain intensity scales provide the simplest and most commonly used approach to quantifying pain. While these remain the generally accepted assessment paradigm, and while the numeric pain rating score is a highly subjective entity, we nevertheless rely on it, and use it to make judgments about effectiveness of the treatments and/or procedures that we provide on behalf of our patients. Misinterpretation of pain complaints can lead practitioners to underestimate or overestimate the patient's medical condition, thus misguiding them in providing unintended or unindicated therapies. The purpose of this study was to analyze how the numeric rating pain scores given by patients with low back pain correlate with their functional activity levels.

Methods: After IRB approval, we included consecutive 100 patients with radicular low back pain and followed them for one year. All patients were asked to complete pain scores on an 11-point numeric rating scale (NRS) from 0 to 10 both at rest and during movement, as well as an Oswestry Disability Index (ODI) questionnaire, and to do so 10 times during a 12-month period. The ODI questionnaire consists of 6 multiple choice questions targeting a patient's activities and physical limitations due to pain plus 4 questions targeting a patient's ability to manage stationary everyday duties (sitting, standing, and sleeping). Statistical analysis was performed by using SPSS Software version 20 (IBM Corporation, Armonk, NY).

Results: Patients included in the study ranged in age from 24 to 78 years old (average 48.85±14); 56% women and 44% men. The average duration of low back pain was 14±22 months prior to joining the study. Differences between ODI and pain scores in the range -10% to +10% were considered "normal"; between 11% and 30% as mild, between 31% and 50% as moderate; and severe if differences were more than 50%.

Our data showed that pain scores at rest correlate well with ODI in 65% of patients. In 30% of patients mild discrepancies were present (negative in 21% and positive in 9%), 4% of patients had moderate and 1% severe discrepancies. "Negative discrepancy" means that patients graded their pain scores much higher than their functional ability tested, and most likely exaggerated their pain. "Positive discrepancy" means that patients graded their pain scores much lower than their functional ability, and most likely underrated their pain. Comparisons between ODI and pain scores during movement showed a normal correlation in only 39% of patients. Mild discrepancies were present in 40% of patients (negative in 37% and positive in 3%); moderate in 13% (all negative); and severe in 5% (all negative) of patients. A very high percentage of patients (55%) unknowingly exaggerated their pain during movement. Inconsistencies were equal in male and female patients ($p=0.606$ and $p=0.928$). Our results showed that there was a negative correlation between patients' satisfaction and the degree of inconsistency in reporting pain scores. Furthermore, patients talking opioids showed more discrepancies in reporting pain intensity scores than did patients taking non-opioid analgesics or not taking medications for LBP ($p=0.038$). There was a highly statistically significant correlation between morphine equivalents doses and the level of discrepancy ($p<0.0001$).

Conclusion: By assessing the inconsistency in reporting pain intensity scores and functional activity level, and showing a direct correlation with patients' satisfaction we have emphasized how important it is to educate patients regarding the necessity to accurately report their pain level using a numeric rating scale. We also must identify other parameters in defining our patients' chronic pain conditions, such as functionality scales, quality of life questionnaires, etc., and should move away from an overly simplistic subjective rating scale.

Poster Sessions

Clin Basic Pain 40 (47)

Mesenchymal Stem Cell Transplantation Reduces Chronic Neuropathic Pain and Opioid-Induced Hyperalgesia in Rats

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Introduction: Chronic pain afflicts 116 million Americans. Opioid therapy is a cornerstone of pain management. Chronic pain due to lesion or disease of the somatosensory nervous system is defined as neuropathic pain which is one of the most difficult forms of pain to treat. Chronic opioid therapy is often associated with increased sensitivity to pain, a phenomenon frequently referred to as opioid-induced hyperalgesia. Both neuropathic pain and opioid-induced hyperalgesia cause incredible human suffering and societal burden and are clinical challenges to patients and clinician alike. What is in common between these two pathological conditions is that both are associated with neuroinflammation in the central nervous system. There is a need for more effective and safe therapies for these chronic pain conditions. We aimed to develop a novel and effective therapy and tested the hypothesis that transplantation of mesenchymal stem cells (MSCs) into the intrathecal space surrounding the spinal cord reduces neuropathic pain due to chronic constriction injury (CCI) of the sciatic nerve or hyperalgesia consequent to repeated daily morphine injections in rats.

Methods: With approval by the Cleveland Clinic IACUC, we conducted this study in four groups of rats. Two groups of rats with neuropathic pain consequent to CCI of the sciatic nerve were treated with either intrathecal MSCs transplantation or PBS injection as control. Other two groups of rats with hyperalgesia induced by repeated daily morphine injections were treated with either intrathecal MSCs transplantation or PBS injection. We compared the withdrawal thresholds of the hindpaws in response to mechanical and thermal stimuli to determine the pain behavior in these groups of rats. In addition, the effects on microglial activation by MSC transplantation and co-culture of microglia with MSCs were further determined by flow cytometry and immunohistochemistry.

Results: We found that the withdrawal thresholds were significantly and consistently higher in the groups treated with MSC transplantation compared to the control groups. The MSC groups exhibited a remarkable reversal of hyperalgesia induced either by chronic constriction injury or by repeated daily morphine injections, indicating a strong anti-hyperalgesia effect of MSCs. MSCs also decreased the level of microglial activation induced by CCI of the sciatic nerve in vivo or induced by lipopolysaccharide stimulation in vitro.

Conclusion: We concluded that MSCs have a remarkable anti-hyperalgesia effect, likely medicated by the anti-inflammatory effects of MSCs. MSC transplantation may emerge as an innovative, safe, and efficacious therapy to treat both neuropathic pain and opioid-induced hyperalgesia.

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Poster Sessions

Clin Basic Pain 41 (51)

Structure-Based Screening of Human Glycine Receptor Potentiators as Novel Analgesics for the Treatment of Chronic Pain

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Introduction: We recently solved the high-resolution NMR structures of the human glycine receptor (hGlyR) transmembrane (TM) domain (1) and discovered a novel positive allosteric modulator (PAM) binding site in the third TM domain of the α1 and α3 subunits of hGlyR (2, 3). We also showed that the binding of Δ9-tetrahydrocannabinol (THC), the main active ingredient in marijuana, to GlyR at this site mediates marijuana's analgesic action independent of its psychoactive effects (2, 3). This finding reveals an exciting possibility of discovering other novel analgesic drugs having specific actions on hGlyR without the psychoactive side effects, thereby offering new hopes to address the prevalent problem of prescription drug dependence and abuse.

Methods: Starting with the experimentally determined high-resolution hGlyR TM structures (PDB ID: 2M6I) as a template, we generated a large ensemble of structure clusters using all-atom molecular dynamics simulations in 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) lipid bilayers with and without cholesterols. These clusters were used to screen and rank the DrugBank database of 1549 FDA-approved drugs for their affinities to the specific cannabinoid binding site the third TM domain of hGlyR. The leading hits from the screening were selected for functional measurements in Xenopus laevis oocytes expressing hGlyR-α1 using electrophysiology. A negative control, which is a known PAM for homologous receptors but did not rank highly in virtual screening for hGlyR, was also tested.

Results and Major Findings: We found that lipids form substantial portion of the THC binding site in hGlyR and that lipid composition strongly affects the results of the virtual screening. The presence of cholesterols did not greatly change the tertiary structure of hGlyR but significantly altered the quaternary structure of the receptor. Several major conformational clusters could be identified. Screening the 1549 FDA-approved drugs against these structure clusters in the presence of lipids showed that most hGlyR TM domain structures bound no more than ~25 compounds, as defined by a predicted binding Kd < 1 μM. However, when lipids were excluded from the virtual screening, the number of hit compounds on individual structures increased significantly, suggesting a higher selectivity of binding when screened in the presence of lipids.

Fourteen compounds overlapped in the top 25 hits in the screening with and without lipids. All 14 compounds were filtered for Pan Assay Interference Compounds (PAINS) (4) and none were found to contain sub-structural features that would label them as "frequent hitters" in high throughput screens.

Four compounds ranking higher than THC in the virtual screening were selected for functional measurements and found to potently potentiate glycine-activated currents of hGlyR- α1. In contrast, the negative control did not affect hGlyR currents.

Conclusion: Our virtual screening with experimental hGlyR-α1 structures in different lipid environments is effective to identify FDA-approved drugs that potentiate hGlyRs. Among the identified drug candidates, about half are known or suspected to have an analgesic effect, although their mechanisms of action were unclear. The potentiation of hGlyRs provides a plausible mechanism for the analgesic effects of these drugs. We also identified candidates that are currently unknown to have an analgesic effect. The screening results provide a valuable basis to further study their abilities to potentiate hGlyRs and evaluate their analgesic action in vivo.

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Poster Sessions

Clin Basic Pain 42 (58)
Does Genetic Susceptibility to Persistent Post-Op Pain (Thermal Hyperalgesia) Correlate with Other Phenotypes in the Mouse Phenome Database (MPD)?

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Background: Thermal pain withdrawal after nerve injury is well accepted as a measure of experimental and clinical pain. We hypothesized that genetic susceptibility to a maladaptive response following nerve injury is due to common pathways that affect pain processing, perception, and neuropsychiatric responses (i.e., anxiety). In this study, we measured thermal hyperalgesia after nerve injury in 16 inbred mouse strains, by calculating the Persistent Pain Index (PPI). We calculated heritability and compared our PPI neurobehavior phenotype with datasets from other laboratories that measured pain and anxiety phenotypes in multiple inbred strains in the Jackson Laboratories Mouse Phenome Database (MPD).

Methods: Chronic construction injury (CCI) of sciatic nerve was used as a model of persistent post-operative pain. Briefly, the left sciatic nerve was exposed and 3 loose 6.0 silk ligatures were loosely placed around the dissected nerve. Baseline nociception and post-CCI thermal hyperalgesia were tested in each animal using a mobile infrared heat lamp device, positioned underneath the targeted hind paw. Baseline measurements were obtained two days prior to CCI surgery. Behavioral tests were performed at Baseline, Days 1, 7, 14 and 21 after CCI. The PPI was calculated as the area under the curve based on cumulative thermal measurements (Hargreaves) over 21 days. Strains of inbred mice with greater PPI are demonstrating less thermal hyperalgesia, as measured by minimal change in their withdrawal latency over time. Using the MPD, we compared our thermal PPI data with pain phenotype data from Mogil et al., (Pain 2002;97:75-86) and anxiety phenotype data from O'Leary et al.. (Behav Genet 2013;43:34-50), using Pearson coefficients.

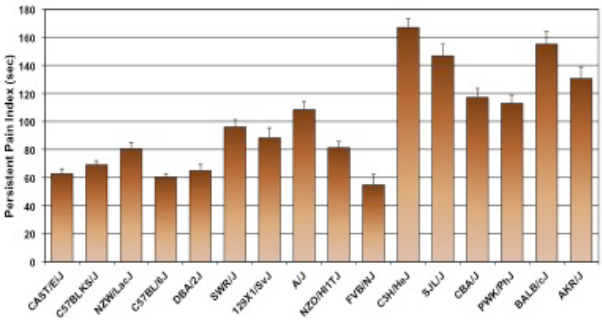

Figure 1. Susceptibility to thermal hyperalgesia after CCI in 16 inbred strains for mice calculated as the PPI.

Results: The PPI response of 16 inbred strains of mice is shown in Figure 1. Heritability estimates based on 16 strains for thermal hypersensitivity at Baseline and for PPI were calculated. We found a thermal PPI heritability of 75% and the calculation of effective factors on the order of 2.73 estimates the number of independently segregating genes with equivalent phenotypic effects that can account for the observed strain differences. Comparison with two datasets in the MPD showed that there was statistically significant Pearson coefficients for the following: 1) head dipping anxiety behavior (r=0.8560, P=0.0017), 2) thermal hyperalgesia after carrageenan hindpaw inflammation (r=0.814, P=0.023), and 3) von Frey neurosensory mechanical withdrawal (r=0.877, P=0.049).

Discussion: The thermal PPI is heritable and preliminary analysis indicates that thermal PPI after nerve injury correlates with several neurobehavior phenotypes in the MPD. These data suggest that common pathways of genetic susceptibility may explain cognitive and neurosensory behaviors.

Clin Manag 43 (2)

Predicting Operating Room Scheduling Error via Automated Anesthesia Information Management System (AIMS)

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Introduction: Improvements in operating room (OR) efficiency can have a major impact on hospital finances, staff and OR management. The aim of this study is to determine scheduling error in OR scheduled versus actual OR times and scheduling performance between surgical specialties in an acute academic tertiary care specialty hospital.

Methods: After local IRB approval, a review of the West Virginia University Hospital's (WVUH) Anesthesia Information Management System (AIMS) was conducted for all surgical procedures (n=44,503) scheduled over a period of 2 years (March 2012 through April 2014). After removal of study subject identifiers, the following data were extracted from the electronic medical record (EMR); (1) scheduled time when the patient was expected to enter the OR, (2) scheduled time when the patient was expected to leave the OR, (3) the actual time when the patient entered an OR, (4) the actual time when the patient left the OR, and (5) surgical case specialty. Scheduling error is defined as the paired difference between the actual and scheduled times. Surgical specialties examined included adult cardio-thoracic surgery, cardiology, chronic pain, organ procurement, otolaryngology (ENT), gastroenterology (GI), neurosurgery, obstetrics/gynecology (OB/Gyn), ophthalmology, oral surgery, orthopedic surgery, pediatric cardio-thoracic surgery, pediatric dentistry, plastic surgery, podiatry, pulmonology, general surgery, urology, and vascular surgery. Data was analyzed using paired t-tests, results reported as mean difference ± SD with 95% confidence intervals. A P value < 0.05 is considered significant.

Results: For all procedures and specialties, mean scheduled surgical duration was 101.38 ± 87.11 minutes compared to a mean actual surgical duration of 108.18 ± 102.27 minutes with a mean difference of 6.80 ± 52.83 minutes; $P < 0.001$. Further analysis by specialty revealed most specialties (79%) under estimated scheduled surgical times, where actual durations were higher than predicted scheduled durations, thus resulting in a consistent too high scheduling error (Table). Pediatric cardio-thoracic surgery had the highest mean scheduling error (36.11 ± 102.25 minutes, $P < 0.0001$) followed by neurosurgery (21.31 ± 88.40 minutes, $P < 0.0001$) and orthopedic surgery (16.56 ± 53.75 minutes, $P < 0.0001$). Only three specialties over estimated their scheduled surgical times, where actual durations were shorter than predicted scheduled durations, thus resulting in a consistent too low scheduling error. These specialties were pulmonology (-22.92 ± 42.85 minutes, $P < 0.0001$), organ procurement (-12.9 ± 135.1 minutes, $P = 0.11$), and podiatry (-5.53 ± 32.50 minutes, $P = 0.01$). The best scheduling specialty with the least mean scheduling error was urology (-0.28 ± 33.49 minutes, $P = 0.58$) followed by gastroenterology (0.95 ± 21.52 minutes, $P < 0.0001$). There was a significant correlation of 0.27 ($P < 0.001$) between surgical duration and prediction error supporting the idea that surgeries of longer duration tend to have higher mean prediction errors.

Conclusion: By utilizing AIMS to analyze surgical durations, we were able to detect overall scheduling errors and utilization inefficiencies within each surgical specialty, allowing for improved OR scheduling. This method led us to important management changes including the number of ORs to open each day, the allocation of surgeries to ORs, the sequence of surgeries within each OR, and start times for individual surgeons. Continued monitoring of OR inefficiencies and scheduling system performance will allow us to steadily improve OR utilization, enable better OR management, and improve patient care.

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Table. Scheduled surgical durations, actual surgical duration, and difference between both times

Specialty	Scheduled	Actual	Difference	P value	95% CI
Pediatric cardio-thoracic surgery (n=556)	180.55 ± 104.9	216.66 ± 153.96	36.11 ± 102.25	<0.0001	27.60-44.63
Neurosurgery (n=2278)	209.00 ± 97.88	230.31 ± 131.49	21.31 ± 88.40	<0.0001	17.68-24.94
Orthopedic surgery (n=7450)	111.04 ± 72.88	127.60 ± 92.65	16.56 ± 53.75	<0.0001	15.34-17.78
Adult cardio-thoracic surgery (n=1002)	241.95 ± 116.65	255.00 ± 143.19	13.05 ± 94.50	<0.0001	7.19-18.9
Oral surgery (n=328)	109.67 ± 59.8	122.70 ± 92.78	13.03 ± 68.88	0.0007	5.55-20.51
Cardiology (n=5)	142.00 ± 27.7	155.00 ± 49.50	13.00 ± 26.80	0.56	-20.28-46.28
Vascular surgery (n=1138)	147.68 ± 76.98	158.03 ± 100.58	10.35 ± 82.53	<0.0001	5.55-15.14
Plastic surgery (n=859)	188.50 ± 150.04	198.03 ± 155.42	9.53 ± 81.54	0.0006	4.07-14.99
Obstetrics/gynecology (n=2652)	102.50 ± 65.50	110.16 ± 72.53	7.66 ± 43.42	<0.0001	6.00-9.32
General surgery (n=5282)	119.72 ± 82.81	124.16 ± 98.35	4.43 ± 62.98	<0.0001	2.73-6.13
Pediatric dentistry (n=294)	130.31 ± 26.90	134.16 ± 45.68	3.85 ± 45.37	0.15	-1.36-9.06
Ophthalmology (n=4417)	56.65 ± 34.59	60.39 ± 44.15	3.74 ± 26.32	<0.0001	2.97-4.52
Otolaryngology (n=4713)	114.83 ± 97.27	116.84 ± 111.57	2.01 ± 52.17	0.008	0.53-3.52
Chronic pain (n=254)	33.38 ± 24.09	34.94 ± 29.87	1.56 ± 15.52	0.34	-0.37-3.48
Gastroenterology (n=8442)	46.82 ± 24.24	47.77 ± 26.04	0.95 ± 21.52	<0.0001	0.49-1.40
Urology (n=4431)	71.11 ± 71.79	70.83 ± 77.85	-0.28 ± 33.49	0.58	-1.27-0.70
Podiatry (n=233)	81.62 ± 37.48	76.09 ± 40.87	-5.53 ± 32.50	0.01	-9.72—1.33
Organ procurement (n=38)	298.95 ± 59.96	286.10 ± 121.80	-12.9 ± 135.1	0.11	-57.27-31.53
Pulmonology (n=131)	121.23 ± 44.18	98.31 ± 36.89	-22.92 ± 42.85	<0.0001	-30.32-15.50

Legend: red signifies overestimation of scheduled OR duration, green underestimation of scheduled OR duration

Poster Sessions

Clin Manag 44 (15)

Electronically Mediated Time-Out Reduces the Incidence of Wrong Surgery: An Intervention Observation Study

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Introduction: Nearly half of surgical "never" events resulting in indemnity payments in the United States result from "wrong surgeries" - a concept encompassing either a wrong procedure, wrong site, or surgery on the wrong person. Wrong surgery often results in patient death and is devastating to the care team. Wrong surgery incidence estimates range from 1:1129941 to as high as 1:50002 and may be on the rise. Checklist application3,4 has reduced the frequency of complications previously resulting injury and death and has been a requirement by the Joint Commission since 2003. However, checklists must be performed reliably to be effective, which, in turn, requires the care team to consistently achieve optimal performance. This is a potential vulnerability.

To create a technological backstop to team performance, we used automated process monitoring & process control, as well as forced function concepts to implement an electronic timeout checklist to reduce the wrong surgery rate.

Methods: We created an electronic timeout checklist mediated via the intraoperative nursing documentation module of our Vanderbilt Perioperative Information Management System (VPIMS). The questions are sequentially displayed to the entire care team on a large in-room monitor, interposed as a required documentation step between the "patient-in-OR" and "incision" events. System development costs were compared to the cost of a wrong surgery. Poisson approximation of the binomial probability was used to estimate the wrong surgery rate and compare this to wrong surgery rate estimates from observed performance reported in the literature. We used Clopper-Pearson (exact) 95% confidence interval for the observed wrong surgery rate.

Results: All 118,472 main campus OR cases between July 30, 2010 and February 28, 2013 were subject to the electronic time-out procedure. Total development costs were $34,000 and used existing hardware. In a de novo installation, the additional hardware cost would have been $2500 per OR.

The rate of time-out failure (where a time-out is either not performed or performed after procedure start) is between 1 per 140 (Bulka, et al, manuscript in prep) and 1 per 1250 (Vanderbilt University Medical Center, Center for Clinical Improvement, performance tracking data) cases. There was an extremely low documentation failure rate; failures were due to either a planned, documented second time-out or an accidental mouse click. Since implementation there have been no wrong surgeries (0 in 118,472 cases) in the Vanderbilt ORs (Clopper-Pearson 95%CI: 0.0 – 3.11 x 10-5 wrong surgeries per case). The CI does not encompass the expected rate of wrong surgery based on current national performance (1 wrong surgery per 23,600 cases, or 4.24 x 10-5 wrong surgeries per case).

Conclusion: Technology can be used to support and enforce a thoughtfully developed perioperative systems design element. After implementation of an electronically mediated hard-stop timeout before incision, no wrong surgeries occurred, both during the observation period nor afterwards. Despite limitations, the study suggests that the system reduced wrong surgeries in our environment beyond that expected based on chance alone, and the most conservative time return on investment estimate is approximately 2 years.

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Poster Sessions

Clin Manag 45 (23)
Implementation of a Novel Data Collection Tool in a Low and Middle-Income Country

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Background: Access to safe surgery and anesthesia are important contributors to global health. We have previously described the development of a nurse anesthetist training program under the direction of an anesthesiologist trained in the United States.[1] However, in order to characterize disparities in care and to create benchmarks to assess improvements in perioperative morbidity and mortality, it is vital to collect accurate and reliable perioperative data. Absence of electronic medical records and lack of reporting infrastructures in low and middle-income countries (LMIC) makes it challenging to know perioperative outcomes. Additionally, intermittent and unreliable Internet access prohibit the use of currently available online tools. To solve these problems, we developed a robust perioperative data collection tool and implemented it in Kenya to demonstrate feasibility.

Methods: We solicited input from healthcare providers in East African hospitals to drive tool development. Data fields include anesthesia provider training level, patient demographics, surgery performed, anesthetic details, use of the Safe Surgery Checklist, surgical Apgar score [2], and postoperative morbidity and mortality. The tool was created in REDCap (Research Data Capture software) [3]. It allows offline real-time data collection with subsequent automatic data transmission to central servers, whenever Internet connection is made. In June 2014, 89 East African non-physician anesthesia care providers participated in a conference in Kenya that covered principles of quality improvement, real-time data acquisition, data management, and professionalism. Thirty of these providers who work in either one of two urban or 15 rural Kenyan hospitals, were provided with laptops loaded with the REDCap data collection software. Data collection began on June 15, 2014.

Results and Major Findings: After IRB approval, data from the tertiary referral and training hospital are presented; IRB approval is pending for the other sites. There were 3,786 cases reported from June 15 – December 31, 2014 (Table 1). The majority, 97.1% were performed by Kenyan Registered Nurse Anesthetists, with 81.1% of these involving nurse anesthetist trainees. Almost all patients (95.9%) were ASA 1 or 2; patient demographics, type of anesthesia, and monitors used are shown in Table 1. There were two intraoperative deaths; cumulative mortality at 24hrs, 48hrs, and 7 days were 48 (1.3%), 53 (1.4%), and 62 (1.64%) patients, respectively.

Conclusion: To our knowledge, this is the first report of development and implementation of a real-time perioperative data collection tool in a LMIC that is granular enough to collect perioperative mortality rate (POMR) and key perioperative data affecting POMR. The tool is novel in that it can be implemented on commodity laptops and needs only intermittent internet connection for automated data uploads. Initial data from a tertiary referral hospital shows acceptable POMR. As data is collected from urban and rural Kenyan hospitals, we will be able to determine baseline perioperative outcomes in Kenya, which will be used to track the effects of education capacity building.

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Poster Sessions

Clin Manag 46 (63)
The Anesthesiologist as Operating Room Manager: Essential Part of the Comprehensive Care Model

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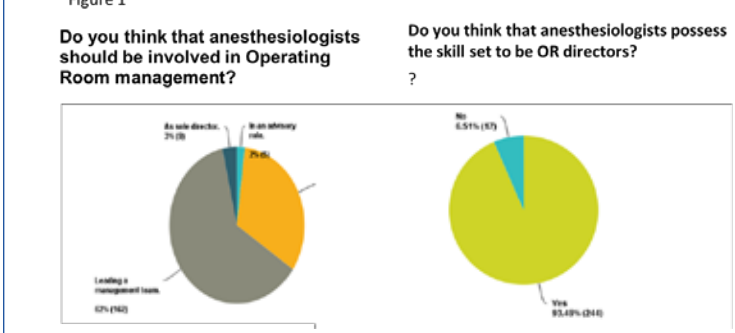
Introduction and General Purpose of the Study: Operating Room (OR) management is increasingly complex but integral to patient care. Traditionally a profit center, the OR accounts for 60% of hospital revenue and 40% of expenses. Numerous factors in the perioperative period can be optimized and standardized to improve patient outcome, surgeon satisfaction and resource utilization. A recent study demonstrated that cancelled surgeries can cost $4,500/case 1. Additionally, bundled payments for care improvement place further pressure on patient care optimization. Anesthesiologists have the clinical proficiency to serve as medical directors. OR directors must provide perioperative process leadership, a collaborative work ethic and enforce policies. A recent literature review, investigating OR management demonstrated a US focus on data-driven management and a European focus on OR management staffing2. We identified an underlying theme that rational OR management requires appropriate data collection for strategic and tactical decisions3. Learning how to obtain these data and act on them is not intuitive and requires education. We then asked: what is the current state of OR management, what metrics are measured, and should anesthesiologists be responsible for OR management? Additionally, we asked, what role does the Peri-operative Surgical Home (PSH) and Enhanced Recovery after Surgery (ERAS) play in OR management?

Figure 1



Methods: In November 2014 a survey was sent to anesthesiologist registrants at the PGA. Information sought consisted of basic demographic data, OR management at individual facilities, views on the role of the anesthesiologist in that position and use and familiarity with PSH/ERAS. Additional, data were collected by direct yes or no voting to the position of anesthesiologist as operating room managers at the conference.

Results and Major Findings: Of the 3069 anesthesiologist registrants 280 responded. An additional 70 voted directly. 52% stated that an anesthesiologist, 46% a nurse and 16% a surgeon were currently managing their OR. Only 18% noted team management. 71% were familiar with PSH/ERAS but only 34% used these models. Multiple metrics were measured at most facilities. At 2%, no metrics were measured. 60-40% of respondents thought that change in management techniques and fiscal decision making skills should be required of OR directors. However, only 34% of respondents had any management training and of that number only 8% had 1-2y of training. Manual voting plus the survey results resulted in a 94% positive response to the query about whether anesthesiologists possess the skills to be OR directors as either the team leader or as part of a team (Fig 1).

Conclusion: The majority of anesthesiologists believe that they are suited to be OR directors. Uniformity in OR metrics is lacking. Many different skill sets must be learned and should be incorporated into anesthesia training programs.

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Poster Sessions

Tox Cogn Dysfx 58 (56)
Low-Dose Isoflurane Induces Profound Cognitive Dysfunction in Rats

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Introduction: Post-operative delirium (POD) and post-operative cognitive dysfunction (POCD) are growing public health problems, particularly in elderly patients. Current preclinical research in POD and POCD using rodents is hampered by the lack of robust cognitive testing paradigms. In this study, we employed customized touchscreen-based cognitive testing chambers [1] to establish a dose-response relationship for isoflurane-induced cognitive dysfunction in rats.

Methods: Sixteen male Sprague-Dawley rats were used for these IACUC-approved experiments. Cognitive testing chambers (Fig. A) contained a food pellet dispenser, video camera, speaker, gas sampling port, a gas inlet for isoflurane (with air as carrier gas) and a gas outlet for scavenging. The correct image (Fig. B, left, marbles), and incorrect image (Fig. B, right, fan) were presented by touchscreen, and rats were trained to perform a two-choice visual discrimination task for a food reward over the course of several weeks. To maintain adequate motivation to perform the task, animals underwent food restriction with daily weight checks to ensure adequate caloric intake. During each session, rats were placed in the chamber and the two images were displayed. The placement of the images (left vs. right) was pseudo-random. When the correct image was touched, a sugar pellet was dispensed, and a 30 second timeout period was provided until the next trial. Each session lasted for 100 trials or one hour, whichever came first. Each rat was provided with one session per day, Monday-Friday, and the animals were fed ad lib after each session and also during weekends. Two criteria were used to assess cognitive performance: (1) number of trials completed per minute, and (2) overall accuracy (percent correct). The control group (n=8) underwent the same number of training and testing sessions as the experimental group (n=8). However, after the rats consistently reached 80% correct responses, the experimental group underwent surgical implantation of intracranial electrical stimulation electrodes and extradural EEG electrodes under isoflurane anesthesia. A minimum of 1 week was provided to recover from the procedure, with appropriate post-operative analgesia. During the 2 weeks when the experimental group underwent surgery and recovery, the control group was fed ad lib, and did not undergo cognitive testing. Both groups were then re-introduced to the chambers after the 2-week hiatus, to test whether surgery had a detrimental impact on cognitive performance. After 10 weeks of post-operative testing, standard training sessions were held Mon-Thurs, but on Fridays, the experimental group was exposed to isoflurane 1.5% x 45 minutes, and then placed in the cognitive testing chamber, which was held at a fixed dose of isoflurane ranging from 0-0.5%. Only one dose of isoflurane was tested per week.

Results: The performance of the control and experimental groups is shown in Figs. C and D. Overlapping 95% confidence intervals indicate that by 3 weeks post-surgery, the performance of the experimental group had recovered to baseline, and there were no significant differences between the control group and the experimental group.

Figs. E and F show performance levels of the experimental group without anesthesia (pooled data from Mon-Thurs) vs. continuous isoflurane inhalation (Friday only). In general, isoflurane at all doses (0.1-0.5%) reduced the number of trials per minute (Fig. E). Doses of isoflurane above 0.3% caused accuracy to decline precipitously (Fig F).

Conclusion: Cranial surgery by itself does not permanently affect cognitive performance on a two-choice visual discrimination task. However, continuous exposure to isoflurane profoundly impairs cognitive function at subanesthetic doses. Visual discrimination tasks presented with touchscreens may be useful to develop novel therapeutic strategies for POD and POCD in rodent models.

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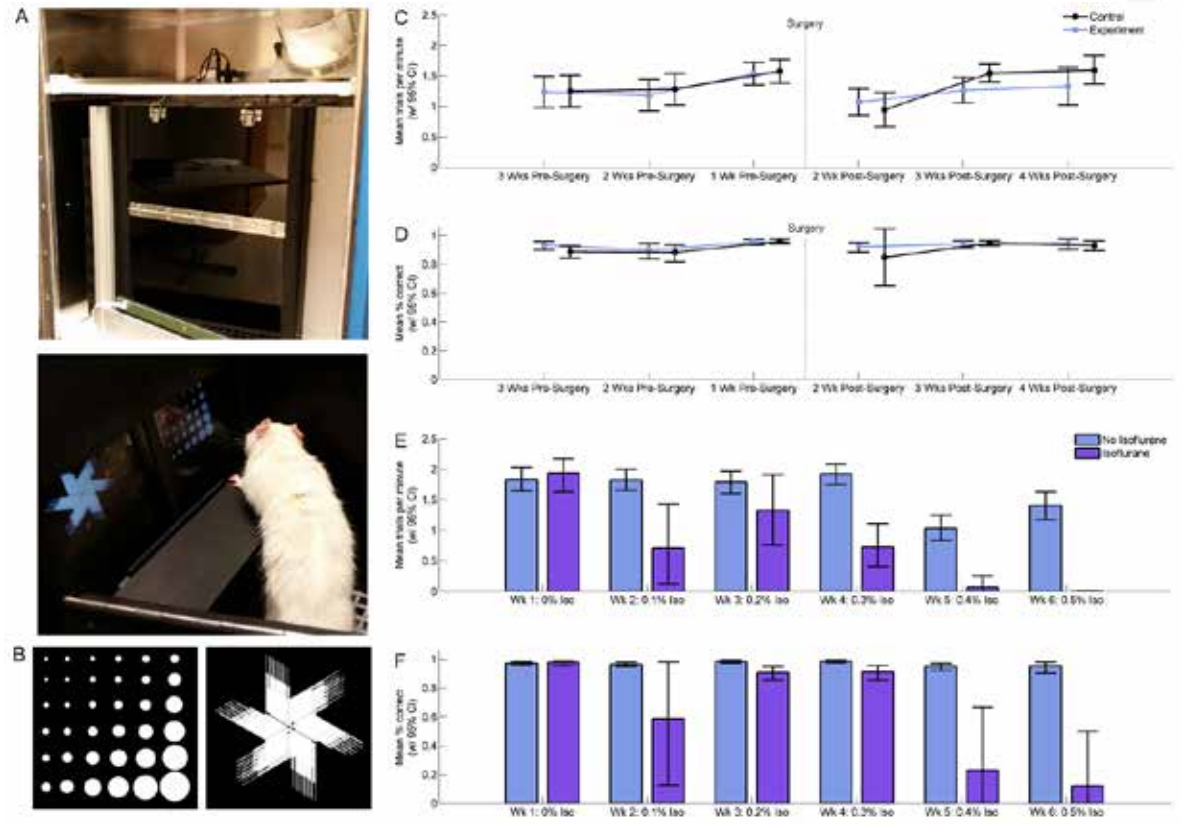
continued on page 110


A
B
C
Surgery
Control
Experiment
3 Wks Pre-Surgery
2 Wks Pre-Surgery
1 Wk Pre-Surgery
2 Wk Post-Surgery
3 Wks Post-Surgery
4 Wks Post-Surgery
D
Surgery
E
No Isoflurane
Isoflurane
Wk 1: 0% Iso
Wk 2: 0.1% Iso
Wk 3: 0.2% Iso
Wk 4: 0.3% Iso
Wk 5: 0.4% Iso
Wk 6: 0.5% Iso
F

Poster Sessions

Tox Cogn Dysfx 59 (60)

Neuronal Marker Growth in the Rat Thalamus During Development is Impeded by Anesthesia Exposure(s)

Rany Makaryus, MD[1], Tian Feng, BS[1], Hedok Lee, PhD[1], Mei Yu, BS[1]

[1]*Stony Brook Medicine, Stony Brook, New York*

Background: We are in the process of developing and refining a novel imaging approach for non-invasively identifying neurotoxicity in the live developing brain after anesthesia exposure(s). Specifically, our approach is focused on tracking N-acetyl aspartate (NAA), a neuronal marker, using quantitative in vivo proton magnetic resonance spectroscopy (1HMRS). We first demonstrated that the rate of rise in [NAA], reflecting normal brain growth in the developing brain is delayed after long exposure to sevoflurane anesthesia on post-natal day (PND) 7. We subsequently, proceeded to characterize changes in [NAA] that occur over the course of the first 4 weeks of the neonatal period. We hypothesized that [NAA] in the developing brain would continue to increase, even after anesthesia exposure; however, this would be at a slower pace particularly for those who received more than one exposure.

Figure 1 – [NAA] Changes After Anesthesia Exposure(s)

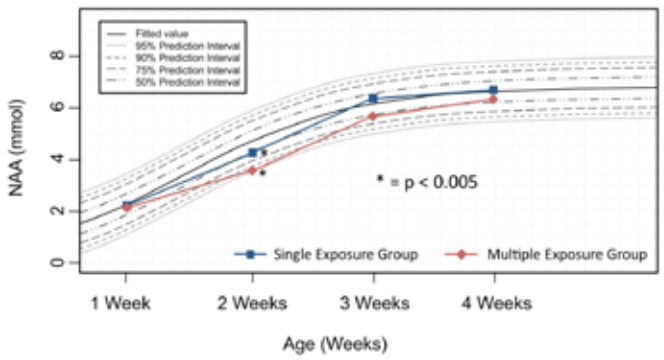


Figure 1 – Those animals who received multiple short exposures demonstrated a more significant difference in [NAA] on week 2 as compared to those who received a single long exposure. Comparing the 2 exposure groups on week 2 demonstrated a significant difference between them, with a p value of 0.01.

Methods: Using 1HMRS data from previously anesthesia naïve animals, we created a "growth chart" to reflect rising [NAA] in the rat thalamus over the course of 30 days starting from PND5. We used sigmoidal regression to quantify the association between [NAA] in the thalamus and the animal age. We then compared the normalized [NAA] to those derived from two groups of animals, namely a single long exposure group and a multiple short exposure group. The animals in the single long exposure group were exposed to 1MAC sevoflurane on PND7 for 5 hours, while those in the multiple short exposure group were exposed to 1MAC sevoflurane on PND5, 7, and 10 for only 2 hours each time. Each animal was scanned four times, at 1, 2, 3 and 4 weeks of age.

Results: The normalized curve for [NAA] growth in the thalamus during the neonatal period was created by taking [NAA] values as determined by 1HMRS from 62 previously anesthesia naïve animals. Using a sigmoidal regression model with an R2 of 0.91, we quantified the link between [NAA] in the thalamus and animal age. We then added 4 prediction intervals to the fitted value, thus creating 10 categories for tested NAA values. We proceeded to plot the average category for the animals in each of the two groups, at each of the 4 times tested, on the normalized NAA growth curve (Figure 1). We demonstrated that the single exposure group (n=10) exhibited a significant drop in [NAA] at 2 weeks (p=0.003), returning to near normal [NAA] by weeks 3 and 4. The repetitive short exposure group animals (n=6) demonstrated a more severe drop in their [NAA] at 2 weeks (p=0.002), followed by an inadequate recovery of their [NAA], remaining below the 75% prediction value until 4 weeks of age.

Conclusion: We demonstrated that, [NAA] in the thalamus continues to increase during development in normal rats. We also showed that independent of anesthesia exposure regimen (short, repetitive and/or long exposure) there is a measurable slow-down of [NAA] growth trajectories 1 week after anesthesia exposure. Furthermore, we also show that repetitive anesthesia exposures cause a longer lasting change in [NAA] (Figure 1). This correlates with clinical studies in children, demonstrating that those with 2 or more anesthetic exposures tend to have more learning and behavioral issues. Future studies should focus on correlation to behavioral findings.

Poster Sessions

Tox Cogn Dysfx 60 (76)

A Single Exposure to Isoflurane in Neonatal Mice Impairs Hippocampal Neuronal Development

Christy Gray, MD, PhD[1], Orion Furmanski, PhD[1], Cyrus Mintz, MD, PhD[1], Roger Johns, MD, PhD[1]

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Anesthetics are administered to millions of children yearly to enable them to undergo stressful procedures or surgeries. Epidemiological studies suggest an association between undergoing surgery with anesthesia in early childhood and the later development of learning disabilities. Various animal models, including rodents and non-human primates, demonstrate that early anesthetic exposure alone can have prolonged effects on learning and memory. These animal model systems are valuable in allowing us to explore the mechanisms through which anesthetics promote cognitive decline.

We previously exposed post-natal day 7 (PND 7) mice to 1 MAC of isoflurane for 4h, and we demonstrated that this results in prolonged alterations in learning and memory, with deficits both in long-term potentiation and in hippocampal-dependent learning that extend well beyond the anesthetic time course. We hypothesize that one mechanism by which this occurs is through a disruption in neuronal development, which may include an impact on neuronal proliferation, migration, maturation, and/or integration into appropriate neuronal circuitry. After exposing PND 7 rodents to a single dose of isoflurane (1 MAC, 4h), we probed for markers of neuronal development and differentiation, including Pax6, nestin, Tbr2, doublecortin, and NeuN. We now demonstrate that this single anesthetic exposure does not impact cell proliferation within the hippocampus, but impairs normal neuronal development. PND 7 mice exposed to isoflurane have a decrease in markers of neuronal development (i.e., Pax6 and Tbr2). Our data suggest that a single anesthetic exposure can delay neuronal development, which may have major consequences in the developing brain, where guidance cues and the extracellular environment may evolve over a limited time course.

Poster Sessions

Tox Cogn Dysfx 61 (22)

Sevoflurane Impairs Hippocampal Neuritic Extension and Increases Dendritic Spine Head F-Actin Concentration

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Introduction: Early postnatal anesthesia causes long-lasting learning and memory impairment in rodents [1], reviewed in [2], however, the underlying mechanisms remain largely unknown. Alterations in dendritic spine morphology caused by defects in Rho GTPase signaling are implicated in severe forms of cognitive dysfunction [3]. Activation of the Rho A/Rho kinase pathway by anesthetic isoflurane causes spine shrinkage and filopodial F-actin depolymerization [4]. We therefore set out to test a hypothesis that clinically relevant concentrations of the volatile anesthetic sevoflurane alters the morphology in developing mouse hippocampal neurons via Rho A/Rho kinase signaling pathway.

Methods: The animal protocol was approved by the Massachusetts General Hospital Standing Committee on the Use of Animals in Research and Teaching (Boston, Massachusetts). Mouse embryonic day 16 hippocampal neurons were cultured in Neurobasal medium for 7 days in vitro (DIV) prior to a single (4 hour) exposure to 3% sevoflurane in 95% air/5% CO2 or control condition (95% air/5% CO2). Control or sevoflurane-treated DIV 7 neuronal cultures were either immediately fixed in 4% paraformaldehyde or maintained for up to 7 additional days in culture prior to staining with Alexa Fluor555-Phalloidin (5 units/mL), specific for filamentous (F)-actin. Proximal and distal dendritic segments were randomly selected for analysis. Fluorescence images were acquired using a 100x NA 1.40 oil immersion objective. Spine head F-actin concentration was determined as the phalloidin-immunofluorescent intensity per unit area (μm2) [5].

Results: Sevoflurane induced acute significant decreases in mean dendritic filopodial length (n=49), as compared to control condition in DIV7 neurons (n=105; $P < 0.00001$).

Co-incubation with Y27632 (10 μM), a selective Rho kinase inhibitor, completely prevented the filopodia shrinkage consistent with a RhoA/Rho kinase-mediated mechanism of F-actin depolymerization in immature protrusions. Mean filopodial length recovered to 99% of control levels (on DIV14) in the sevoflurane-treated neurons suggesting that acute effect on immature filopodia was completely reversible. On the other hand, sevoflurane caused a 27% mean increase in head diameter (0.73 μm) in 50% of maturing spines compared to DIV7 control (n=10; 0.53 μm; P=0.02) or unaffected stubby or mushroom spines (0.46 μm; $P = 0.003$). Y27632 also significantly ($P < 0.001$) increased mean head diameter (0.73 μm) in 22/57 maturing spines. Mean head diameter in sevoflurane-treated maturing spines still significantly exceeded control (0.83 μm vs 0.61 μm, $P = 0.0001$, n= 52) on DIV 14; and mean head diameter (0.78 μm) in Y27632-treated neurons was also significantly (n= 13; $P = 0.05$) increased, suggesting that inhibiting local Rho kinase activation permits spine head enlargement. Finally, spine head F-actin concentration was significantly ($P = 0.047$) increased by 27% (on DIV14) in sevoflurane-treated vs. control neurons, and it was increased, but to a non-significant extent ($P = 0.12$) by Y27632.

Conclusion: These data demonstrated that sevoflurane mimicked the effects of Y27632 in causing spine head expansion and increased F-actin concentration. These data suggest that sevoflurane may inhibit RhoA/Rho kinase activity in the dynamic pool of membrane-associated spine head actin.

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Poster Sessions

Clin Int OC 66 (34)
Reducing Serious Intraoperative Peripheral Intravenous Catheter Infiltrations

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Introduction and General Purpose of the Study: Peripheral intravenous catheters (PIVs) are used ubiquitously in the perioperative setting and carry the potential for severe complications. These complications include infiltration of potentially caustic drugs or large volumes of fluid into the extravascular space. Infiltration can produce significant morbidity, potentially including the need for fasciotomy. An analysis of the American Society of Anesthesiologists closed claims database showed that a significant number of claims were associated with PIVs, and that more than half of those claims were the result of extravasation of fluid or drugs (1).

Methods: As a component of a process improvement project based on a concern raised related to PIV infiltration requiring fasciotomy, the Department of Anesthesiology created a new process to improve the safety of intraoperative PIVs. Based on previous reporting of improving team behavior using a stepwise video board during the time out process (2), we implemented documentation of PIV awareness during the preoperative "timeout" and documentation of PIV function by the in-room anesthesiology team member, in the anesthesiology information system (AIMS), every two hours. We then reviewed data from a multimodal non-routine event reporting system to compare the incidence of severe PIV infiltration, defined as infiltration requiring fasciotomy, before and after the implementation of the time out and documentation changes.

Results: The new timeout process including identification of the PIVs and verbalization of the plan for intraoperative monitoring of the PIVs was implemented on January 23, 2013. Since implementation, the PIV component of the timeout has been documented 128,593 times in the electronic medical record.

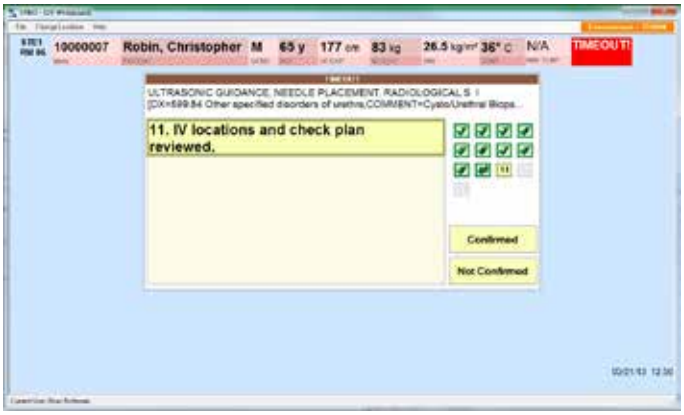

Fig 1. Implemented Whiteboard PIV check function, during timeout

Dates 2011-2012 - 2 PIV infiltrations resulting in fasciotomy (94 days between events)

Dates 2013-2014 – 0 PIV infiltrations resulting in fasciotomy (1,254 days since last event)

Conclusion: Team behavior can be modified through the use of electronic documentation tools. Implementation of a peripheral IV review and safety plan as part of a multidisciplinary preoperative time out and intraoperative record keeping system can reduce the incidence of severe PIV related complications. Since implementation, there have been no IV infiltrations which have resulted in fasciotomy. However, due to the rarity of this event, it is unclear if this process change resulted in the reduction of incidences observed.

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Clin Int OC 67 (45)
Randomized Pilot Trial of Tubes to Prevent Ventilator-Associated Pneumonia

Miriam M. Treggiari, MD, PhD, MPH[1], N. David Yanez, PhD[1], Michael Aziz, MD[1], Steven Deem, MD[2]

[1]Oregon Health & Science University, Portland, Oregon, [2]Swedish Medical Center, Seattle, Washington

Introduction and General Purpose of the Study: Ventilator-associated pneumonia (VAP) is a highly prevalent and expensive nosocomial infection that is largely related to instrumentation of the airway with an endotracheal tube (ETT), followed by microaspiration of contaminated secretions. Modification of the ETT design to reduce microaspiration and/or biofilm formation may play an important role in VAP prevention. However, there is insufficient evidence upon which to base strong recommendations regarding the use of modified ETT, and significant safety concerns remain regarding the use of these devices. We performed a pilot, randomized controlled trial comparing two new types of ETT, designed specifically to prevent VAP, with the standard ETT to test the feasibility of and inform planning for a large, pivotal randomized trial.

Methods: This study was conducted with IRB approval under exception from informed consent. We randomized in a blinded fashion patients undergoing emergency endotracheal intubation both out-of- and in-hospital to receive one of three different ETT types: 1) A polyurethane-cuffed tube (PUC-ETT); 2) A polyurethane-cuffed tube equipped with a port for continuous aspiration of subglottic secretions (PUC-CASS-ETT), and 3) A standard, polyvinylchloride-cuffed tube (PVC-ETT). In addition to investigate feasibility and safety, the study co-primary endpoints were tracheal bacterial colonization reaching a CFU count >106 and the incidence of invasively-diagnosed VAP.

Results and Major Findings: A total of 102 subjects were randomized and met eligibility criteria for enrollment in the study. Randomization procedures performed well and integrity of blinding at randomization was maintained. The majority of intubations occurred in the hospital setting (n = 77) and the remainder occurring in the field (n = 25). The frequency of ventilator associated events is shown in the table. Compared with the standard ETT, there were no significant differences in tracheal colonization for PUC-ETT (RR: 0.93; 95%CI: 0.45, 1.92) or for PUC-CASS-ETT (RR: 0.97; 95%CI: 0.49-1.93). There were no differences in the risk of invasively-diagnosed VAP (RR: 0.85; 95%CI: .21, 3.5 for PUC-ETT, and RR: 0.73; 95%CI: 0.18, 3.0 for PUC-CASS-ETT), or clinically-diagnosed VAP by either clinical signs or CXR criteria. We did not observe unexpected or serious adverse events.

Table: Frequency of Ventilator-Associated Events

Variable	PVC-ETT	PUC-ETT	PUC-CASS-ETT
	N = 33	N = 29	N = 34
Tracheal aspirate, n (%) (colony count ≥10^6 CFU/mL)	11 (33)	9 (31)	11 (32)
VAP criteria, n (%)			
Clinical signs	3 (9)	5 (17)	5 (15)
CXR	3 (9)	5 (17)	4 (12)
Invasive VAP, n (%)	4 (12)	3 (10)	3 (9)

PVC: polyvinylchloride cuff, PUC: polyurethane cuff, PUC-CASS polyurethane cuff with continuous aspiration of subglottic secretions, ETT: endotracheal tube, CFU: colony forming units: VAP: ventilator associated pneumonia. CXR: chest x-ray.

Conclusion: A randomized trial of ETTs inserted during emergency intubation for the prevention of VAP is feasible and did not appear to carry heightened safety concerns. These preliminary data did not suggest different patterns of tracheal colonization or occurrence of VAP between the study groups.

References

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Poster Sessions

Clin Int OC 68 (71)
Markers of Immune Suppression Following Severe Burn Injury

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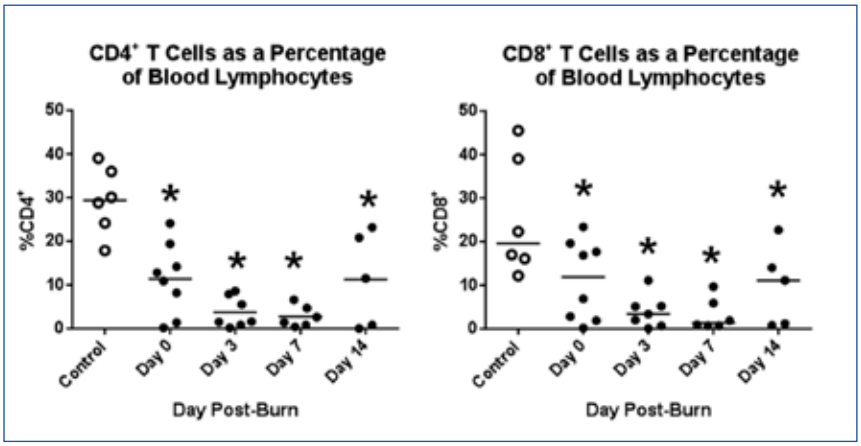
Background: Patients exhibit functional immunosuppression following severe burn injury, which may contribute to an increased incidence in infectious complications1. PD-1 and PD-L1 are cell surface receptors that, through their interaction on the surface of immune cells, negatively regulate the host immune response by decreasing the activity of lymphocytes. Increased expression of PD-13 and PD-L12 has been observed in other patient populations with an increased incidence of late infectious complications. A relationship has been demonstrated between peripheral blood T lymphocyte numbers and immune dysfunction in critically ill patients4. Our aim was to determine whether patients with large total surface area burns exhibit T cell dysfunction characterized by decreased peripheral blood T cell numbers and increased expression of PD-1 and PD-L1. This, along with altered cytokine production would suggest functional immunosuppression.



Methods: Cell surface expression of PD-1 and PD-L1 on T lymphocytes and inflammatory monocytes, respectively, was measured in 18 patients with severe burn injury (>30% TBSA) at four time points (Days 0, 3, 7, 14 post-burn) using flow cytometry. Age and sex matched control volunteers were used for comparison. Total CD4+ and CD8+ T cell and inflammatory monocyte numbers were also measured. Ex vivo expression and plasma concentrations of the cytokines IL-6 and IL-10 were determined.

Results: A time-dependent decrease in CD4+ and CD8+ T cell numbers was demonstrated in burn patients, with the nadir at D7 post-burn and a trend towards normalization at D14. Expression of PD-1 on T cells increased over time, achieving significant elevation by D14, compared to normal controls. The numbers of CD14+/CD16+ inflammatory monocytes were elevated relative to controls in most burn patients and their numbers and PD-L1 expression were significantly elevated on day 14 post-burn. Increased plasma concentrations of IL-6 (peak D3) and IL-10 (peak D0) were observed relative to controls.

Conclusion: Given the high rate of late infection patients with severe burn injury, the presence of a functionally immunosuppresed state is likely. Injury-induced alterations in expression of the T cell co-inhibitory receptor PD-1 and its ligand, PD-L1, on inflammatory monocytes in burn patients may contribute to this process. Furthermore, burn patients show a significant decrease in peripheral blood CD4+ and CD8+ T cells that remains evident out to 14 days post-injury. Our study outlines a time course for altered lymphocyte function in a population of severely burned patients. We posit that functional immunosuppresion is present as early as 3 days following severe burn injury.

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Poster Sessions

Clin Int OC 69 (78)
Blood Volumes Discarded With Surgical Sponges

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Introduction: When making estimates of intraoperative blood loss, the anesthesiologist must estimate the amount of blood contained within suction canisters, surgical sponges, surgical drapes, and on the operating room floor. Quantitative measurements of the blood contained within surgical sponges are rarely made. The objective of this study was to make quantitative measures of the volume of blood contained within surgical sponges at the end of common surgical procedures.

Methods: Prospective cohort study of the Hb content of surgical sponges. Consecutive cesearean section (C/S), abdominal (GI), hysterectomy, liver resections, and total hip replacement (ortho) surgeries were enrolled. Total blood volume contained within each sponge used during the surgical case was measured and totaled for the surgical case using a previously validated visual-algorithm system (1,2). Cases were grouped by type, and reported as mean, standard deviation (SD), median, 25th percentile, 75th percentile, and interquartile range (IQR).

Results: A total of 68 surgical cases were enrolled (30 C/S, 12 GI, 7 hysterectomy, 7 liver, 12 ortho). The mean volume of blood for c/s were 369mL, SD 198mL, median 312mL (245mL, 454mL, IQR 209mL). The mean volume of blood for GI cases were 205mL, SD 202mL, median 121mL (57mL, 287mL, IQR 231mL). The mean volume of blood for hysterectomies were 102mL, SD 62mL, median 112 (55mL, 144mL, IQR 89mL). The mean volume of blood for liver resections were 426mL, SD 275mL, median 460mL (229mL, 534mL, IQR 305mL). The mean volume of blood for total hip replacements were 84mL, SD 112mL, median 53mL (40mL, 65mL, IQR 25mL).

Conclusion: There is a significant amount of blood contained within surgical sponges at the end of surgery in many common surgical procedures. An accurate estimated blood loss for the surgery should include a measure of the blood contained within the surgical sponges removed from the field.

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Poster Sessions

Clin Int OC 77 (80)

Agreement Between Central Laboratory and Blood Gas Laboratory Sodium Concentrations - Do They Correlate for Therapeutic Decision Making?

Michael L. Ault, MD, FCCP, FCCM[1], Louanne M. Carabini, MD[1], Ntesi A. Asimi, MD[1], Eric M. Liotta, MD[1], Dhanesh K. Gupta, MD[1]

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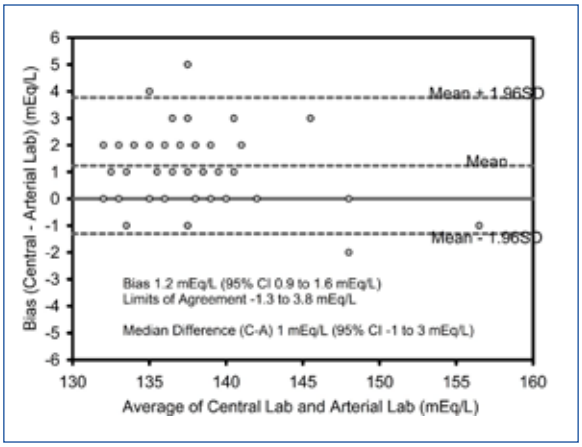
Background: Metabolic derangements in sodium concentrations are a common problem in critical care medicine. The timeliness, accuracy and reliability of sodium measurements is integral to patient care. The normal range of blood sodium concentration is 137-142mEq/L; however, there is no current gold standard methodology for measuring the total content of sodium in the blood. The most current United States Clinical Laboratory Improvement Amendment (US CLIA 2006) accepts a difference of 4mmol/L in sodium concentrations measured with ancillary testing methodologies such as a blood gas analyzer.(1,2) Arguably, this difference is clinically significant and would change management for patients with neurologic injury, sodium diathesis, or those undergoing treatment for acid base disorders. The source of this difference in reported concentrations has been attributed to several things including technologic methodology, arterial versus venous blood samples, whole blood analysis by blood gas analyzers versus serum samples in the central laboratory, travel time to the central laboratory, different brands of blood gas analyzers, and syringe composition with anticoagulants.(3) We hypothesize that with the use of dried lithium heparin blood gas syringes and proper sample collection, the difference in sodium concentration measurements between central laboratory analysis and the blood gas analyzers will be clinically insignificant.



Methods: This is a prospective observational study for Limits of Agreement analysis of laboratory methodologies for measuring sodium concentration. We included consecutive patients undergoing craniotomy, complex spine surgery, and medical management of cerebral edema or sodium diathesis over the course of a 2 month period from October to November, 2014. Simultaneous arterial samples were collected into a standard 3ml plastic blood gas syringe (at least 2mls of arterial blood; Edwards Lifesciences Marquest Aspirator Syringe containing 100units of dried lithium heparin) and a standard vacutainer tube (at least 5mls; Becton Dickson vacutainer containing PST Gel and 83 units lithium heparin). All of the data were tested for normality using the Shapiro-Wilk W test. Normally distributed data are presented as mean ± standard deviation, and these data were compared between groups using a paired t-test. Non-normally distributed data are presented as median (95% Confidence Interval), and these data were compared using the Wilcoxon Signed Rank Test. Categorical data are presented as number (percent) and compared using Fisher's exact test or Chi square test. A two-sided $P < 0.05$ was considered statistically significant. The agreement between the blood gas lab and the central lab was determined using limits of agreement analysis.

Results: Please see attached graph.

Conclusion: There was no significant clinical difference between laboratory methodologies. Results obtained via blood gas analysis laboratories are obtained more quickly. Due to the lack of analytic error, our results confirm the importance of minimizing errors that occur in the pre-analytic component of sample interrogation.

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Poster Sessions

Clin Int OC 78 (85)

The Extent of Cephalad Spread of Sensory Anesthesia Following a 5 ml Lidocaine 1.5% Test Dose Is Inversely Associated With 1 and 24 Hour Local Consumption After Uterine Artery Embolization

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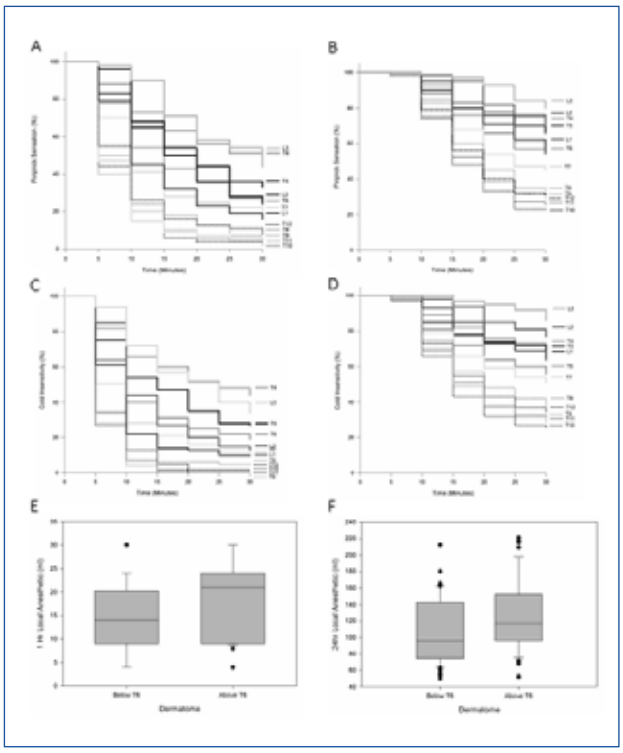
Background: Thoracic epidural analgesia is effective for pain management following lower abdominal surgery and may be useful in women undergoing uterine artery embolization. The importance of evaluating the spread of sensory blockade after a test dose of local anesthetic (LA) following thoracic epidural catheter placement has been evaluated. We investigated the relationship between the spread of sensory analgesia, hemodynamics and postoperative consumption of local anesthetic following a 5 ml test dose of lidocaine 1.5% after thoracic epidural catheter placement for uterine artery embolization.

Methods: Following IRB approval, written informed consent was obtained from 100 ASA I-III female patients (>18 y/o) undergoing uterine artery embolization. Subjects had thoracic epidural catheters placed using loss of resistance to air technique at the T10 to T11 vertebral interspace. Subjects then received a test dose of lidocaine 1.5% with epinephrine 1:200,000. Pinprick sensory evaluations and cold insensitivity were assessed every 5 minutes for thirty minutes for the dermatome levels between L3 to T4 by a blinded observer. The cephalad and caudad extent of analgesia, anesthesia, and cold discrimination were tested bilaterally in the mid-clavicular line. Absence of pinprick or cold prep was defined bilaterally analgesia. Arterial blood pressure and heart rate were recorded at baseline and at each study time. One and twenty-four hour local anesthetic consumption was recorded. The relationship between the upper level of sensory analgesia spread and LA consumption was evaluated using the Mann-Whitney test.



Results: Onset and complete analgesia to pinprick or cold stimulus is shown in Figure 1A-D. The 5 ml test dose injected in the thoracic epidural space results in a discernable (onset) sensory and cold analgesia after 5 minutes in 5 dermatomes in all the cases. Complete absence of sensory and cold response in the dermatomes was achieved within 10 minutes of the initial response. The test dose had similar temporal and spatial effect on the decreased response to pinprick and cold sensation although these stimulus are transmitted by different fibers. The maximum observed decrease in systolic and diastolic blood pressure was observed at 15 minutes and, when compared to the 30 minutes measurements, the drop was not significant beyond 5 minutes. Analgesia to pinprick above the T6 dermatome was associated with an increase in the consumption of LA in both the 1st and at 24 hours following surgery (P=0.02) (Figure 1E-F).

Discussion: An important finding of our study is that the extent of cephalad sensory analgesia spread following a 5ml test dose of 1.5% lidocaine was an independent predictor of the amount of local anesthetic solution required in the 1st 24 hours following uterine artery embolization. This may reflect the difference in the level of the catheter tip following placement, or may represent decreased paravertebral spread of local anesthetic in some patients following epidural drug administration.

References

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