Syllabus

AUA 61st Annual Meeting

April 24-26, 2014

Stanford University School of Medicine
Stanford, California

Stanford University School of Medicine designates this live activity for a maximum of *11.0 AMA PRA Category 1 Credit(s)™.*

A Continuing Medical Education Conference presented by the
Department of Anesthesia at the Stanford University School of Medicine

Sponsored by the Stanford University School of Medicine in collaboration with

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AUA
Association of University Anesthesiologists

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Table of Contents

AUA
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Welcome to the AUA 61st Annual Meeting from the Association of University Anesthesiologists

April 24, 2014

Welcome to Association of University Anesthesiologists 61st Annual Meeting on the beautiful campus of Stanford University! Over the next 3 days, we know you will find the exchange of new ideas and the opportunity to develop new methods for teaching anesthesia both rewarding and energizing. Our Annual Meeting Planning Committee, led by Dr. Ronald G. Pearl, Dr. Charles W. Emala, and Dr. David J. Murray, has developed a robust educational and scientific program including sessions focused on lung injury, remodeling and repair, the effectiveness of the classroom model, original investigations in the clinic and laboratory, and much more!

Annual Meeting highlights include:

SAB Program

The SAB Program (Part 1) and Moderated Poster Discussion Session on Thursday will highlight original research. On Saturday, SAB Program (Part 2) will finish what Part 1 started. The SAB Plenary Session, sponsored by *The American Journal of Physiology: Lung Cellular and Molecular Physiology,* will provide unique insight into lung injury, remodeling and repair. Be sure to visit the poster room to view all of the abstract submissions, covering a wide array of topics and featuring the 2014 abstract awards winners.

EAB Program

Education grant recipients will share their best practices for teaching anesthesia during EAB Program (Part 1). The EAB Program (Part 2) will draw from the results of an AUA Survey of members, answering the question "Is Face-to-Face Learning in a Classroom Model Obsolete?"

Host Program

The special Host Program panel, featuring Stanford University's President, Dr. John L. Hennessy, and Dr. Lloyd B. Minor, the Carl and Elizabeth Naumann Dean of the School of Medicine, and the President's Panel will explore Stanford University School of Medicine's unique programs and advancements in the practice of anesthesia.

Take advantage of even more time to interact with your colleagues during the many special events offered this year, including:

- **Resident Meet and Greet Reception,** Thursday, 5:00 pm – 8:00 pm
- **Welcome Reception,** Thursday, 6:00 pm – 8:00 pm
- **Stanford University School of Medicine Reception,** Friday, 6:30 pm – 8:00 pm
- **Social Event Reception and Dinner,** Saturday, 6:00 pm – 10:00 pm

We are confident that you will find this time together meaningful and gratifying while discovering all the Stanford University School of Medicine campus has to offer. We look forward to seeing you in Stanford!

Sincerely,

Lee A. Fleisher, MD
President, Association of University Anesthesiologists

Welcome to the AUA 61st Annual Meeting!

Welcome to Stanford!

The Stanford Department of Anesthesiology, Perioperative and Pain Medicine is pleased to host the 61st Annual Meeting of the Association of University Anesthesiologists. This meeting is the first since the affiliation of the AUA with the International Anesthesia Research Society, and we have been fortunate to combine the talents of Stanford, the AUA, and the IARS in planning this exciting meeting. The educational sessions will be held in the beautiful Li Ka Shing Center for Learning and Knowledge on the Stanford Medical School campus. The weather in Palo Alto should be beautiful, and attendees can choose to walk or take the shuttle for the mile trip between the headquarters hotel and the educational sessions. We have planned social events for all three evenings, with a reception at the Sheraton Hotel on Thursday night, a reception at the top of the Stanford football stadium on Friday night (including entertainment by the infamous Stanford Marching Band), and a gala dinner at the Arrillaga Alumni Center on campus on Saturday night. The Sheraton Hotel is adjacent to downtown Palo Alto, so you may enjoy strolling through the city after the receptions.

The AUA Scientific and Educational Advisory Boards have again created an innovative program which will share relevant cutting-edge information with the attendees. The President's Panel will focus on applications of Big Data. The Host Program will be highlighted by John Hennessey, the president of the university, speaking on "Silicon Valley and the Role of Stanford University." The other speakers will be David Kennedy, a Pulitzer Prize-winning historian, speaking on "Rethinking the Modern American Military," Sam Gambhir on "New Strategies for Early Cancer Detection" and Caitlin O'Connell-Rodwell on "The Secret Life of Elephants." As always, throughout the meeting there will be ample opportunities for discussion, networking, and poster viewing.

In the 22 years since Stanford last hosted the AUA meeting, the department, the medical school, and the university have all undergone dramatic change, resulting in a vibrant campus which continues to grow. The Planning Committee wishes to thank the many people who have collaborated to make this the best AUA meeting ever, and we hope you enjoy your visit to Stanford.

Ronald G. Pearl, M.D., Ph.D.
Edward J. Bertaccini, M.D.
Larry Chu, M.D., M.S.
David J. Clark, M.D., Ph.D.
Rona Giffard, M.D., Ph.D.
Alex Macario, M.D., M.B.A.
Sean Mackey, M.D., Ph.D.
Myer H. Rosenthal, M.D.
Lisa Wise-Faberowski, M.D.

General Information

The Sheraton Palo Alto Hotel is the Headquarters Hotel of the AUA 61st Annual Meeting. The Welcome Reception and Resident and Junior Faculty Meet and Greet Reception will both take place at the Sheraton Palo Alto. Shuttle buses will be available for attendees from the hotel throughout the day to the education sessions at the Li Ka Shing Center for Learning and Knowledge (LKSC) and evening social events at the Stanford Stadium Skydeck and Frances C. Arrillaga Alumni Center.

Headquarters Hotel • Sheraton Palo Alto Hotel

625 El Camino Real • Palo Alto, CA 94301
Phone: (800) 325-3535 • Fax: (650) 327-7362
www.starwoodhotels.com/sheraton

Education Program*
Paul Berg Hall, Li Ka Shing Center (LKSC) for Learning and Knowledge

Stanford University School of Medicine
291 Campus Drive • Stanford, CA 94305
Phone: (650) 721-2656
Please note the **Program Schedule,** included in your registration packet, will list the locations for all education sessions, food functions and special events.
*All education sessions will take place at the LKSC at Stanford University.

Registration

Registration Area

Your personalized registration materials will be available for pick up at the Registration Desk (locations noted below). Onsite registration is also welcome here.

Badge Pick-Up and Onsite Registration Hours and Location

Thursday, April 24	10:00 am – 11:30 am	Sheraton Hotel
	12:30 pm – 4:30 pm	LKSC at Stanford
	5:00 pm – 8:00 pm	Sheraton Hotel
Friday, April 25	6:30 am – 5:30 pm	LKSC at Stanford
Saturday, April 26	6:30 am – 5:00 pm	LKSC at Stanford

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. If you misplace your badge, please visit the Registration Desk for a replacement.

Services

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 61st Annual Meeting is business / business casual.

Internet Availability

Complimentary wireless internet is available in the LKSC at Stanford University School of Medicine. To access the wireless internet, please enter the username and password: AUAApril2014. Please no streaming or video downloads.

No Smoking

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 or require specific accommodations in order to fully participate in the Annual Meeting, 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:

Dean B. Andropoulos, M.D.
Texas Children's Hospital
Houston, Texas

Charles Emala, Sr., M.D.
Columbia University
New York, New York

Alina M. Grigore, M.D.
University of Maryland
Baltimore, Maryland

Max B. Kelz, M.D., Ph.D.
University of Pennsylvania
Philadelphia, Pennsylvania

Timothy E. Morey, M.D.
University of Florida
Gainesville, Florida

Peter Nagele, M.D.
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Dolores B. Njoku, M.D.
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AUA 61st Annual Meeting

Sponsored by Stanford University School of Medicine in
Collaboration with the Association of University Anesthesiologists
April 24 - 26, 2014
Li Ka Shing Center for Learning and Knowledge, Stanford, CA

Dear Course Participants,

On behalf of Course Directors Drs. Ronald Pearl, Charles Emala, David Murray, and Lee Fleisher, it is our pleasure to welcome you to the Stanford symposium, *AUA 61st Annual Meeting*, presented by the Department of Anesthesia at Stanford University School of Medicine.

The AUA Annual Meeting is designed for AUA Members / anesthesiologists in the clinical and laboratory setting who desire to improve development of anesthesiology teaching methods by engaging in an interchange of ideas as represented in this meeting.

Learning Objectives:

- Analyze new teaching methods that can be utilized in teaching anesthesiology learners, including simulation-based training for catheter insertion, computer-based visual learning, and simulation-based performance assessment
- Develop strategies to apply new teaching methods to various teaching situations
- Evaluate key elements of the Learning Management System
- Evaluate the utilization of lung repair to treat lung injury
- Evaluate the benefits of using stem cells for lung repair
- Analyze recent research findings in airway management, neurotoxicity, regional anesthesia, and other areas relating to their subspecialty interests
- Develop strategies for implementing these research findings in clinical practice

This course is designed to meet the educational needs of national and international audience of anesthesiologists in clinical and laboratory settings who desire to improve development of anesthesiology teaching methods by engaging in an interchange of ideas as represented in this meeting.

Take this opportunity to network with colleagues and to spend time with the faculty. Please contact us if we can be of assistance.

Course Coordinators
Irina Tokareva BSN, MAS, CPHQ
CME Curriculum and Outcomes Manager

Cassandra Alcazar
CME Conference Coordinator

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http://www.cme.stanford.edu/

GENERAL INFORMATION

Conference registration desk hours:	April 24, 2014	10:00am – 8:00pm
	April 25, 2014	6:30am – 5:30pm
	April 26, 2014	6:30am – 5:00pm

Instructions on How to Receive Credit: The ACCME requires that CME providers have a mechanism in place to verify physician participation in CME activities. For this conference, please be certain to **sign in each morning** at the Registration Desk.

CME Certificates: Participants will receive an email within one week of the course with a link to an online evaluation survey. **Please complete the survey within 2 weeks from receipt of this email.** Upon completion of the online evaluation survey and attesting to the number of hours of participation in the educational activity you are eligible to receive, a printable certificate will be generated for your records.

Commercial Support Acknowledgement: The Stanford University School of Medicine has received and has used undesignated funding from Pfizer, which supports a portion of general CME operations and the development of innovative CME activities; this course did not receive any activity specific funding.

Accreditation & Credit Designation: The Stanford University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Stanford University School of Medicine designates this live activity for a maximum of 11.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Security: We urge caution with regard to your personal belongings and your syllabus materials. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended in the meeting room during breaks.

Cultural and Linguistic Competency: California Assembly Bill 1195 requires continuing medical education activities with patient care components to include curriculum in the subjects of cultural and linguistic competency. It is the intent of the bill, which went into effect July 1, 2006, to encourage physicians and surgeons, CME providers in the State of California and the Accreditation Council for Continuing Medical Education to meet the cultural and linguistic concerns of a diverse patient population through appropriate professional development. The planners and speakers of this CME activity have been encouraged to address cultural issues relevant to their topic area. The Stanford University School of Medicine Multicultural Health Portal also contains many useful cultural and linguistic competency tools including culture guides, language access information and pertinent state and federal laws. You are encouraged to visit the portal: http://lane.stanford.edu/portals/cultural.html

FACULTY

*Faculty denoted with an * are participating in AMA PRA Category 1 Credit(s)™ eligible program sessions*

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Chair, AUA

Planners for Plenary Session: Lung Injury, Remodeling and Repair:

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Alice McNeal Chair & Vice Chair for Research,
Department of Anesthesiology
Director, Pulmonary Injury and Repair Center
School of Medicine, University of Alabama at Birmingham
Editor-in-Chief, *American Journal of Physiology – Lung Cellular and Molecular Physiology*

Y. S. Prakash, M.D., Ph.D.
Professor of Anesthesiology
Professor of Physiology
Mayo Clinic
Rochester, Minnesota

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5= Fees for Speakers' Bureaus
6= Contracted Research
7= Ownership Interest
8= Consulting Fees
9= Other

Planning Committee Disclosures

The following planning committee members have disclosed that they have **NO relevant financial relationship(s)** with any commercial interests related to the content of this educational activity:

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Charles W. Emala, M.D.
David J. Murray, M.D.
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Y.S. Prakash MD, PhD

Course Faculty, Moderators & Poster Presenter Disclosures

The following course faulty, moderators and poster presenters indicated having relevant financial relationship(s) with the following commercial interests related to the content of this educational activity:

Steven M. Frank MD	5 – Medtronic 6, 8 – Haemonetics
Roy Levit MD	7 – Bristol Myers Squib, Lilly, Merck
Edward R. Mariano MD, MAS	9 – I-FLOW/Kimberly Clark and B Braun, unrestricted educational program funding paid to institution
Tim Morey MD	7, 8 – Xhale, Inc.
Peter Nagele MD, MSc	6 – Roche Diagnostics, Siemens, Express Scripts
Charles N. Serhan PhD	2, 3, 7 – Resolvyx Pharma 3, 8 – Solutex 4 – Inflammation Research Foundation

The following course faulty, moderators and poster presenters indicated having **NO** relevant financial relationship(s) with any commercial interests related to the content of this educational activity:

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Frederic T. Billings MD, MSCI
Michael P. Bokoch MD, PhD
Zeljko J. Bosnjak PhD
Juan P. Cata MD
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George Gallos MD
Brice Gaudilliere PhD, MD
Kamrouz Ghadimi MD
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Yandong Jiang MD, PhD
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Roger A. Johns MD, MHS, PhD
Rachel M. Kacmar MD
Max Kelz MD, PhD
Evan D. Kharasch MD, PhD
Minjae Kim MD
Nebojsa Nick Knezevic MD, PhD
Ines P. Koerner MD, PhD
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Viji Kurup MD
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John W. Severinghaus MD
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Liza M. Weavind MBBCh, FCCM
Matthew B. Weinger MD, MS
Louise Wen MD
Zhongcong Xie MD, PhD
Gene T. Yocum MD
Lara N. Zador MD

Special Events

Special Events

Thursday, April 24
Resident and Junior Faculty Meet and Greet Reception
5:00 pm – 8:00 pm
Sheraton Palo Alto Hotel
(Included in the Resident/Fellow registration fee)
The Resident and Junior Faculty Meet and Greet Reception gives residents and fellows an opportunity to meet their peers and the AUA Council Members in an informal setting.

Welcome Reception
6:00 pm – 8:00 pm
Sheraton Palo Alto Hotel
Mingle with your colleagues and peers at a reception to kick off the AUA 61st Annual Meeting.

Friday, April 25
Stanford University School of Medicine Reception
6:30 pm – 8:00 pm
Stanford Stadium Skydeck, Stanford University
(601 Nelson Drive)
Join the Stanford University School of Medicine at a special reception for all attendees. Guests should enter the Stanford Stadium at Gate 4.

Saturday, April 26
Resident Luncheon
Noon – 1:30 pm
Li Ka Shing Center
(Included in the Resident/Fellow registration fee)
At the All Attendee 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 academic anesthesiology leaders.

Social Event Reception and Dinner
6:00 pm – 10:00 pm
Frances C. Arrillaga Alumni Center, Stanford University
(326 Galvez Street)
Join your friends and colleagues for a perfect ending to the 61st Annual Meeting. This Saturday event offers an opportunity to unwind and relax. This is an ideal opportunity to catch up with friends and colleagues and enjoy live jazz entertainment.

Restaurant Guide

Attendees may find dinner at a wide selection of restaurants near the Sheraton Palo Alto Hotel. The Stanford Shopping Center (660 Stanford Shopping Center) is located nearby and offers a wide range of shops and restaurants. Reservations are recommended.

Evvia
420 Emerson St.
650-326-0983
www.evvia.net

Joya Restaurant
339 University Ave.
650-853-9800
www.joyarestaurant.com

Nola
535 Ramona St.
650-328-2722
www.nolas.com

Oren's Hummus Shop
261 University Ave.
650-752-6492
www.orenshummus.com

Pampas
529 Alma St.
650-327-1323
www.pampaspaloalto.com

Patxi's Chicago Pizza
441 Emerson St.
650-473-9999
www.patxispizza.com

Reposado
236 Hamilton Ave.
650-833-3151
www.reposadorestaurant.com

Restaurant Soleil
(Inside the Westin Palo Alto)
675 El Camino Real
650-321-4422
www.starwoodhotels.com

Saint Michael's Alley
140 Homer Ave.
650-326-2530
www.stmikes.com

Sam's Chowder House
185 University Ave.
650-614-1177
www.samschowderhousepa.com

Sprout Café
168 University Ave.
650-323-7688
www.cafesprout.com

Thaiphoon Restaurant
543 Emerson St.
650-323-7700
www.thaiphoonpaloalto.com

Vero Ristorante Italiano
530 Bryant St.
650-325-8376
www.veroristorante.com

TOWN AND COUNTY VILLAGE RESTAURANTS
855 El Camino Real

Asian Box
650-391-9305
www.asianbox.com

Calafia Café
650-322-9200
www.calafiapaloalto.com

Gott's Roadside
650-326-1000
www.gotts.com

Howie's Artisan Pizza
650-327-4992
www.howiesartisanpizza.com

Kirk's Steakburgers
650-326-6159
www.kirks-steakburgers.com

Lulu's Town and Country Village
650-327-8226
www.lulusmexicanfood.com

Mayfield Bakery & Café
650-853-9200
www.mayfieldbakery.com

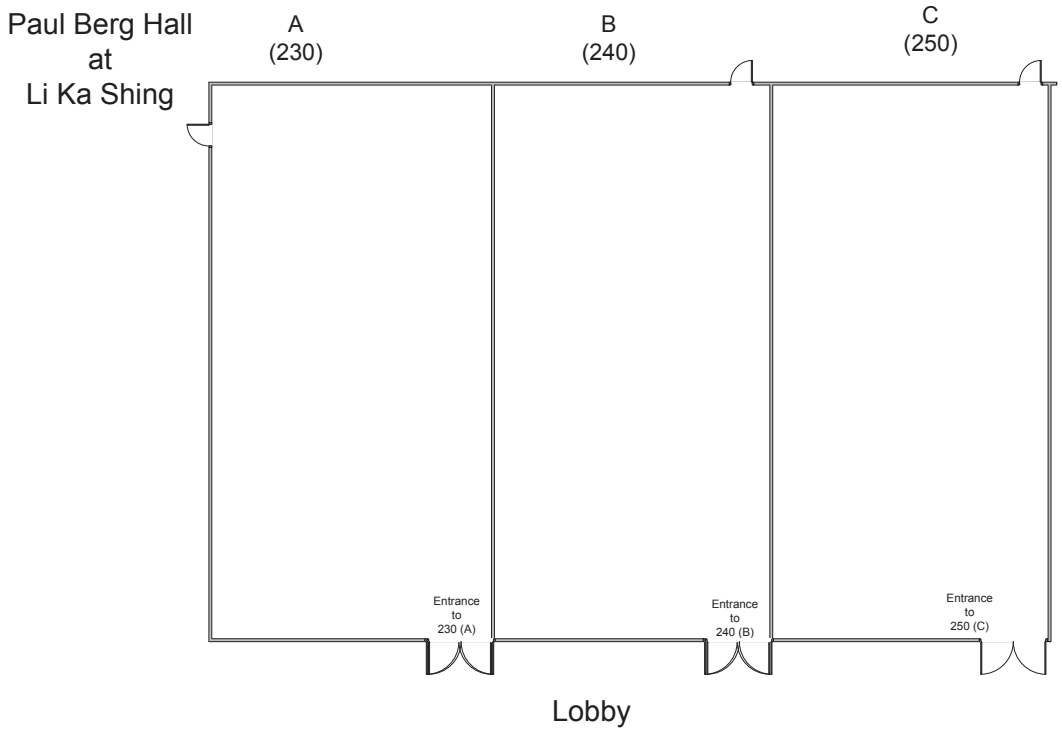
Scott's of Palo Alto
650-323-1555
www.scottsseafoodpa.com

San Francisco International Airport and San Jose International Airport

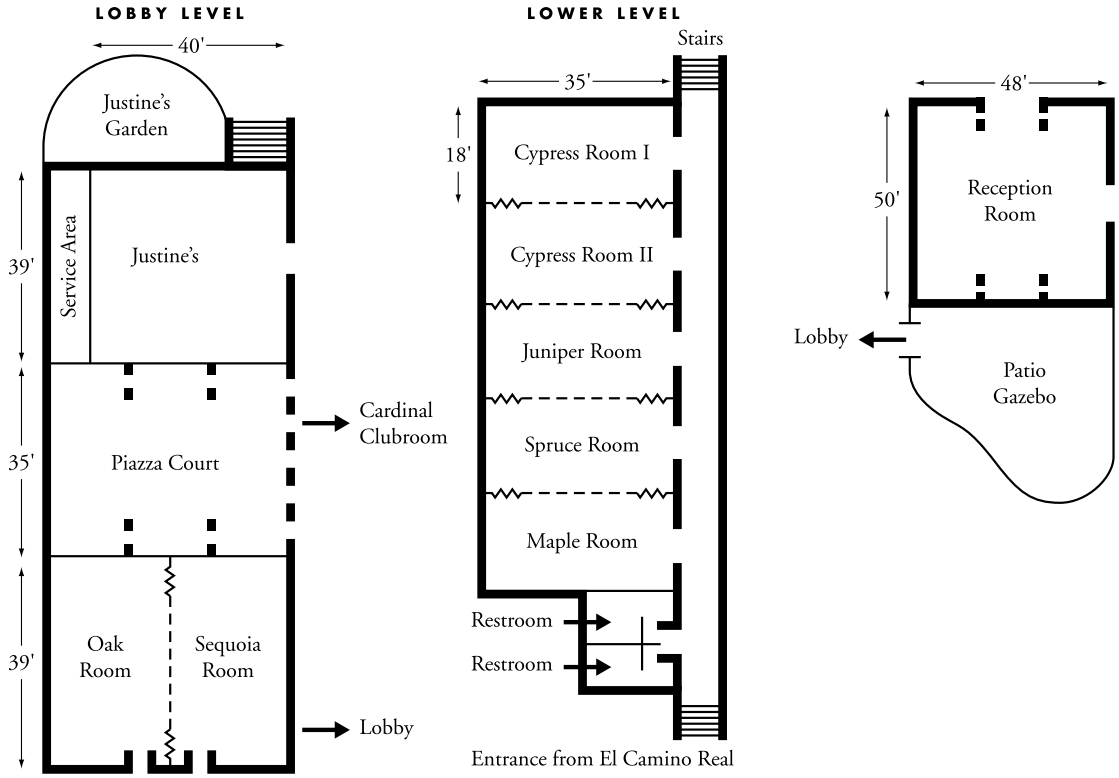
The Sheraton Palo Alto Hotel is located 17 miles from the San Francisco International Airport and 14 miles from the San Jose International Airport. The estimated taxi fare from San Jose International Airport is $40-$56. The estimated taxi fare from the San Francisco International Airport is $96. Not all taxis accept credit cards, so please ask in advance to avoid confusion.

Floor Plans

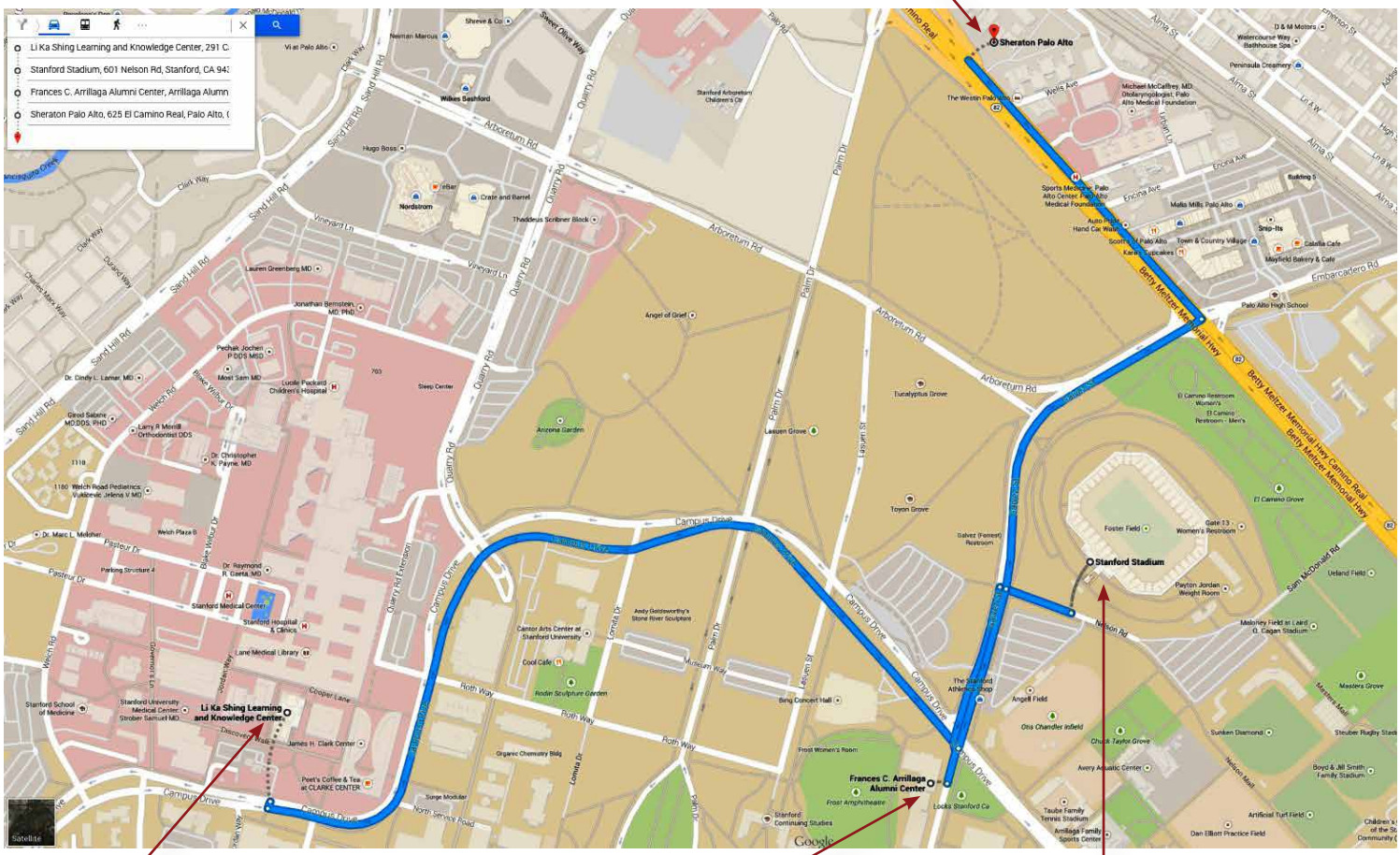
Li Ka Shing Center for Learning and Knowledge



Sheraton Palo Alto Hotel



Stanford University Map

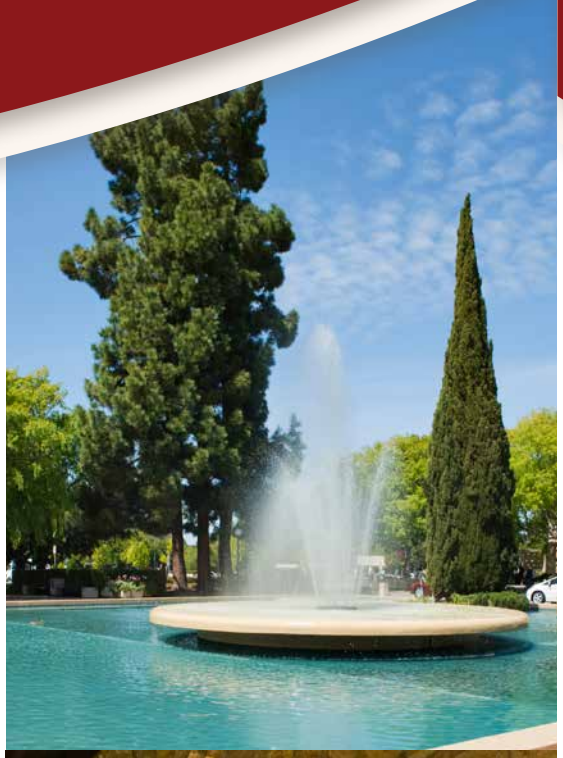


Program Schedule

*ONLY agenda items denoted with an * are eligible for AMA PRA Category 1 Credit(s)™*

Thursday, April 24, 2014

10:00 am – 11:30 am	**Registration – Sheraton**
12:30 pm – 4:30 pm	**Registration** – Li Ka Shing Center for Learning and Knowledge (LKSC), Stanford University School of Medicine
1:00 pm – 1:15 pm	**Introduction and Welcome to the 61st Annual Meeting – LKSC** Ronald G. Pearl, M.D., Ph.D.
1:15 pm – 1:20 pm*	**SAB Program Introduction** Charles W. Emala, M.D.
1:20 pm – 3:00 pm*	**SAB Oral Session (Part 1)**
Junior Faculty Award	**Inflammation Increases Brain Sensitivity to General Anesthetics** Sinziana Avramescu, MD, PhD, FRCPC, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
	Increased Gaba-B Receptor Inhibition Contributes to Anesthetic-Induced Depression of Synapses Bruce M. Maciver, MSc, PhD, Stanford University, Stanford, California
Resident Travel Award	**Genetic Deletion of the $GABA_A$ ∝4 Subunit Leads to Increased Airway Resistance and Inflammation** Gene T. Yocum, MD, Columbia University, New York, New York
	Pediatric Delirium in Infants and Preschool-Aged Children: Validation of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU) Heidi A.B. Smith, MD, MSCI, Vanderbilt University, Nashville, Tennessee
Margaret Wood Resident Research Award	**Postoperative Dementia: Role of Anesthesia and APOE4** Katie J. Schenning, MD, MPH, Oregon Health & Science University, Portland, Oregon
	Propofol Infusion Impairs Complex 1 activity in Human Muscle David M. Polaner, MD, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado
	Pharmacogenetic Determinants of Interindividual Variability in Methadone Metabolism and Disposition: The Role of Cytochrome P4502B6 (CYP2B6) Evan D. Kharasch, MD, PhD, Washington University in St. Louis, St. Louis, Missouri
	Single Nucleotide Polymorphism-Specific Regulation of Matrix Metalloproteinase-9 by Multiple miRNAs Targeting the Coding Exon Tyler Duellman, BS, University of Wisconsin-Madison, Madison, Wisconsin
3:00 pm – 4:30 pm*	**Moderated Poster Discussion Session**
5:00 pm – 8:00 pm	**Registration – Sheraton**
5:00 pm – 8:00 pm	**Resident Meet and Greet Reception** **Sheraton Palo Alto Hotel**
6:00 pm – 8:00 pm	**Welcome Reception – Sheraton**



Resident and Junior Faculty Meet and Greet Reception

Sheraton Palo Alto Hotel
Thursday, April 24, 2014
5:00 pm – 8:00 pm
(Included in the Resident/Fellow registration fee)

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

Program Schedule

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Friday, April 25, 2014

6:30 am – 5:30 pm — **Registration – LKSC**

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

8:15 am – 9:45 am* — **EAB Program (Part 1) – LKSC**
Research and Research Career Outcomes: Anesthesiology Education Grants
Moderator: Cathy Kuhn, M.D.
- **Introduction/Background FAER Education Grant**

Panelists:
- **An Efficacy Study of Simulation-Based Training on Practicing Anesthesiologists' Acquisition of Ultrasound-Guided Perineural Catheter Insertion Skills**
  Edward R. Mariano, M.D., M.A.S., Education Grant Recipient 2011
- **Regional Anesthesia Education in Infants: A Novel Computer Based Visual Learning Technique to Improve Confidence and Performance in Anesthesia Residents**
  Santhanam Suresh, M.D., Education Grant Recipient 2008
- **Teaching Residents to Question and Challenge: An Experiential Approach**
  May C. Pian-Smith, M.D., M.S., Education Grant Recipient 2004
- **Acute Care Skills in Anesthesia Practice: A Simulation-Based Performance Assessment**
  David J. Murray, M.D., Education Grant Recipient 2005

9:45 am – 10:15 am — **Break/Poster Viewing and Discussion – LKSC**

10:15 am – 11:45 am* — **EAB Program (Part 2)**
Evidence, Economics, and Outcomes in Educational Methodology: Is Face-to-Face Learning in a Classroom Model Obsolete?
- **Introduction, Background, AUA Survey Results**
  Randall M. Schell, M.D., MACM
- **Evidence and Economics**
  Manuel C. Pardo, Jr., M.D.
- **Practical Implementation and Learning Management Systems**
  Larry F. Chu, M.D., M.S.
- **Panel Question and Answer**

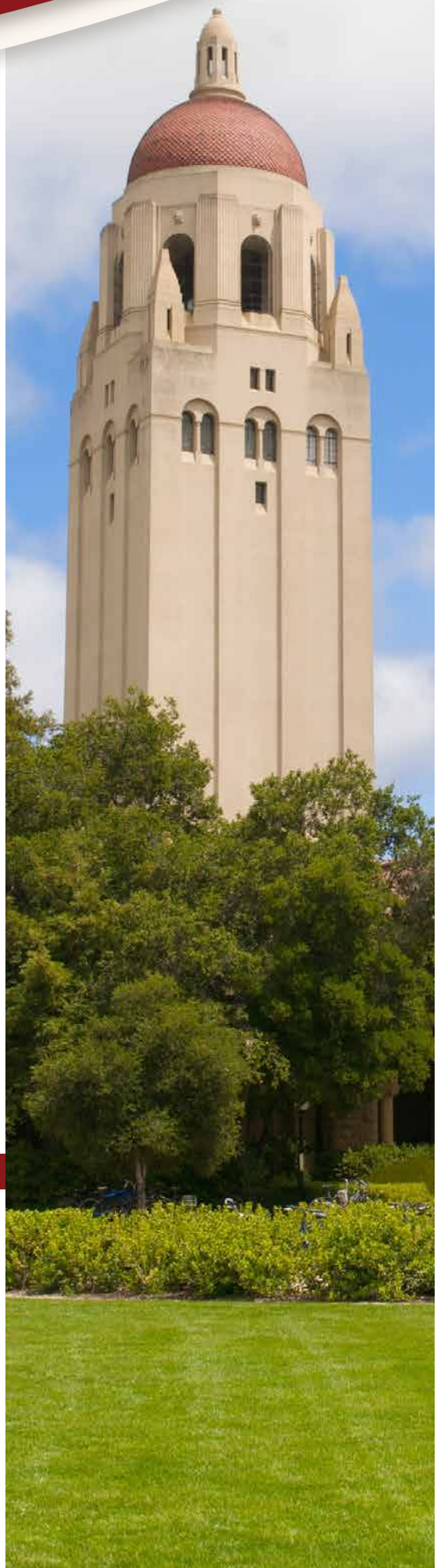
11:45 am – 1:00 pm — **Luncheon – LKSC**

1:00 pm – 3:00 pm* — **Plenary Session**
Lung Injury, Remodeling and Repair

Symposium Sponsor:
The American Journal of Physiology: *Lung Cellular and Molecular Physiology*

Symposium Organizing Committee:
Sadis Matalon, Ph.D., Dr.Sc. (Hon.)
Charles Emala, M.D.
Y. S. Prakash, M.D., Ph.D.

Symposium Moderator:
Sadis Matalon, Ph.D., Dr.Sc. (Hon.)



Program Schedule

*ONLY agenda items denoted with an * are eligible for AMA PRA Category 1 Credit(s)™*

Friday, April 25, 2014, continued

1:00 pm – 1:40 pm*	**Symposium Keynote Speaker: Novel Pro-Resolving Mediators & Mechanisms in Inflammation: Immunoresolvents** Prof. Charles N. Serhan, Ph.D.
1:40 pm – 2:00 pm*	**Speakers:** • **IL-8 and cAMP-stimulated Alveolar Epithelial Fluid Transport in Acute Lung Injury: Why did the Multicenter NIH/ARDS Network and BALTI-2 Trials with β2-adrenergic agonists Fail?** Brant M. Wagener, M.D., Ph.D.
2:00 pm – 2:20 pm*	• **Cell-Based Therapy for Acute Lung Injury** Jae Woo Lee, M.D.
2:20 pm – 2:40 pm*	• **Platelet function and ARDS pathogenesis: A path to prevention?** Daryl J. Kor, M.D.
2:40 pm – 3:00 pm*	• **Panel Discussion** Moderator: Sadis Matalon, Ph.D., Dr.Sc. (Hon.)
3:00 pm – 3:30 pm	**Break/Poster Viewing and Discussion – LKSC**
3:30 pm – 5:00 pm	**President's Panel** • **Genomics and Personalized Medicine** Michael Snyder, M.D., F.A.C.S. • **What Big Data Can Teach Us About Human Behavior** Jure Leskovec, B.Sc., Ph.D. • **Pitfalls in the Analysis of Published Data** John Ioannidis, M.D.
5:00 pm – 5:10 pm	**FAER Update** **Denham S. Ward, M.D., Ph.D.**
5:10 pm – 6:00 pm	**AUA Business Meeting – LKSC**
6:30 pm – 8:00 pm	**Stanford University School of Medicine Reception** **Stanford Stadium Skydeck**

Saturday, April 26, 2014

6:30 am – 5:00 pm	**Registration – LKSC**
7:00 am – 8:00 am	**Continental Breakfast – LKSC**
8:00 am – 12:00 pm	**Host Program – LKSC** Ronald G. Pearl, M.D., Ph.D., Lloyd B. Minor, M.D.
8:00 am – 8:10 am	**Host Program Introductions** Ronald G. Pearl, M.D., Ph.D.
8:20 am – 8:20 am	**Welcome from Stanford Medicine** Lloyd B. Minor, M.D.
8:20 am – 9:10 am	**Who Bleeds? Who Pays?** **Rethinking the Modern American Military** David M. Kennedy, Ph.D.
9:10 am – 10:00 am	**Recent Advances in Multi-Modality Molecular Imaging** Sanjiv Sam Gambhir M.D., Ph.D.
10:00 am – 10:30 am	**Break/Poster Viewing and Discussion**
10:30 am – 11:15 am	**The Secret Life of Elephants** Caitlin E. O'Connell-Rodwell, Ph.D.
	Host Program **Silicon Valley and the Role of Stanford University** John L. Hennessy, Ph.D.

Program Schedule

*ONLY agenda items denoted with an * are eligible for AMA PRA Category 1 Credit(s)™*

Saturday, April 26, 2014, continued

Noon – 1:30 pm	**All Attendee Luncheon – LKSC**
1:30 pm – 2:00 pm	**ASA President's Update** Jane Fitch, M.D.
2:00 pm – 2:10 pm*	**SAB Session #2 Introduction** Charles W. Emala, M.D.
2:10 pm – 3:30 pm*	**SAB Oral Session (Part 2)**
Junior Faculty Award	**Specialized Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline** Niccolo Terrando, BSc (hons), DIC, PhD, Karolinska Institute, Stockholm, Sweden
	The Usefulness of a Cognitive Screening Test in Predicting Postoperative Delirium Lawrence S. Long, MD, University of California, San Francisco, Oakland, California
	Delta Opioid Receptors Presynaptically Regulate Cutaneous Mechanosensory Neuron Input to the Spinal Cord Dorsal Horn Vivianne L. Tawfik, MD, PhD, Stanford University of Medicine, Stanford, California
	Anesthesia-induced Neurotoxicity in the Developing Murine Retina: A Window of Opportunity? Richard J. Levy, MD, FAAP, Children's National Medical Center, Washington, District of Columbia
	Peptidylarginine deiminase-4 Exacerbates Kidney Ischemia and Reperfusion Injury HT Lee, MD, PHD, Columbia University, New York, New York
Resident Travel Award	**miR-200c Contributes to Injury From Transient Cerebral Ischemia in Mice by Targeting Reelin** Creed M. Stary, MD, PhD, Stanford University, Stanford, California
	Single-Cell Deep Immune Profiling Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates Brice Gaudilliere, PhD, MD, Stanford University, Stanford, California
	Deletion of CD36 Induces M2 Response to Brain Injury and Supports Ischemic Tolerance Ines P. Koerner, MD, PhD, Oregon Health & Science University, Portland, Oregon
3:30 pm – 3:45 pm	**Break**
3:45 pm – 5:00 pm*	**Moderated Poster Session**
6:00 pm – 10:00 pm	**Social Event Reception and Dinner** **Frances C. Arrillaga Alumni Center**

Opportunities for Q&A will be provided at the conclusion of each presentation.

Resident Luncheon

Li Ka Shing Center
Saturday, April 26, 2014
Noon – 1:30 pm
(Included in the Resident/Fellow registration fee)

At the All Attendee 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 academic anesthesiology leaders.

Social Event Reception and Dinner

Frances C. Arrillaga Alumni Center
Stanford University
Saturday, April 26, 2014
6:00 pm – 10:00 pm

Join your friends and colleagues for a perfect ending to the 61st Annual Meeting. This Saturday event offers an opportunity to unwind and relax. This is an ideal opportunity to catch up with friends and colleagues and enjoy live jazz entertainment.

Program Materials

Friday, April 25, 2014

EAB Program (Part 1)
8:15 am - 9:45 am

An Efficacy Study of Simulation-Based Training on Practicing Anesthesiologists' Acquisition of Ultrasound-Guided Perineural Catheter Insertion Skills
Edward R. Mariano, M.D., M.A.S., Education Grant Recipient 2011

Acute Care Skills in Anesthesia Practice: A Simulation-Based Performance Assessment
David J. Murray, M.D., Education Grant Recipient 2005

EAB Program (Part 2)
10:15 am - 11:45 am

Evidence, Economics, and Outcomes in Educational Methodology: Is Face-to-Face Learning in a Classroom Model Obsolete? Introduction, Background, AUA Survey Results
Randall M. Schell, M.D., MACM

Plenary Session: Lung Injury, Remodeling and Repair
1:00 pm - 3:00 pm

Symposium Sponsor:
The American Journal of Physiology: Lung Cellular and Molecular Physiology

Cell-Based Therapy for Acute Lung Injury
2:00 pm - 2:20 pm
Jae Woo Lee, M.D.

Platelet Function and ARDS Pathogenesis: A Path to Prevention?
2:20 pm - 2:40 pm
Daryl J. Kor, M.D.

Saturday, April 26, 2014

SAB Oral Session (Part 2)
2:10 pm - 3:30 pm
Junior Faculty Award Winner
Specializing Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline
Niccolo Terrando, B.Sc. (hons), DIC, Ph.D.

EAB Program (Part 1)
An Efficacy Study of Simulation-Based Training on Practicing Anesthesiologists' Acquisition of Ultrasound-Guided Perineural Catheter Insertion Skills
Edward R. Mariano, M.D., M.A.S., Education Grant Recipient 2011

Notes: _____

Efficacy of simulation-based training on practicing anesthesiologists' acquisition of ultrasound-guided perineural catheter insertion skills

Edward R. Mariano, MD, MAS
Associate Professor of Anesthesiology
Stanford University School of Medicine
Chief, Anesthesiology and Perioperative Care
Veterans Affairs Palo Alto Health Care System

Simulation-Based Training for Regional Anesthesia

Financial Disclosures

- I-Flow/Kimberly-Clark, B Braun – Unrestricted educational program funding paid to my institution

The contents of the following presentation are solely the responsibility of the speaker without input from any of the above companies.

Simulation-Based Training for Regional Anesthesia

Benefits of Regional Anesthesia

- RCT: 32 patients scheduled for outpatient shoulder surgery with an US-guided interscalene nerve block
- All subjects received a nerve block catheter and one-time ropivacaine bolus
- After surgery, subjects discharged home with portable infusion device
  - Half received ropivacaine infusion for 2 days
  - Half received saline infusion for 2 days

Mariano ER, et al. A&A 2009;108:1688

Simulation-Based Training for Regional Anesthesia

Results

- The placebo group experienced:
  - Higher average pain on POD 1 and 2
  - Higher worse pain on POD 1 and 2
  - Greater sleep disturbance
  - Lower patient satisfaction with pain control

Mariano ER, et al. A&A 2009;108:1688

Simulation-Based Training for Regional Anesthesia

Results from Previous Studies

- Ultrasound (US) requires less time to perform catheter insertion vs. stimulation
- US: *less procedure-related pain*
  - Femoral, popliteal
- US: *less inadvertent vascular punctures*
  - Femoral, infraclavicular
- US: *higher success rate*
  - Infraclavicular

Mariano ER, et al. RAPM 2009;34:480
Mariano ER, et al. JUM 2009;28:1211
Mariano ER, et al. JUM 2009;28:1453
Mariano ER, et al. JUM 2010;29:329

Simulation-Based Training for Regional Anesthesia

We Have Evidence

The ASRA Evidence-Based Medicine Assessment of Ultrasound-Guided Regional Anesthesia and Pain Medicine

Executive Summary

Joseph M. Neal, MD, Richard Brull, MD,† Vincent W. S. Chan, MD,† Stuart A. Grant, MBChB,‡ Jean-Louis Horn, MD,§ Spencer S. Liu, MD,|| Colin J.L. McCartney, MBChB,¶ Samer N. Narouze, MD, MSc,# Anahi Perlas, MD,† Francis V. Salinas, MD,* Brian D. Sites, MD,** and Ban Chi-ho Tsui, MD††*

Neal JM, et al. RAPM 2010;35:S1

Simulation-Based Training for Regional Anesthesia

We Have Training Guidelines

The American Society of Regional Anesthesia and Pain Medicine and the European Society of Regional Anaesthesia and Pain Therapy Joint Committee Recommendations for Education and Training in Ultrasound-Guided Regional Anesthesia

So Why Isn't Everyone Doing This?

Sites BD, et al. RAPM 2009;34:40

Simulation-Based Training for Regional Anesthesia

Need for Adequate Training

- In recent years, residency training in peripheral nerve blocks has been lacking

Regional Anesthesia and Pain Medicine 24(1): 1–4, 1999

Editorial

Regional Anesthesia Training: Do We Have the Confidence to Go On?

"The things we have to learn before we can do them, we learn by doing them."

Aristotle (384–322 B.C.)

Simulation-Based Training for Regional Anesthesia

Challenges for Practicing MDs

- Finished with formal training
- Cost of CME courses
- Time off = loss of income
- Limited availability (i.e., "on call" obligations, family)

Simulation-Based Training for Regional Anesthesia

Simulation Model

Simulation-Based Training for Regional Anesthesia

Specific Aims

- Primary: To determine the efficacy of a teaching program incorporating hybrid simulation in training *practicing anesthesiologists* on ultrasound (US)-guided continuous peripheral nerve block (CPNB)

Simulation-Based Training for Regional Anesthesia

Specific Aims

- Secondary: To determine the extent of *change implementation* following participation in a regional anesthesia teaching program; assess *obstacles*; identify potential future interventions and "tool-kits" for setting up perineural catheter programs

Program Materials

Simulation-Based Training for Regional Anesthesia

Hypotheses

- Primary: Scores for procedural performance and ergonomics based on video analysis using a composite assessment tool derived from previously-published studies will be significantly increased following the teaching program when compared to baseline.

Simulation-Based Training for Regional Anesthesia

Hypotheses

- Hypothesis 2a: The number of US-guided CPNB procedures performed by subjects will increase over baseline at 3 months.
- Hypothesis 2b: Systems issues rather than individual skill or willingness will be the predominant remaining obstacles to incorporating the use of US-guided CPNB at 1 year follow-up.

Simulation-Based Training for Regional Anesthesia

Methods

- Design: single-center time-series study in volunteers conducted in the simulation center of the Veterans Affairs Palo Alto (VAPA) hospital
- Determined exempt by IRB
- Prospectively registered NCT016888271 (http://ClinicalTrials.gov)

Simulation-Based Training for Regional Anesthesia

Eligibility Criteria

- Inclusion: anesthesiologists in practice ≥10 years; active board certification; active medical license.
- Exclusion: fellowship training in regional anesthesia; currently performing US-guided PNB (≥10 blocks per month); physical limitations or other communication impairment.

Simulation-Based Training for Regional Anesthesia

Study Flow

Pre-Course Survey

↓

Orientation to Simulator and Equipment

↓

Skills Assessment with Video Capture (Baseline) followed by:
Didactic Lectures and Model Scanning

↓

Skills Assessment with Video Capture (Interval) followed by:
Immersive Learning in Simulation Lab with One-on-One Proctoring

↓

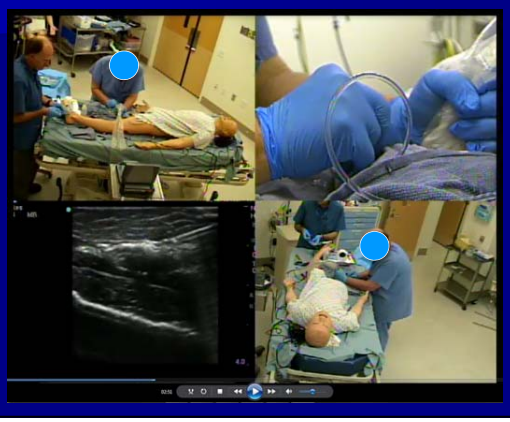
Skills Assessment with Video Capture (Final) followed by:
Debriefing

↓

Interval Practice Survey Every 3 Months for 1 Year

Simulation-Based Training for Regional Anesthesia

Video Capture and Scoring



Program Materials

Simulation-Based Training for Regional Anesthesia

Category	Description	Points
Procedural Time (min)	Starting when US probe touches skin and ending when placement needle is removed	2 (≤5 min) 1 (5-10 min) 0 (>10 min)
Needle Passes (#)	Withdrawal of the placement needle >1 cm with readvancement	2 (1) 1 (2) 0 (>2)
Procedural Performance	Needle visualization during advancement	2 (All the time) 1 (Part of the time) 0 (None of the time)
	Equipment preparation (e.g., probe selection, machine settings)	2 (Excellent) 1 (Good) 0 (Poor)
	Target positioning (eg, able to see target and feasible needle trajectory)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	Probe stability (eg, no unintentional movement)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	Needle manipulation (eg, comfortable grip on needle and catheter)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	Visual focus (eg, appropriately focused on machine and not hands during procedure)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	Confirmation of proper injectate spread	2 (Excellent) 1 (Good) 0 (Poor)
	Confirmation of proper catheter tip position	2 (Excellent) 1 (Good) 0 (Poor)
Ergonomic Factors	Positioning of ultrasound machine	2 (Excellent) 1 (Good) 0 (Poor)
	No thoracolumbar flexion (≥45°)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	No head/neck rotation (≥45°)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	No lateral shoulder tilt (≥30°)	2 (All the time) 1 (Part of the time) 0 (None of the time)
	No crossing sterile field to non-dominant side	2 (All the time) 1 (Part of the time) 0 (None of the time)

Simulation-Based Training for Regional Anesthesia

Sample Size Estimate

- Primary outcome: composite score based on the video analysis assessment tool.
- Sample size estimate: 32 subjects assuming final composite scores will be 50% greater than baseline within group, SD=5, α=0.05, and β=0.2.

Simulation-Based Training for Regional Anesthesia

Statistical Plan

- Within group comparisons of continuous variables: paired t test or RMANOVA with pairwise post-hoc testing.
- Inter-rater reliability for the reviewers' composite scores: kappa statistic.
- Categorical variables: Z test or McNemars test when correlated.
- $p<0.05$ will be considered statistically-significant.

Simulation-Based Training for Regional Anesthesia

Project Mentor and Advisor

Mentor

- Steven K. Howard, MD
  - Associate Professor
  - Co-Director of Simulation at VAPAHCS
  - Chair, APSF Scientific Committee

Advisor

- David Gaba, MD
  - Professor
  - Associate Dean of Immersive/Simulation-Based Learning

Simulation-Based Training for Regional Anesthesia

Progress Report

- Received award notice May 2012
- IRB-exemption July 2012
- Registration August 2012
- Funds received October 2012
- First course November 2012; all 16 courses (32 subjects completed June 2012)
- All videos scored by reviewers March 2014
- Project completion on schedule June 2014

Program Materials

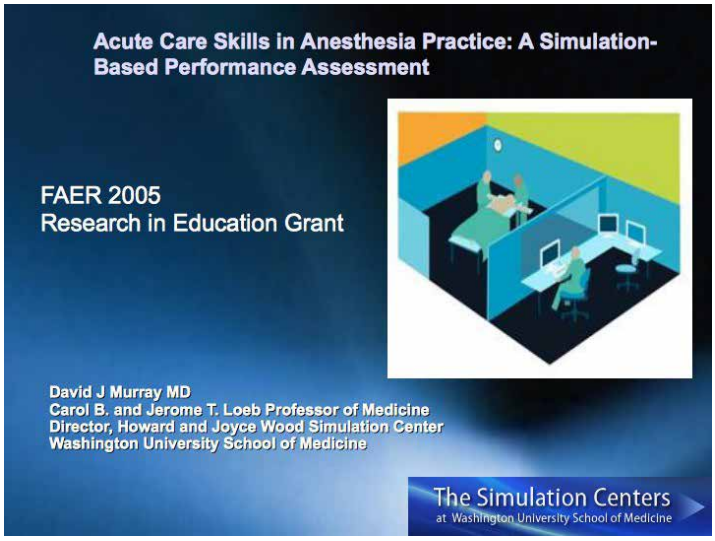
EAB Program (Part 1)

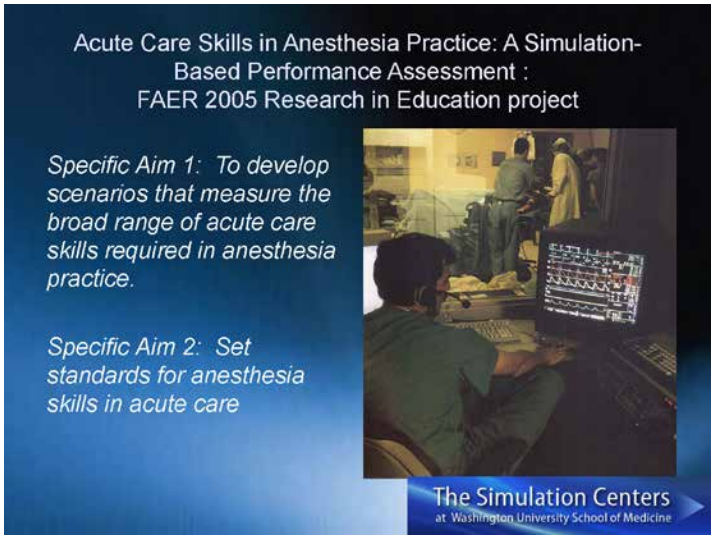
Acute Care Skills in Anesthesia Practice: A Simulation-Based Performance Assessment

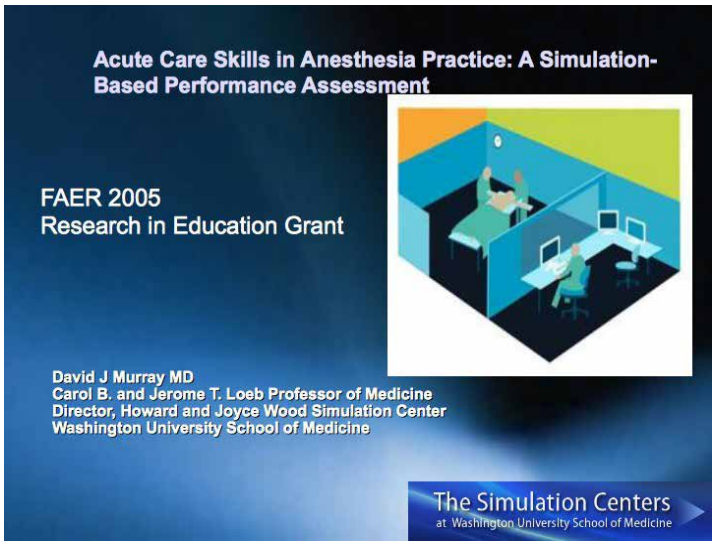
David J. Murray, M.D., Education Grant Recipient 2005

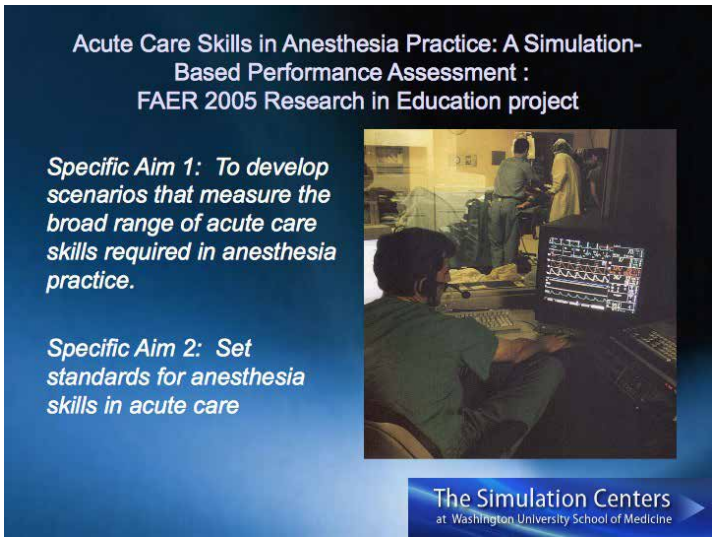
Notes: _____

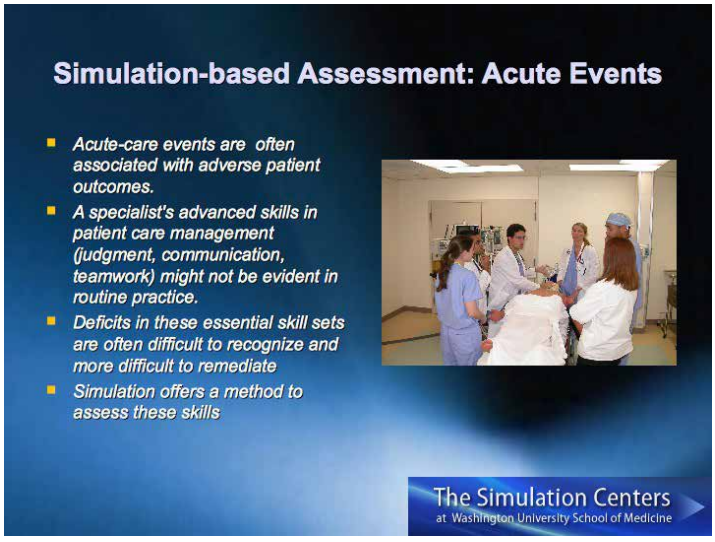
Program Materials

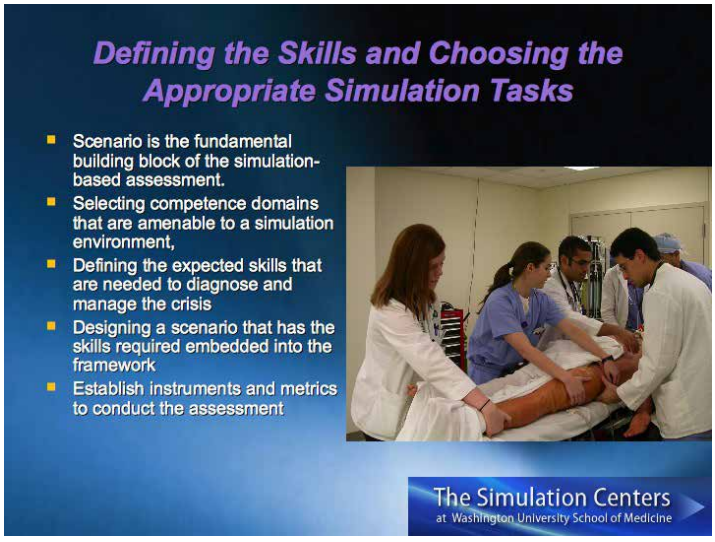




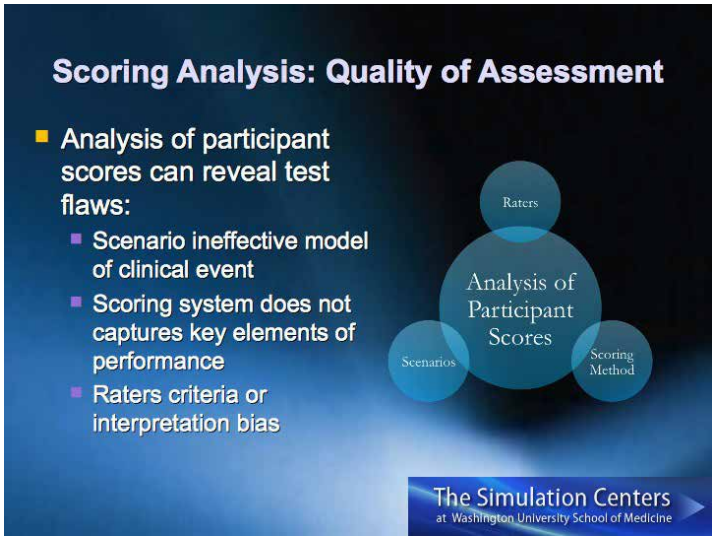


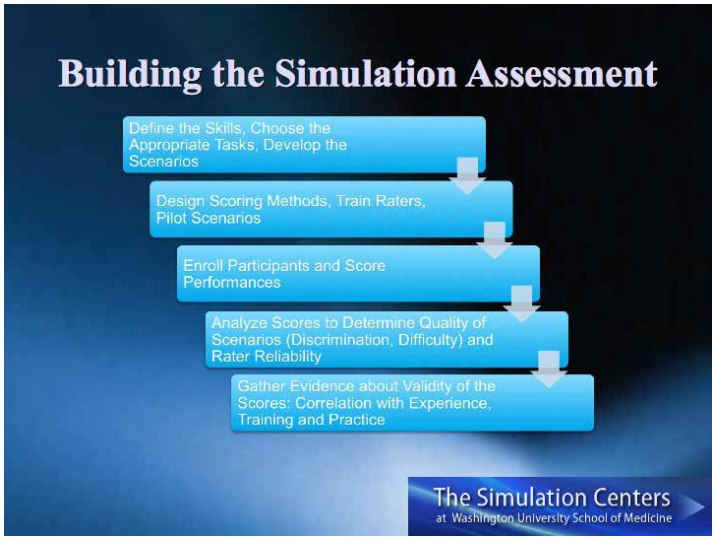


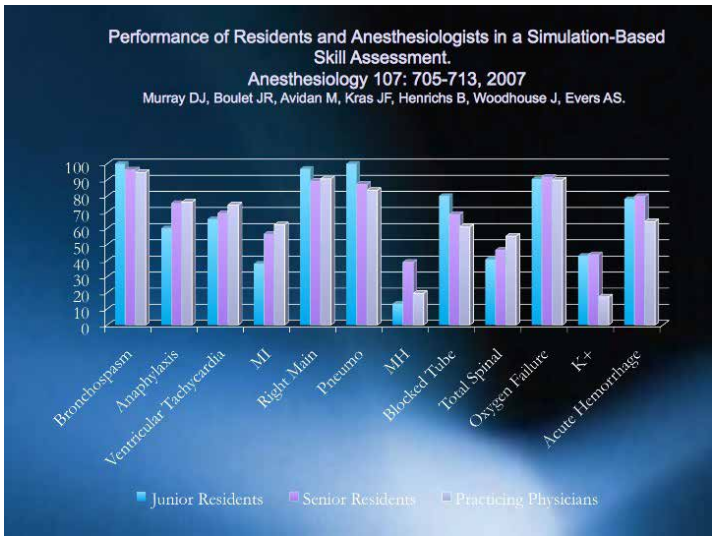


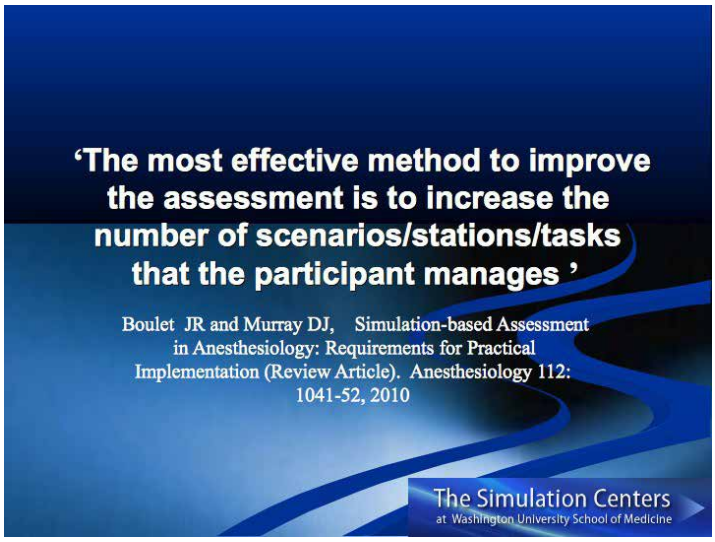


Program Materials









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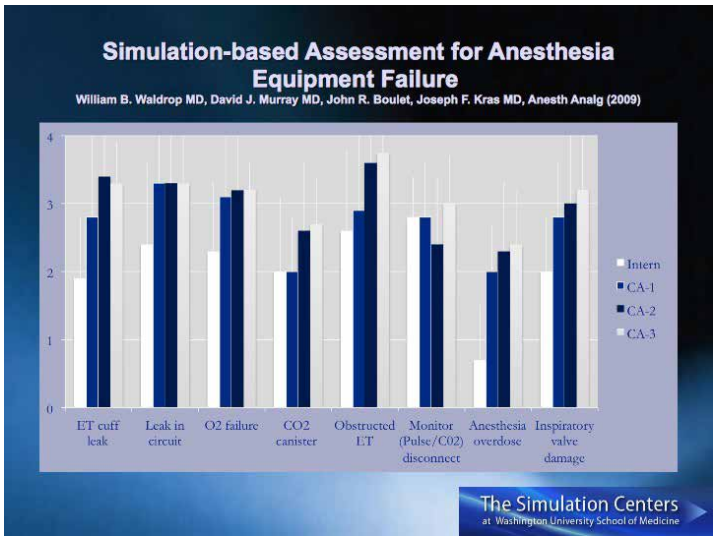
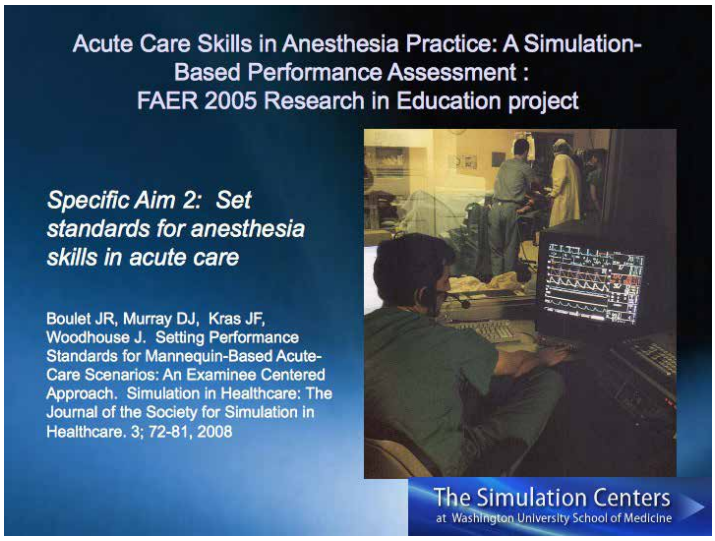
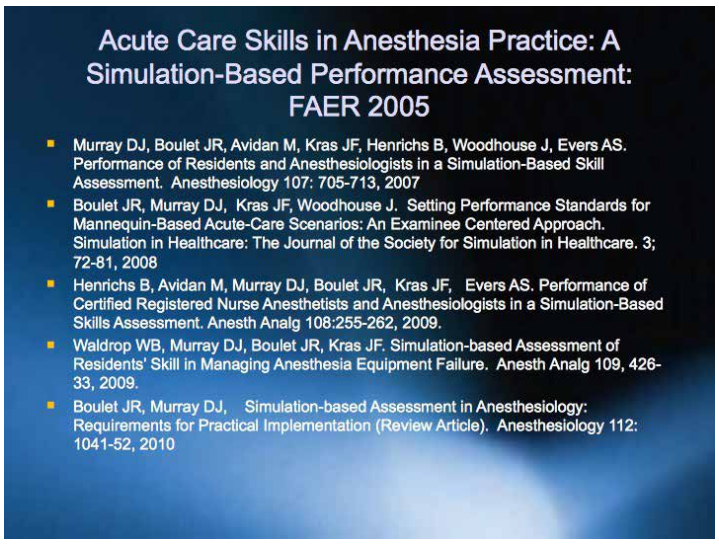






EAB Program (Part 2)
Evidence, Economics, and Outcomes in Educational Methodology: Is Face-to-Face Learning in a Classroom Model Obsolete? Introduction, Background, AUA Survey Results
Randall M. Schell, M.D., MACM

Notes: _____

Is Face-to-Face Learning in a Traditional Class Model Obsolete?

Evidence, Economics, and Outcomes in Educational Methodology

AUA EAB Panel : April 25, 2014

Larry Chu, M.D., M.S.
Manny Pardo, M.D.
Randy Schell, M.D., MACM

EAB Panel

Presenters and Topics

1. **"Introduction, Background and AUA Survey Results"** (20 minutes)
   – R. Schell, M.D., MACM
2. **"Evidence and Economics"** (30 minutes)
   – M. Pardo, M.D.
3. **"Practical Implementation and Learning Management Systems"** (25 minutes)
   – L. Chu, M.D., M.S.
4. **Panel Discussion** (15 minutes)

Objectives

- Define the "traditional classroom" in Anesthesiology education
- Review modes/models of delivery of educational content and instruction outside of the operating room
- Describe alternatives to the traditional classroom that use active learning methods
- Compare and contrast the consensus practice and opinion of the AUA

Learning Outcomes

What do we measure and desire?

- **Retention**
  - Solve same or very similar "problem"
- **Transfer**
  - Something you know from prior learning affects your performance on a new task
    - **Near Transfer**: Solve new problem that requires applying the same principle or method in new situation
    - **Far Transfer**: Solve new problem that requires applying a new principle or method in a new situation
- **Other**
  - Increase motivation, improve interpersonal skills, develop critical thinking
- **Economics/Efficiency**
  - All of the above in the most "cost effective" manner

Richard E. Mayer. Applying the Science of Learning 2011

GME in Anesthesiology

Clinical Experience

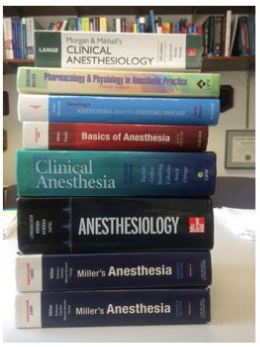
- *Operating Room*
- *ICU*
- *Preoperative Clinic*
- *Pain Clinic*
- *Other*

Traditional Class Model

Students read textbooks outside of the classroom and attend class for lectures and tests.

Unguided Pure Discovery Learning

"Give them textbooks and let them learn on their own."



"The debate about discovery learning has been replayed many times in education but each time, the evidence has favored a guided approach to learning"

-R. Mayer 2004

AUA Member Survey 2014

Evidence, Economics, and Outcomes in Educational Methodologies

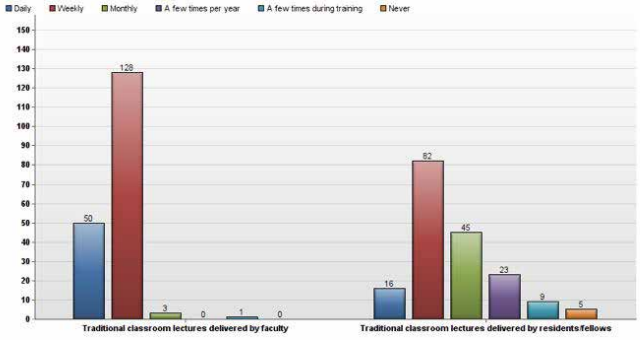
n=254

- **Demographics**
  - > 45 y/o (92%)
  - Male (81%)
  - > 20 years in academia (72%)
  - Northeast (35%)

Traditional Classroom

Current Practice

"Frequency with which your institution uses the following modalities to deliver educational content"

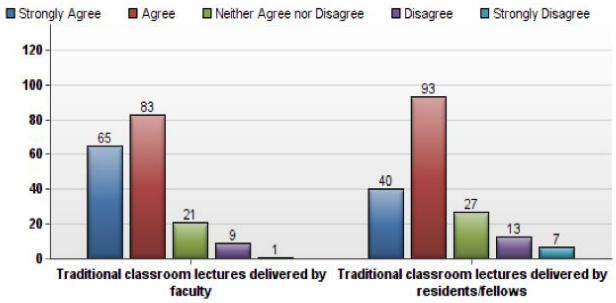


AUA Survey 2013/2014; Schell, DiLorenzo, Murray, Pardo, Chu

Traditional Classroom

Perception

"Believe this is a valuable method to deliver educational content to the learners in my program"

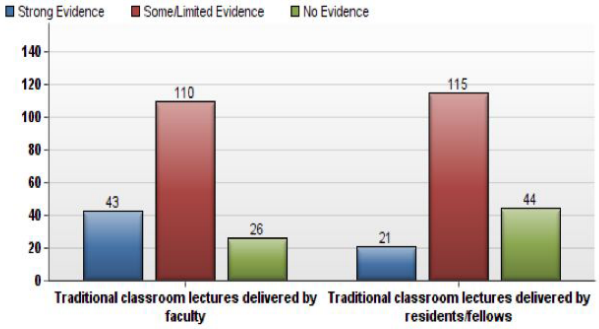


AUA Survey 2013/2014; Schell, DiLorenzo, Murray, Pardo, Chu

Traditional Classroom

Perception

"Strength of the evidence, in regards to learning, to support use…"



AUA Survey 2013/2014; Schell, DiLorenzo, Murray, Pardo, Chu

Lecture Halls without Lectures — A Proposal for Medical Education

Charles G. Prober, M.D., and Chip Heath, Ph.D.

- Little change in way we teach medical students over last 100 years (Flexner 1910)
- Need to transfer more knowledge, but hours in day have not increased.
  - Make lessons "stickier"; More comprehensible and memorable
  - Embrace learning strategy that is self-paced and mastery based, and boost engagement
- In current era of near perfect video delivery platforms, move **lectures outside the lecture hall** and use **class time** for more **active learning**

C. Prober (Stanford School of Medicine), C. Heath (Stanford Graduate School of Business) N Eng J Med May 2012

"Online Learning will make college cheaper. It will also make it better."

-L. Rafael Reif
President of MIT

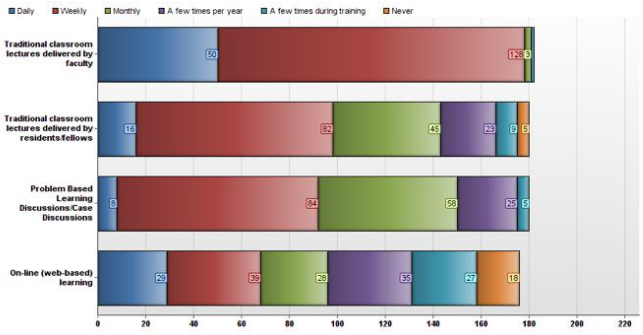
•23% of leaders in academia say online learning is inferior to face-to-face learning--down from 43% in 2003

Time Magazine October 7, 2013

On-Line Learning

Current Practice

"Frequency with which your institution uses the following modalities to deliver educational content"

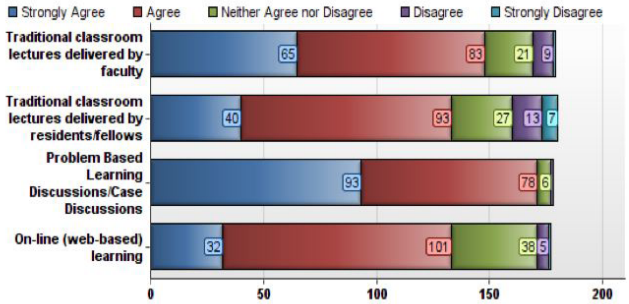


AUA Survey 2013/2014; Schell, DiLorenzo, Murray, Pardo, Chu

On-Line Learning

Perception

"Believe this is a valuable method to deliver educational content to the learners in my program"

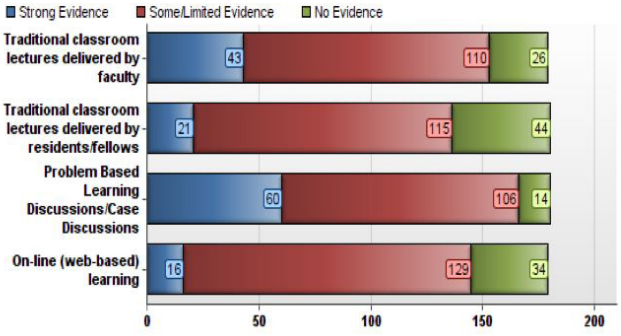


AUA Survey 2013/2014; Schell, DiLorenzo, Murray, Pardo, Chu

On-Line Learning

Perception

"Strength of the evidence, in regards to learning, to support



AUA Survey 2013/2014; Schell, DiLorenzo, Murray, Pardo, Chu

What we know about On-line Learning?

U.S. DEPARTMENT OF EDUCATION

Evaluation of Evidence-Based Practices in Online Learning
A Meta-Analysis and Review of Online Learning Studies

- Instruction conducted entirely **on-line** is **as effective as classroom** instruction but no better (effect +0.05)
- Blends of on-line and face-to-face instruction ("**blended learning**"), on average, had **stronger learning outcomes** than did face-to-face alone (effect +0.35)

US Dept of Education 2010

How Should Face-to-Face Class Time Be Used?

- **Science 2011** study suggests we **use** face-to-face class time with **interactive learning** (active learning) instruction methods
  - Large enrollment undergraduate physics class
  - Traditional lectures by experienced highly rated instructor (n=267) vs Interactive learning by trained but inexperienced instructor (n=271)
    - **Interactive learning ="more than twice the learning"**
      - Increased student attendance
      - Higher engagement

Deslauriers L, et al. Improved Learning in a Large-Enrollment Physics Class Science 2011

Active Learning

- Instructors are **"Guide by Side"** rather than "Sage on Stage"
  - Create opportunities for students to engage with new material, serving as guides to help them understand and apply information
  - Examples:
    - TBL, PBL, Case Based, Questions (ARS), Paired activities (think-pair-share)
- Evidence: Improved critical thinking skills, increased retention and transfer of new information, increased motivation, and improved interpersonal skills

"Medical Education Reimagined: A Call to Action"

- Authors propose a new model for medical education
- **"Flipped classroom"** design:
  1. Students access brief (≈10 min) online videos to learn new concepts on their own time in preparation for class
  2. Classroom time facilitated by expert faculty leading dynamic, interactive sessions where students apply their newly mastered knowledge

Academic Medicine October 2013

Flipped Classroom Preferred Over Traditional Classroom in Resident Education

SM Martinelli, M.D., A DiLorenzo, M.A., DC Mayer, M.D., E Bowe, M.D., H Arora, M.D., DA Zvara, M.D., R Schell, M.D., MACM

- PGY2 Residents (n=26)
- Two Institutions (UNC, UK)
- ABA Basic Exam Preparation
  - Content Outline: Physics, Pharmacology
- Pre- post-test design and survey

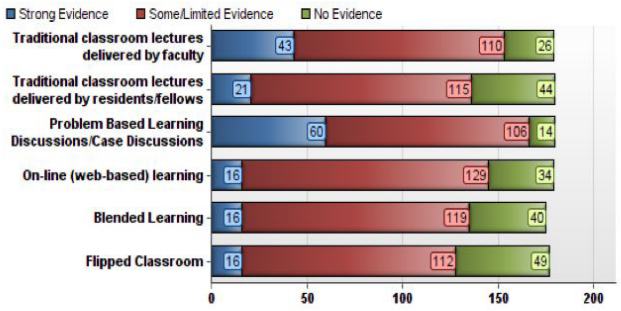
	Traditional	Flipped	p-value
Knowledge acquisition, % (SE)	13.4 (1.8)	16.3 (1.8)	0.28*
Preferred style (post-survey), % agree or strongly agree	5/26 (19%)	22/26 (85%)	0.008**

**p-value from a repeated measures model adjusted for study site*
***Fisher exact test*

Martinelli et al. AUA Abstract 2014, Manuscript in preparation

AUA Survey 2014

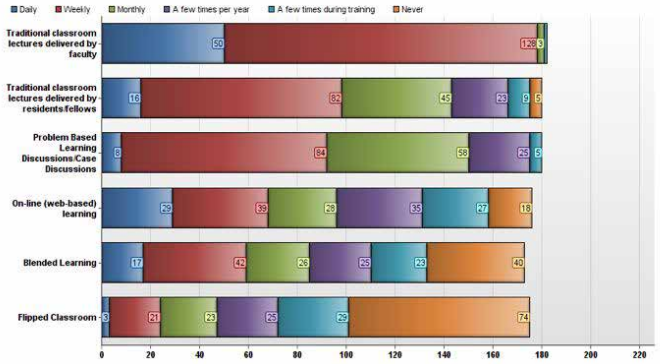
Perception of the strength of the evidence, in regards to learning.



AUA Survey 2014; Schell, DiLorenzo, Murray, Pardo, Chu

AUA Survey 2014

Frequency with which used.



UK Anesthesiology Didactics

Implementing the Concepts

- **Monday**
  - Traditional lecture
- **Tuesday**
  - Traditional Lecture
- **Wednesday**
  - Oral Boards prep
  - Grand Rounds (GCC)
- **Thursday**
  - Traditional Lecture or PBL
- **Friday**
  - Simulation, Subspecialty conferences

March 2013

- **Monday**
  - **Podcast with self-assessment questions**
- **Tuesday**
  - **Podcast with self-assessment questions**
  - **Flipped Class: ABA Basic Exam Prep (PGY2)**
- **Wednesday**
  - Oral Boards prep
  - Grand Rounds (GCC)
- **Thursday**
  - **Face-to-Face Active Learning; Flipped Class, Case Based, PBL**
- **Friday**
  - Simulation, Subspecialty conferences

UK UNIVERSITY OF KENTUCKY

Summary

- Traditional classroom with faculty as "sage on stage" and with passive transfer of information is frequently used in Graduate Medical Education
- Blended learning including "flipped classroom" with active learning techniques may offer advantages
- AUA survey data suggest:
  - Traditional classroom lectures by faculty very common
  - PBL thought to be most valuable and have strongest evidence in support of
  - Blended learning and flipped classroom not used by many and many do not believe there is evidence to support the use of these methods

"Why would anyone waste precious class time on a lecture?"

Charles Prober, M.D.
Senior Associate Dean Medical Education Stanford School of Medicine

Chip Heath Ph.D.
Professor of Organizational Behavior Stanford Graduate School of Business

New England Journal of Medicine 2012 - Lecture Halls Without Lectures

Demographics

Age

#	Answer		Response	%
1	< 35		0	0%
2	36-45		21	8%
3	46-55		66	26%
4	56-65		101	40%
5	> 65		66	26%
	Total		254	100%

Years taught in an academic setting

#	Answer		Response	%
1	< 5		2	1%
2	5-10		8	3%
3	11-20		60	24%
4	21-30		85	33%
5	> 30		100	39%
	Total		255	100%

Location of academic institution

#	Answer		Response	%
1	Northeast		89	35%
2	Midwest		58	23%
3	South		62	24%
4	West		45	18%
	Total		254	100%

Program Materials

Educational Methodologies and Content Delivery

Frequency with which your institution uses the following methodologies to deliver educational content

Question	Daily	Weekly	A few times per year	A few times during training	Never	Total Responses
Traditional classroom lectures delivered by faculty	50	128	0	1	0	182
Problem Based Learning Discussions/Case Discussions	8	84	25	5	0	180
Traditional classroom lectures delivered by residents/fellows	16	82	23	9	5	180
On-line (web-based) learning	29	39	35	27	18	176
Blended Learning	17	42	25	23	40	173
Flipped Classroom	3	21	25	29	74	175

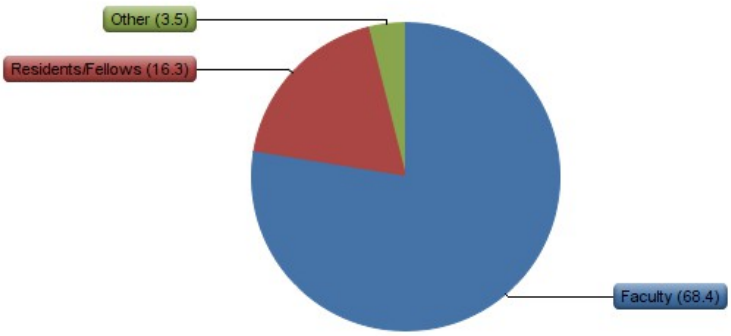
I personally believe this is a **valuable method** to deliver educational content to the learners in my program

Question	Agree	Disagree	Strongly Disagree	Total Responses
Traditional classroom lectures delivered by faculty	83	9	1	179
Traditional classroom lectures delivered by residents/fellows	93	13	7	180
Problem Based Learning Discussions/Case Discussions	78	1	0	178
On-line (web-based) learning	101	5	1	177
Blended Learning	69	7	2	172
Flipped Classroom	59	5	5	174

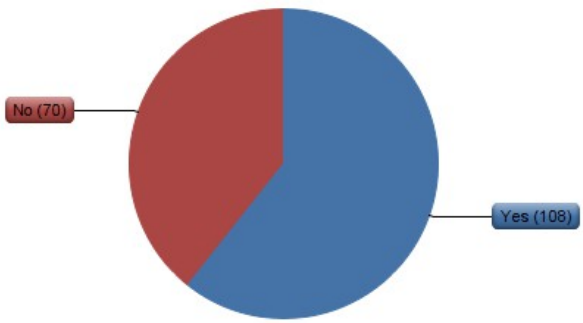
What is your perception of the **strength of the evidence**, in regards to learning, to support the use of the following methods of educational content delivery?

Question	Strong Evidence	Some/Limited Evidence	No Evidence	Total Responses
Traditional classroom lectures delivered by faculty	43	110	26	179
Traditional classroom lectures delivered by residents/fellows	21	115	44	180
Problem Based Learning Discussions/Case Discussions	60	106	14	180
On-line (web-based) learning	16	129	34	179
Blended Learning	16	119	40	175
Flipped Classroom	16	112	49	177

What percentage of your educational content is delivered by the following?



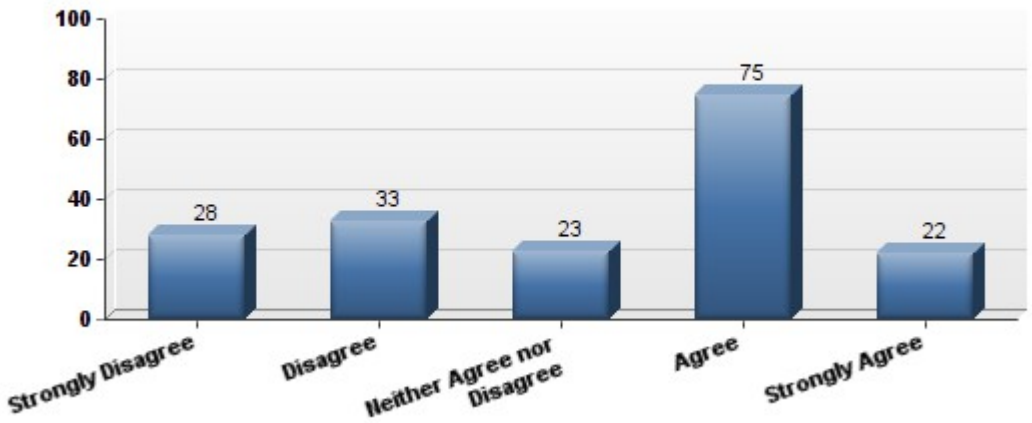
Have you provided faculty development sessions on educational content delivery methods?



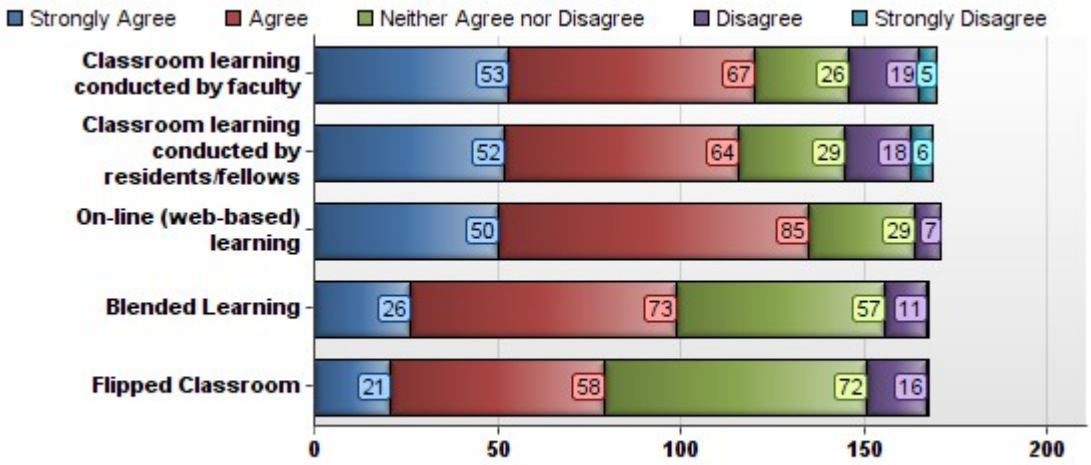
Program Materials

Economics

At your institution, is it your perception that you have sufficient financial resources to provide educational content in the way you believe is most beneficial for the residents/fellows?



I believe this method of educational content delivery is economical.



Program Materials

Plenary Session: Lung Injury, Remodeling and Repair
Symposium Sponsor: *The American Journal of Physiology: Lung Cellular and Molecular Physiology*
Cell-Based Therapy for Acute Lung Injury
Jae Woo Lee, M.D.

Notes: _____

Cell Based Therapy for Acute Lung Injury

Jae-Woo Lee, MD
University of California, San Francisco
April 25, 2014

UCSF University of California San Francisco

Outline

- Background & rationale for the use of Mesenchymal Stem Cells (MSC) in Acute Lung Injury (ALI).
- ALI studies in endotoxin & *E.coli* bacteria injured mice.
- ALI studies in *E.coli* bacteria injured *ex vivo* perfused human lung preparation. Potential translation of MSC therapy for severe ALI with clinical grade human allogeneic MSC from a NIH PACT group.

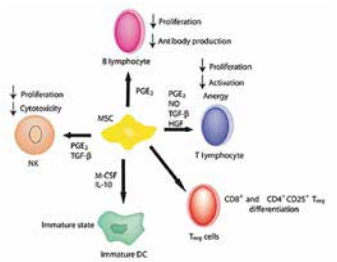
Acute Lung Injury and Pulmonary Edema

- Acute Lung Injury occurs in 200,000 ventilated patients annually in the US with a mortality up to 30% (*NEJM*, 2005).
- Common causes of acute lung injury are bacterial and viral pneumonia, sepsis, shock & aspiration.
- Supportive treatments with Lung Protective Ventilation and a Fluid Conservative Strategy have substantially improved clinical outcomes (NHLBI ARDS Network Trials, *NEJM* 2000 and *NEJM* 2006).
- However, no pharmacological therapy is available.

Key Pathological Features of ALI in Preclinical Models

- Loss of Alveolar Fluid Clearance (Inability to absorb pulmonary edema fluid).
- Increase in lung protein permeability.
- Influx of inflammatory cells into the injured alveolus.
- Profound inflammatory response in the injured alveolus.

Mesenchymal Stem Cells



-Multi-potent

-Immunomodulatory & Immunopriviledged

-Secretion of Soluble Factors

-Finite life span

To date, more than **350** MSC clinical trials registered with **clinicaltrials.gov**.

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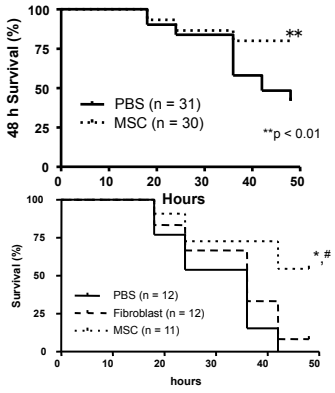
MSC Reduce Acute Lung Injury in Mice

Permission Granted by American Association of Immunologists, Inc. Gupta et al. *J Immunol* 179:1855-63. Copyright 2007.

LPS

Mice ALI model

E.coli

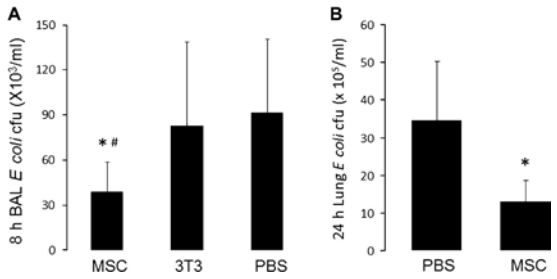


*MSC vs PBS p < 0.01
#MSC vs 3T3 p = 0.03
3T3 vs PBS p = 0.26

Reproduced from *Thorax*, Gupta et al. 67:533 9, 2012 with permission from BMJ Publishing Group Ltd.

Program Materials

MSC Reduce the Number of *E.coli* bacteria in the Lung 24 Hrs After Intra-Tracheal Instillation



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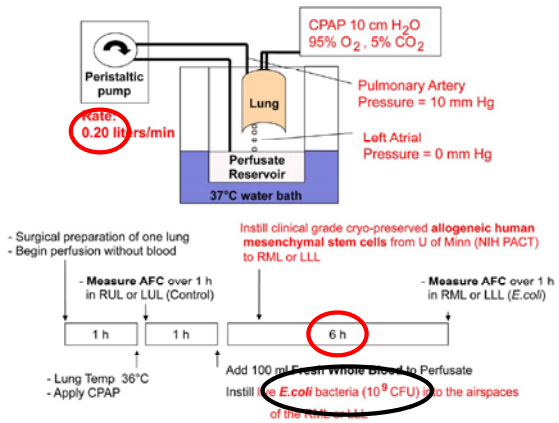
Summary of Results of MSC Studies in Mice

1. Treatment with MSC improved survival and reduced lung injury in the endotoxin model of ALI.
2. MSC down-regulated the pro-inflammatory response to endotoxin, while increasing anti-inflammatory cytokine levels.
3. MSC reduced lung injury and improved survival following *E.coli* bacteria lung injury, which was associated with a decrease in bacterial counts.
4. Some of the anti-bacterial effects were mediated by anti-microbial peptides/proteins, such as LL-37 and Lipocalin2.

Treatment of *E.coli* Pneumonia in the *Ex Vivo* Perfused Human Lung with Mesenchymal Stem Cells

Hypothesis: Clinical grade cryopreserved human mesenchymal stem cells will attenuate *E.coli* pneumonia induced lung injury in an *ex vivo* perfused human lung in part by inhibiting bacteria growth.

E.coli Pneumonia in an *Ex Vivo* Perfused Human Lung



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This project is funded in part by PACT

Production Assistance for Cellular Therapies
National Heart Lung and Blood Program

PACT provides assistance for cellular therapy translational research and the manufacture of cellular therapy products

PACT Cell Processing Facilities

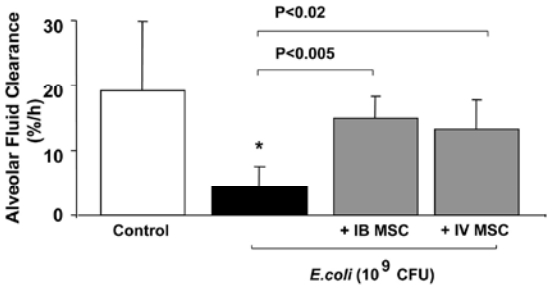
-Baylor College of Medicine, Center for Cell and Gene Therapy Contract#HHSN268201000007C
-Center for Human Cell Therapy Boston Contract#HHSN268201000009C
-City of Hope, Center for Applied Technology Development Contract#HHSN268201000011C
-University of Minnesota, Molecular and Cellular Therapeutics Contract#HHSN268201000008C
-University of Wisconsin - Madison, Waisman Clinical BioManufacturing Facility Contract# HHSN268201000010C

The EMMES Corporation serves as the Coordinating Center Contract#HHSN268201000006C

PACT website
www.pactgroup.net

PACT is federally funded by National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services

IB & IV MSC Restore Alveolar Fluid Clearance in the Injured Alveolus



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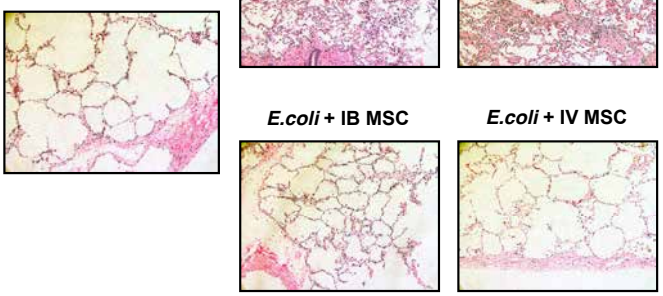
* P vs. Significant Control

Program Materials



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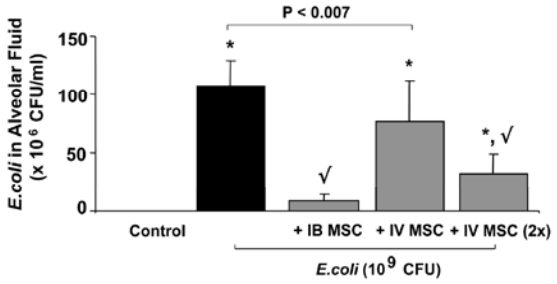
IB & IV MSC Reduce Absolute Bacterial Counts in the Injured Alveolus



* P vs. Significant Control
√ P vs. Significant *E.coli*

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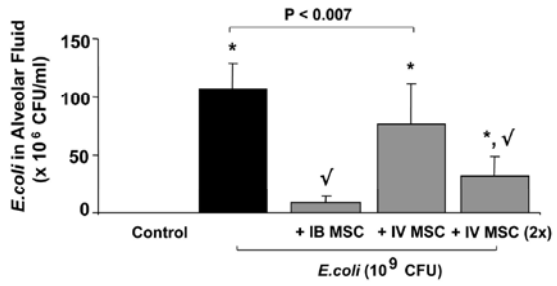
IB & IV MSC Reduce Absolute Bacterial Counts in the Injured Alveolus



* P vs. Significant Control
√ P vs. Significant *E.coli*

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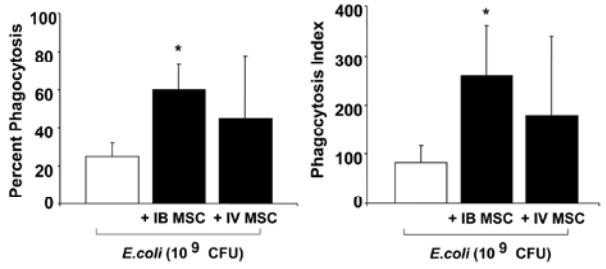
IB MSC Increase the Percent Phagocytosis and Phagocytosis Index of Alveolar Macrophages in the Injured Alveolus Against *E.coli bacteria*.



* P vs. Significant Control

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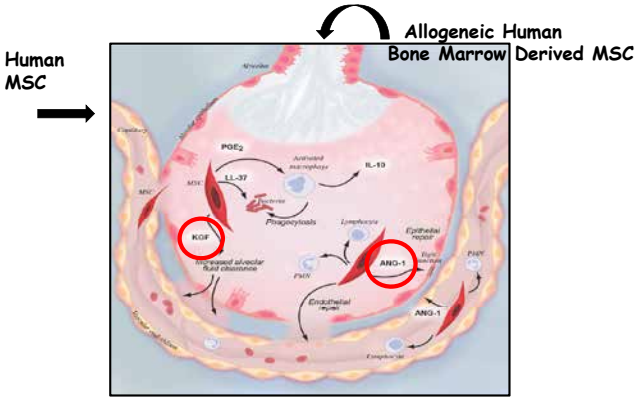
Summary of MSC in *E.coli* Pneumonia in The *Ex Vivo* Perfused Human Lung

1. Clinical grade cryopreserved allogeneic human mesenchymal stem cells restored alveolar fluid clearance in the *ex vivo* perfused human lung injured by *E.coli* pneumonia.
2. The restoration of lung fluid balance was associated with a decrease in *E.coli* CFU counts in the injured alveolus.
3. Human MSC also reduced the influx of inflammatory cells as well as the level of inflammatory cytokines in the injured alveolus.

Role of MSC Cell Based Therapy in Acute Lung Injury



Reprinted with the permission of John Wiley and Sons. Lee et al. *Stem Cells* 29:913-9, 2011.

MSC Paracrine Soluble Factors: Potential Role in Acute Lung Injury

Soluble Factors *	Functional effects
Keratinocyte Growth Factor	Alveolar fluid transport Lung protein permeability
Angiopoietin-1	Lung epithelial & endothelial permeability
Interleukin-1 Receptor Antagonist (IL-1ra) Interleukin-10 Prostaglandin E_2	Anti-Inflammatory Anti-Inflammatory Anti-Inflammatory
LL-37 Lipocalin 2	Antimicrobial

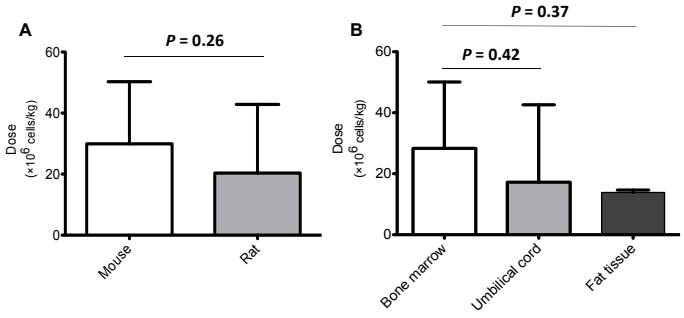
* Secretion of some soluble factors may depend on cell-cell contact or the alveolar milieu itself, such as IL-10 or Prostaglandin E_2.

Lee, JW. (Unpublished Data)

Remaining Questions & Concerns for MSC

1. Optimal dosage and route of MSC delivery.
2. Optimal timing of administration.
3. Lack of a potency assay.
4. Are MSCs the best cell-based therapy?

Dosage & Source of MSC in Pre-Clinical Animal Models



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Recent advances in preclinical stem cell research in sepsis/ALI

	Embryonic stem cells	Mesenchymal stem cells	Endothelial progenitor cells	Hematopoietic stem progenitor cells
Origination	Embryonic	Bone marrow Adipose Placenta	Bone Marrow	Bone marrow
Potency	Pluripotent	Multipotent	Differentiated	Multipotent
Widely studied	++	++++	++	+
Preclinical models used	CLP	Endotoxemia CLP Colitis Peritonitis	Endotoxemia CLP	CLP
Therapeutic mechanism observed	*Immuno-modulatory	* Engraftment * Immunomodulatory * Growth factors secretion * Antimicrobial peptides secretion	* Engraftment * Angiogenesis	* Immuno-modulatory
Further directions	* Generation functional progenitor cells before administration	* Evaluating timing of therapy for maximal benefit * Preconditioning and genetic modifications of MSCs * Manipulating the beneficial properties of sex-specific MSCs	* Understanding the relationship between EPC levels and outcomes * Modification of EPCs	* Demonstrating the beneficial effects in late-sepsis

Reprinted with the permission of SAGE. Zhu et al. *ICU Director* 3:166, 2012.

On-going Clinical Trials

- Phase I/II Human Allogeneic Bone Marrow Derived Mesenchymal Stem Cells for Acute Lung Injury (UCSF, NCT02097641).
  Dose: 5 – 10 x 10^6 cells/kg IV.
- Phase I Human Allogeneic Adipose Tissue Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome (Shaoxing Second Hospital, China, NCT01902082).
  Dose: 1 x 10^6 cells/kg IV.
- Phase I Human Allogeneic Umbilical Cord-Derived Mesenchymal Stem Cells for Severe Bronchopulmonary Dysplasia (Samsung Medical Center, Korea, NCT01297205).
  Dose: 10-20 x 10^6 cells/kg IT.

Acknowledgements

- Antoine Monsel, MD
- Ying-gang Zhu, MD
- Qi Hao, PhD
- Jia Liu, MD
- Stephane Gennai, MD
- Michael Matthay, MD
- Jason Abbott, BS
- Xiao-hui Fang, MD

Funding

- NHLBI 093026 and 113022,
- UCSF Hamilton Endowment Fund,
- Some of the materials (human allogeneic mesenchymal stem cells) employed in this work were provided by the Tulane Center for Gene Therapy through a grant from NCRR of the NIH, Grant # P40RR017447.

Program Materials

Plenary Session: Lung Injury, Remodeling and Repair
Symposium Sponsor: *The American Journal of Physiology: Lung Cellular and Molecular Physiology*
Platelet function and ARDS pathogenesis: A path to prevention?
Daryl J. Kor, M.D.

Notes: _____

Program Materials

Platelet Function and ARDS Pathogenesis
A Path to Prevention?

Daryl J. Kor, MD
Department of Anesthesiology
Division of Critical Care Medicine
Mayo Clinic, Rochester, MN
Chair, Transfusion Subcommittee
Vice-Chair, Critical Care Research

Kor.daryl@mayo.edu

Objectives

- At the end of the presentation, the audience will be able to:
  - Recognize the importance of ARDS prevention
  - Appreciate the role of platelets in ARDS pathogenesis
  - Appreciate the potential role for aspirin (ASA) as an ARDS prevention agent

Problem Statement

- Approximately 200,000 cases of ALI per year in the US alone
- Mortality continues to exceed 25%
- Among survivors, significant impact on long-term functional outcomes

Rubenfeld et al. NEJM 2005; 353:1685
Erickson et al. Crit Care Med 2009; 37:15
Herridge et al. NEJM 2011; 364:1293.

Problem Statement

- Despite improved understanding of ARDS pathophysiology, clinical benefits have been limited to supportive therapies
  - Mechanical ventilation, fluid management, rehab
  - Mechanistic treatments uniformly negative
    - When applied late in the course of illness?
- Surprisingly little research has been done on the prevention of ARDS

Platelets and ARDS: Mechanism

- Pathophysiology
  - Thromboxane A_2 production
  - Enhanced P-selectin expression with platelet-neutrophil aggregates
  - CCL5/CXCL4 heteromer deposition
  - Neutrophil Extracelluar Traps
- ARDS resolution
  - Resolvins
  - 15-epi-LXA_4

Protective effects of anti-platelet agents in patients at risk for Lung Injury

- ALI in anti-platelet group: 12.7%
- ALI in patients without anti-platelet agents: 28.0%
- Unadjusted OR: 0.37, 95% CI: 0.16 to 0.84; p = 0.02
- Adjusted OR (Propensity to receive antiplatelet therapy, APACHE III, LIPS score):
  - 0.35, 95% CI: 0.13 – 0.88; p = 0.03

Erlich, Kor et al. Chest 2011; 139:289.

Program Materials

Protective effects of anti-platelet agents in the LIPS study cohort

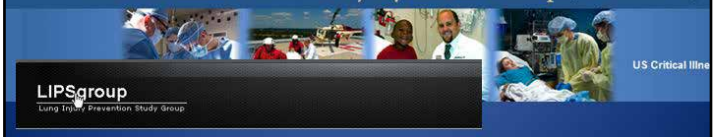
- 3855 patients analyzed after excluding surgical patients
- ASA protective against ALI in univariate analysis
- On multivariate analysis adjusted for propensity to receive ASA
  - OR = 0.70, 95% CI: 0.48- 1.03; p= 0.072

Kor et al. CCM 2011; 39:2393.

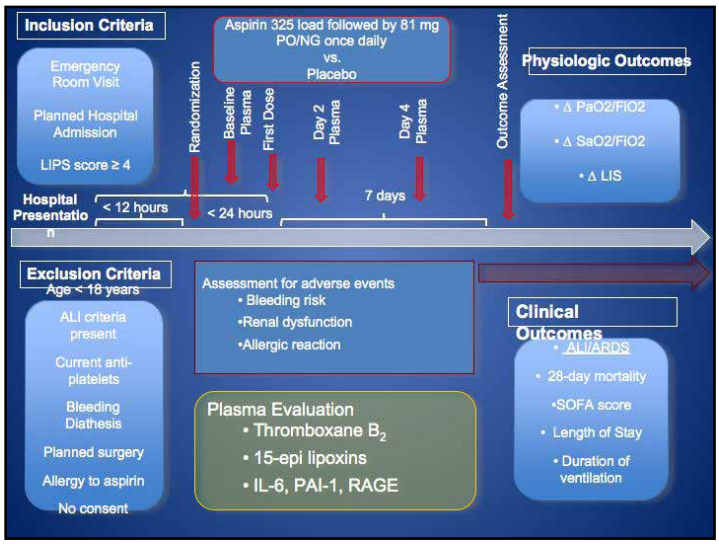
Lung Injury Prevention Study with Aspirin (LIPS-A)

- Phase II multicenter clinical trial
  - 14 US LIPS-A sites
  - NHLBI: U01-HL108712-01

U.S. Critical Illness *and* Injury Trials Group (USCIITG)



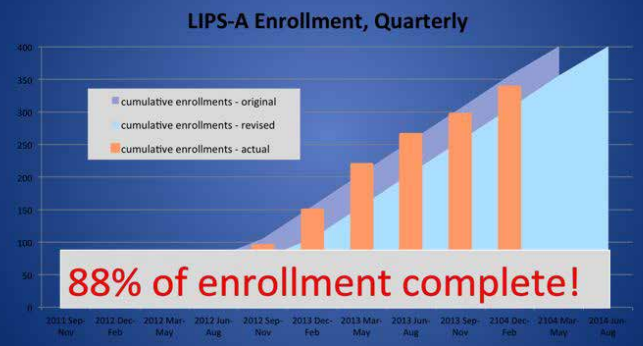
http://www.lipsgroup.org/



LIPS-A Study Centers

- Mayo Clinic –Gajic, Kor
- Beth Israel –Talmor
- Montefiore – Gong
- Bridgeport Hospital – Kaufman
- Brigham & Women's - Hou
- Duke - Welsby
- Harborview – Watkins
- Mass General - Bajwa
- Stanford – Levitt
- Temple - Gentile
- U FL - Elie
- U Michigan - Park
- Wake Forest – Hoth
- Mayo Clinic Jacksonville - Festic

LIPS-A Study Enrollment

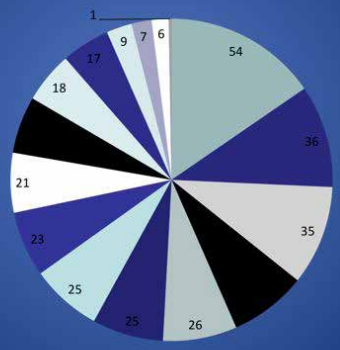


88% of enrollment complete!

As of Feb 28, 2014: original target 355, revised target 305, actual enrollment 338

11

Enrollment By Center



12

Program Materials

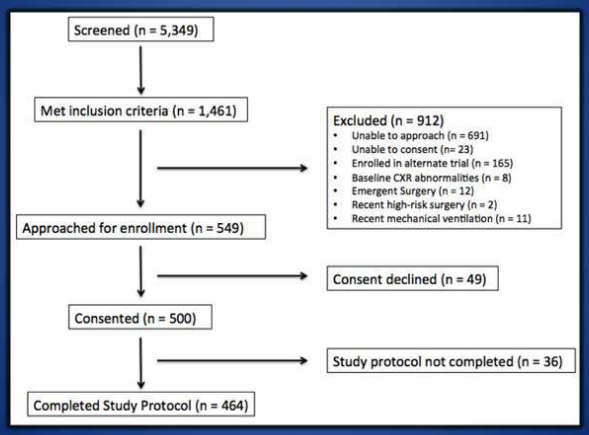
Risk Prediction and Mechanistic Evaluation of Postoperative Acute Lung Injury

- K23 HL 112855-01 (PI: Kor)
- **Aim 1:** To develop/validate an ARDS prediction model including evidence-based variables from both the preoperative and intraoperative domains using innovative, scalable, real-time perioperative data capture strategies.
- **Aim 2:** To compare serum levels of intraoperative and early postoperative sCD40L and TXA2 in those who develop postoperative ARDS versus those who do not using a nested case-control design.

Risk Prediction and Mechanistic Evaluation of Postoperative Acute Lung Injury – Aim 2

- Nested Case-control study
- Adult high-risk cardiac, vascular, thoracic surgery
  - 500 total enrollments
  - Expected rate of ARDS ≈ 10%
  - 50 Cases, 100 controls
- Outcome: Early postoperative ARDS
- Predictors: sCD40L and TXA2
  - 3, 6, 24 hours following surgical incision

Enrollment: K23 HL 112855-01



Conclusions

- ARDS prevention may prove more effective than treatment in modifying the onset/impact of ARDS
- The role of platelets in ARDS pathogenesis is increasingly appreciated
- Markers of platelet activation may facilitate the identification of patients at risk of postoperative ARDS
- Aspirin is an attractive preventative agent whose role is currently being defined

Acknowledgements

Mentors
- Ognjen Gajic, MD
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- Brad Narr, MD
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- Lavonne Liedl, RRT
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- Anita Baumgartner, RN
- Greg Wilson, RRT
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- Abbasali Akhoundi, MD
- Nagesh Madde

Platelet Function and ARDS Pathogenesis A Path to Prevention?

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SAB Oral Session (Part 2)

Junior Faculty Award Winner

Specializing Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline

Niccolo Terrando, B.Sc. (hons), DIC, Ph.D.

Notes: _____

Specialized Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline

Niccolò Terrando, Ph.D., Assistant Professor, Karolinska Institutet

- **Hospitalization for major surgery or critical illness often associates with cognitive decline. Inflammation and dysregulation of the innate immune system can exert broad effects in the periphery and central nervous system (CNS)**
- **Using a mouse model of orthopedic surgery we defined a key role of systemic cytokines, blood-brain barrier impairment and subsequent macrophage infiltration in contributing to neuroinflammation and hippocampal-dependent memory deficits.**
- **Resolvins are potent endogenous lipid mediators biosynthesized during the resolution phase of acute inflammation that display immunoresolvent actions and have potential to regulate the inflammatory sequelae and neuronal-glial function after trauma.**

AUA Association of University Anesthesiologists

Overall objective:

To understand mechanisms of postoperative cognitive dysfunction and define safer therapeutic strategies to control unresolved inflammation in a mouse model.

Intended learning outcomes:

1. To discuss novel evidence for the role of specialized pro-resolving mediators, namely aspirin-triggered resolvin D1, in preventing neuroinflammation and cognitive decline after orthopedic surgery.
2. To discuss novel evidence of neuronal dysfunction, including changes in synaptic plasticity (long-term potentiation) and glia homeostasis, after surgery.

AUA Association of University Anesthesiologists

2014 Abstract Award Winners

Junior Faculty Award	**CBN 1 (116)** **Inflammation Increases Brain Sensitivity to General Anesthetics** Sinziana Avramescu, MD, PhD, FRCPC[1], William T.H. To, MSc[2], Dian-Shi Wang, MD, PhD[2], Antonello Penna, MD, PhD[2], Irene Lecker, MSc[2], Beverley A. Orser, MD, PhD, FRCPC[3] [1]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [2]Department of Physiology, University of Toronto, Toronto, Ontario, Canada, [3]Department of Anesthesiology and Department of Physiology, University of Toronto Toronto, Ontario, Canada	*Oral Presentation:* SAB Oral Session (Part 1) Thursday, April 24, 2014 1:15 pm - 3:00 pm *Poster Discussion:* Moderated Poster Discussion: Clinical / Basic Neuroscience Thursday, April 24, 2014 3:00 pm - 4:30 pm
Junior Faculty Award	**CBN 9 (37)** **Specialized Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline** Niccolo Terrando, BSc (hons), DIC, PhD[1], Ting Yang, MD, PhD[1], Marta Galan, PhD[1], Ralph E. Harding, DO[2], Lars I. Eriksson, MD, PhD, FRCA[1] [1]Karolinska Institute Stockholm, Sweden, Karolinska, [2]The Carl Vinson Veterans Affairs Medical Center Dublin, Georgia	*Oral Presentation:* SAB Oral Session (Part 2) Saturday, April 26, 2014 2:10 pm - 3:30 pm *Poster Discussion:* Moderated Poster Discussion: Clinical / Basic Neuroscience Saturday, April 26, 2014 3:30 pm - 5:00 pm
Margaret Wood Resident Research Award	**Tox Pain 59 (112)** **Postoperative Dementia: Role of Anesthesia and APOE4** Katie J. Schenning, MD, MPH[1], Charles F Murchison, MS[1], Nora C. Mattek, MPH[1], Jeffrey A. Kaye, MD[1], Joseph F. Quinn, MD[1] [1]Oregon Health & Science University, Portland, Oregon	*Oral Presentation:* SAB Oral Session (Part 1) Thursday, April 24, 2014 1:15 pm - 3:00 pm *Poster Discussion:* Moderated Poster Discussion: Anesthetic Neurotox / Pain Thursday, April 24, 2014 3:00 pm - 4:30 pm
Resident Travel Award	**CBN 12 (85)** **miR-200c Contributes to Injury from Transient Cerebral Ischemia in Mice by Targeting Reelin** Creed M. Stary, MD, PhD[1], Lijun Xu, MD[1], Xiaoyun Sun, MD[1], Yibing Ouyang, PhD[1], Jason Leong, BS[2], Rona G. Giffard, MD, PhD[1] [1]Stanford University, Stanford, California, [2]Albert Einstein College of Medicine, Bronx, New York	*Oral Presentation:* SAB Oral Session (Part 2) Saturday, April 26, 2014 2:10 pm - 3:30 pm *Poster Discussion:* Moderated Poster Discussion: Clinical / Basic Neuroscience Saturday, April 26, 2014 3:30 pm - 5:00 pm
Resident Travel Award	**CS 68 (71)** **Genetic Deletion of the GABA-A α4 Subunit Leads to Increased Airway Resistance and Inflammation** Gene T. Yocum, MD[1], Damian L. Turner, PhD[1], Jennifer Danielsson, MD[1], Matthew B. Barajas, BS[1], Gregg E. Homanics, PhD[2], Charles W. Emala, MD, MS[1] [1]Columbia University, New York, New York, [2]University of Pittsburgh, Pittsburgh, Pennsylvania	*Oral Presentation:* SAB Oral Session (Part 1) Thursday, April 24, 2014 1:15 pm - 3:00 pm *Poster Discussion:* Moderated Poster Discussion: Cell Signaling Thursday, April 24, 2014 3:00 pm - 4:30 pm

CBN 1 (116)

Junior Faculty Award

Inflammation Increases Brain Sensitivity to General Anesthetics

Sinziana Avramescu, MD, PhD, FRCPC[1], William T.H. To, MSc[2], Dian-Shi Wang, MD, PhD[2], Antonello Penna, MD, PhD[2], Irene Lecker, MSc[2], Beverley A. Orser, MD, PhD, FRCPC[3]

[1]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [2]Department of Physiology, University of Toronto, Toronto, Ontario, Canada, [3]Department of Anesthesiology and Department of Physiology, University of Toronto, Toronto, Ontario, Canada

Introduction and General Purpose of the Study: Modern anesthetic drugs have revolutionized medical care and each year over 234 million anesthetics are administered for surgical procedures worldwide. The sensitivity to general anesthetics is often enhanced in critically ill patients through mechanisms that are poorly understood[1]. This hypersensitivity is frequently attributed to indirect mechanisms such as altered drug pharmacokinetics[2] or patient hemodynamic instability[3]. Most general anesthetics are positive allosteric modulators of the inhibitory γ-aminobutyric acid type A (GABAA) receptor[4]. Recent evidence shows that inflammation, which usually accompanies critical illnesses, increases the surface expression of GABAA receptors[5]. Here, we studied the hypothesis that inflammatory factors increase the sensitivity of neurons to anesthetics.

Methods: Cultured hippocampal neurons were pre-treated with the pro-inflammatory cytokine IL-1β or a control solution. GABA-evoked currents were recorded in the absence and presence of an intravenous anesthetic (etomidate) or an inhalational anesthetic (isoflurane) using whole-cell patch clamp techniques. In addition, we studied the effects of systemic inflammation on behavioural sensitivity to etomidate and isoflurane in adult male mice in vivo. Animals were treated with the pro-inflammatory agent lipopolysaccharide (LPS) and anesthetic-induced loss of righting reflex (LORR) and loss of tail-clamp withdrawal reflex (LOTW) were measured.

Results and Major Findings: The amplitude of GABA-evoked current was 2-fold greater in IL-1β-treated neurons compared to controls (Control: 80 +/- 10 pA, n =24; IL-1β: 162 +/- 18 pA, n =28, $p < 0.001$). Etomidate (3 μM) further increased the GABA current up to 12-fold in IL-1β treated cells compared to controls. Isoflurane-mediated (1 MAC) GABA conductance was 8-fold greater in IL-1β-treated neurons compared to controls. The concentration-response plot for etomidate showed that IL-1β increased the maximal etomidate current 3 fold (Imax control: 1017 +/- 202 pA, n=5; Imax IL-1β: 3314 +/- 260 pA, n=9, $p<0.001$) but did not change its half maximal concentration (EC50 control: 11 +/- 6 μM, n=5; EC50 IL-1β: 13 +/- 3 μM, n=9, p=0.7). Similarly, IL-1β increased the maximal isoflurane current 1.5 fold (Imax control: 1037 +/- 92 pA, n=8; Imax IL-1β: 1544 +/- 145 pA, n=10, p=0.01) but not its maximal concentration (EC50 control: 314 +/- 37 μM, n=6; EC50 IL-1β: 348 +/- 29 μM, n=8, p=0.5). Systemic inflammation induced by LPS increased the sensitivity to etomidate- and isoflurane-induced LORR and etomidate-induced LOTW. Isoflurane-induced LOTW, which is not a GABAA receptor dependent behavioural endpoint, was unaffected by LPS.

Conclusions: Neuronal sensitivity to both an injectable and inhaled anesthetic was much greater in cells treated with IL-1β compare to controls. Behavioural studies corroborated our in vitro findings. These results need to be considered when selecting an appropriate dose of anesthetics for critically ill patients.

References:

1. Anesth & Analg 2005; 100:4-10.
2. J Pharm Sci 2003; 92:104-114.
3. Anesthesiology 2003; 99:409-420.
4. Nat Rev Neurosci 2004; 5: 709-20.
5. Cell Rep 2012, 2(3):488-96.

CBN 9 (37)

Junior Faculty Award

Specialized Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline

Niccolo Terrando, BSc (hons), DIC, PhD1, Ting Yang, MD, PhD[1], Marta Galan, PhD[1], Ralph E. Harding, DO[2], Lars I. Eriksson, MD, PhD, FRCA[1]
[1]Karolinska Institute Stockholm, Sweden, Karolinska, [2]The Carl Vinson Veterans Affairs Medical Center, Dublin, Georgia

Introduction: Cognitive decline following surgery and acute illness is a common complication without defined etiology. Systemic inflammation after surgical trauma has been related to changes in blood-brain barrier permeability, macrophage infiltration in the hippocampus, and subsequent neuroinflammation with memory impairments[1]. Herein we further our understanding on how peripheral surgery disrupts synaptic circuitry in the hippocampus and, for the first time, describe how treatment with aspirin-triggered resolvin D1 (AT-RvD1), a novel specialized pro-resolving mediator derived by omega-3 fatty acids[2], counter regulates deleterious effects of exacerbated inflammation within the brain in a mouse model of postoperative cognitive decline.

Methods: 12-wk-old male C57BL/6 mice were randomly assigned as follows: 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 AT-RvD1 treatment (IP bolus, 100 ng dose/mouse), or 4) AT-RvD1 alone. Separate cohorts of animals were used to perform electrophysiology, systemic and central inflammatory changes including astrocytes (GFAP) immunofluorescence, and hippocampal-dependent cognition using trace fear conditioning (TFC). Results: Peripheral surgery impairs synaptic plasticity and long-term potentiation (LTP) starting at 24h and peaking 72h postoperatively. This neuronal dysfunction was further associated with astrocyte activation in the hippocampus, characterized by changes in morphology marked by enlarged cell bodies and reduced filaments. Pre-emptive administration of AT-RvD1 (as little as 100 ng/mouse) improved neuronal function (Figure 1), restoring astrocytic dysfunction and neuroinflammation. Microarray gene expression patterns were analyzed in hippocampal tissue after surgery and following treatment. Gene ontology (GO) analyses of downregulated genes show a marked effect of AT-RvD1 on cognitive and neurological system processes. Functionally, at 72h surgical animals were tested with TFC to assess hippocampal-dependent memory function and further displayed memory dysfunction that was fully reverted by treatment with AT-RvD1.

Conclusion: Overall, peripheral surgery affects synaptic transmission and plasticity causing postoperative cognitive decline. Administration of specialized proresolving mediators, including AT-RvD1, may be an effective therapeutic option to effectively modulates the inflammatory sequelae and restore neuronal-glial function after trauma[3].

References:

1. Ann Neurol, 70(6):986-95, 2011
2. J. Biol. Chem. 282, 9323–9334, 2007
3. FASEB J, 27(9):3564-71, 2013

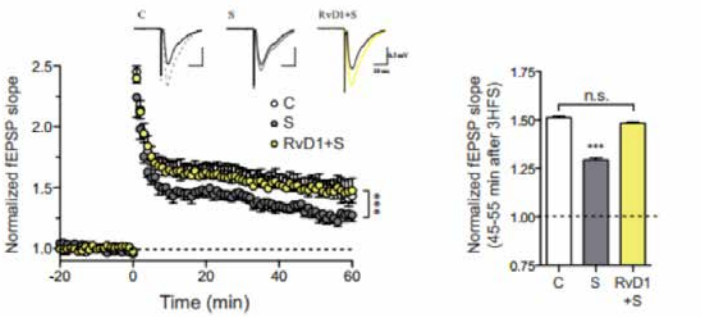

Figure 1: AT-RvD1 prevents surgery-induced hippocampal synaptic transmission and plasticity impairments. LTP of CA1-CA3 pyramidal cell synapses after surgery. Systemic AT-RvD1 pretreatment reverted 72-h LTP levels to control ($P<0.0001$; 2-way ANOVA). Mean of the last 10 min (45–55 min) of LTP recording. Data are means ± sem (n=11–7 slices from 6–4 animals/group).

Tox Pain 59 (112)

Margaret Wood Resident Research Award

Postoperative Dementia: Role of Anesthesia and APOE4

Katie J. Schenning, MD, MPH[1], Charles F Murchison, MS[1], Nora C. Mattek, MPH[1], Jeffrey A. Kaye, MD[1], Joseph F. Quinn, MD[1]
[1]Oregon Health & Science University, Portland, Oregon

Introduction: The elderly receive more than 1/3 of the over 40 million anesthetics delivered yearly in the US, and evidence suggests that the elderly have the highest risk for deleterious postoperative neurocognitive outcomes, including dementia.[1] Studies suggest that surgery and/or anesthesia contribute to cognitive decline and enhance neuropathologic changes that underlie Alzheimer's disease (AD).[2-4] Despite this evidence, controversies remain regarding whether exposure to anesthesia is associated with the development of AD. Whether certain individuals are predisposed to postoperative dementia by virtue of genetic makeup or other factors is unknown. While presence of an apolipoprotein E ε4 (APOE4) allele increases the risk of developing AD, an association between APOE4 and postoperative dementia is not established.[5] The overall objective of the study was to determine how general anesthetic (GA) exposure and APOE genotype expression affect cognition, brain volume, functional status, and activity in two existing natural history studies of cognitive aging. We hypothesized that exposure to GA in the elderly leads to an accelerated rate of cognitive decline that is more rapid in those with an APOE4 allele.

Methods: We performed a retrospective cohort analysis of two natural history studies of cognitive aging: Study "O" and Study "I". We used mixed-effects models to assess the relationship between exposure to surgery/GA and the longitudinal rate of change in cognition, functional status, brain volumes, and activity using the outcome measures in Table 1. Next, APOE genotype was added to the model to investigate its role in moderating the relationship between GA exposure and the listed outcomes.Results were considered significant at $p<0.05$.

Results: Analysis was performed in 304 participants in Study "O" and 223 participants in study "I." 39.5% of participants in Study O and 27.8% of participants in Study I were exposed to GA. In Study O and Study I, 16.8% and 29.4% of participants were APOE4 carriers, respectively. After controlling for age, significant increases in rate of change over time in those exposed to GA were found in the following: ADL ($t=2.29$, $p=0.011$), Cumulative Illness Rating ($t=2.48$, $p=0.0067$), CERAD Word List delayed recall ($t=-2.25$, $p=0.012$), and delayed Logical Memory Recall ($t=-1.81$, $p=0.035$). Taking Logical Memory Recall as a conservative exemplar (15% change), the difference was significant at $\alpha=0.05$ with a power ≥ 88%. In those exposed to GA, significant exacerbation of decline over time was found specific to APOE4 carriers in MMSE score ($t=-2.71$, $p=0.0036$), IADL ($t=2.13$, $p=0.017$), CDR ($t=1.99$, $p=0.024$), and CERAD Word List delayed recall ($t=-3.53$, $p<0.001$). Considering the smallest change observed, 81% lower CDR scores in APOE4 carriers, the significant difference was still observed at a power ≥ 97%.

Conclusions: We found that a history of exposure to GA was significantly associated with an accelerated rate of decline in ADLs and measures of cognitive function in two natural history studies of cognitive aging. Further, among participants with a history of GA exposure, APOE4 carriers had significant exacerbations of rate of decline in cognitive function when compared to participants without an APOE4 allele.

References:

1. Prog Neuro-Psychopharmacol Biol Psychiatry 2013;47:162-6.
2. J Neurosci 2007;27:1247-54
3. J Neurosci 2007;27:3090-7
4. Anaesthesia 2010;65:388-95.
5. Prog Neuro-Psychopharmacol Biol Psychiatry 2013;47:128-34

Table 1

Patient factors	Age, sex, years of education, APOE genotype, family history of dementia, anesthesia exposure, Cumulative Illness Rating
Cognitive outcome measures	Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), CDR sum of boxes, Consortium to Establish a Registry for AD (CERAD) Word List Delayed Recall, Animal Fluency, Trail Making Test B, Digit Symbol Test, Logical Memory Delayed Recall
Function outcome measures	Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Functional Activities Questionnaire (FAQ)
Neuroimaging outcome measures	Total brain volume, hippocampal volume and white matter hyperintensity volume
Activity outcome measures*	In-home activity measures such as walking speed, time out of house, computer use, and nighttime behavior

*"I" cohort only

Awards

CBN 12 (85)

Resident Travel Award

miR-200c Contributes to Injury From Transient Cerebral Ischemia in Mice by Targeting Reelin

Creed M. Stary, MD, PhD[1], Lijun Xu, MD[1], Xiaoyun Sun, MD[1], Yibing Ouyang, PhD[1], Jason Leong, BS2, Rona G. Giffard, MD, PhD[1]
[1]Stanford University, Stanford, California, [2]Albert Einstein College of Medicine, Bronx, New York

Introduction and General Purpose: Stroke remains a devastating peri-operative complication, with limited treatment options available to minimize brain injury. MicroRNAs (miRs) are non-coding strands of RNA that regulate gene expression by inhibiting translation of target mRNAs. miR-200c increases acutely in the brain following transient cerebral ischemia (1), however its role in post-stroke brain injury is unclear. In other organ systems, miR-200c contributes to cell death by silencing pro-survival genes (2). Sequence homology identifies reelin, a neurotrophic and neuroprotective protein, as a predicted neuronal target of miR-200c. We hypothesized that miR-200c contributes to injury from transient cerebral ischemia by targeting reelin.

Methods: All experiments were performed according to the Stanford University Animal Care and Use Committee and followed the Stroke Therapy Academic Industry Roundtable recommendations (3). The contribution of miR-200c to stroke-related brain injury was examined in vivo by subjecting male CB57/B6 mice (n = 11-23) to 1 hr of middle cerebral artery occlusion (MCAO) following randomized treatment with intracerebroventricular infusion of miR-200c antagomir, mimic or control. Infarct volume was assessed following 24 hrs of reperfusion. Post-MCAO miR-200c and reelin mRNA (Reln) expression were determined in antagomir pre-treated and control mice by RT-qPCR, and reelin protein by immunoblot. Targeting of reelin by miR-200c was assessed in vitro by: 1) dual luciferase assay; and, 2) assessing cell death following in vitro injury (24 hrs serum deprivation + 500 μM H202) in N2A cells co-transfected with miR-200c mimic/inhibitor with and without Reln siRNA. All cell culture experiments were repeated in triplicate. All data reported are mean±SEM. Statistical analyses: t-test if two conditions, one-way ANOVA with Bonferroni post-test for multiple comparisons; a p-value of <0.05 was considered significant.

Results and Major Findings: In brains of mice subjected to MCAO, by 1 hr reperfusion miR-200c significantly increased (18.8±6.9 fold) relative to sham surgery mice, which was blocked by antagomir pre-treatment (0.18±0.5 fold). miR-200c antagomir resulted in a significant decrease in infarct volume while mimic had no effect (Fig 1-A). MCAO alone caused a significant decrease in Reln mRNA (0.77±0.08 fold) and reelin protein (0.81±0.06 fold), while antagomir pre-treatment significantly increased post-MCAO Reln mRNA (1.56±0.18 fold) and reelin protein (1.38±0.05 fold) expression. Targeting of reelin by miR-200c was verified with dual luciferase assay whereby activity of the luciferase reporter with the Reln 3'UTR was reduced by wild-type miR-200c (0.40±0.04 fold) but not by seed mutant control (1.09±0.18 fold). Treatment of N2A cells with miR-200c inhibitor augmented cell survival, while mimic had the opposite effect (Fig. 1-B). Co-transfection of Reln siRNA abolished the protective effect of miR-200c inhibitor and approximated cell death with mimic (Fig. 1-B).

Conclusions: These findings suggest that the post-stroke increase in miR-200c contributes to neuronal cell death by inhibiting reelin expression, and that reducing post-stroke miR-200c is protective. Future directions will determine the therapeutic potential of post-stroke miR-200c inhibition, including: 1) exploring less invasive methods to deliver miR-based treatments, including intravenous and intraperitoneal delivery; and, 2) examining the effect of miR-200c inhibition on long-term neurobehavioral outcome.

References:

1. MicroRNAs induced during ischemic preconditioning. Stroke 41: 1646-1651, 2010.
2. miR-200c regulates induction of apoptosis through CD95 by targeting FAP-1. Mol Cell 38: 908-915, 2010.
3. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke 40: 2244-2250, 2009.

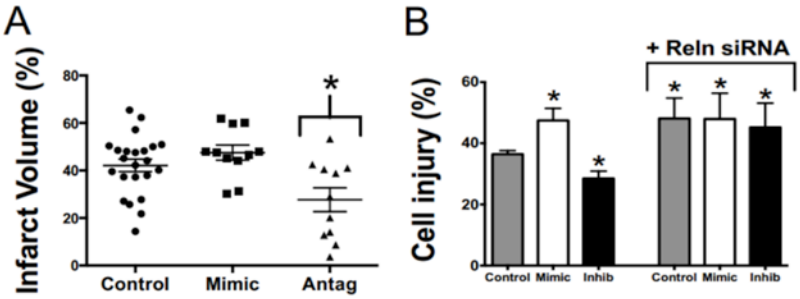

Figure 1 **A.** Infarct volume following 1 hr middle cerebral artery occlusion in mice subjected to intracerebroventricular pre-treatment with miR-200c antagomir, mimic, or mismatch-control (n = 11-23 animals/group). Significant protection was observed with miR-200c antagomir pre-treatment. **B.** Cell death in neuronal N2A cells following *in vitro* injury increased following transfection with miR-200c mimic but decreased with inhibitor. Co-transfection with Reln siRNA resulted in levels of cell injury similar to transfection with mimic alone. All cell culture assays performed in triplicate, n = 4-6 wells/group/experiment. * = P < 0.01 different than control.

Awards

CS 68 (71)

Resident Travel Award

Genetic Deletion of the GABA-A α4 Subunit Leads to Increased Airway Resistance and Inflammation

Gene T. Yocum, MD[1], Damian L. Turner, PhD[1], Jennifer Danielsson, MD[1], Matthew B. Barajas, BS[1], Gregg E. Homanics, PhD[2], Charles W. Emala, MD, MS[1]
[1]Columbia University, New York, New York, [2]University of Pittsburgh, Pittsburgh, Pennsylvania

Introduction: In recent years there has been increasing interest in the potential for anesthetics to affect cancer recurrence[1] and sepsis[2,3]. Many anesthetic agents activate GABA-A channels, and these channels are present on immune cells[4], providing a potential mechanistic link. Asthma is modulated by multiple cells types, including immune cells and hypercontractile airway smooth muscle (ASM) cells. Like immune cells, ASM cells also express GABA-A channels, particularly GABA-A channels containing α4 subunits[5]. Thus, we sought to determine if GABA signaling modulates the contractile and inflammatory phenotype of an allergic asthma model utilizing GABA-A α4 subunit global knockout mice.

Methods: Wild type (WT) and GABA-A α4 subunit knockout (α4 KO) mice were sensitized with house dust mite (HDM) antigen (40 μg) or PBS intranasally 5 days/wk X 3 weeks. In vivo airway resistance and ex vivo tracheal ring smooth muscle contraction force/relaxation were measured using non-sensitized (PBS) and sensitized (HDM) WT and α4 KO mice. Further, relaxation induced by a novel GABA-A α4 selective agonist, CMD-45, was measured using ex vivo tracheal rings from non-sensitized WT and α4 KO mice. Lungs were collected for histologic analysis and, following enzymatic digestion, for immune cell differential and flow cytometric analyses.

Results: Ex vivo tracheal rings from HDM-sensitized WT and α4 KO mice exhibited similar magnitudes of acetylcholine-induced contractile force and isoproterenol-induced relaxation ($p>0.05$; n=4). In contrast, in vivo lung resistance was significantly increased in α4 KO mice ($p<0.05$, n=8, figure). Moreover, the α4 KO mice demonstrated increased eosinophilic lung infiltration, increased markers of T cell activation (CD62L low, CD 44 high) and higher levels of lymphocyte apoptosis (DAPI staining). Tracheal rings from WT mice demonstrated enhanced relaxation in response to CMD-45 compared to α4 KO mice ($p<0.05$, n=6).

Discussion: HDM sensitized α4 KO mice have higher in vivo airway resistances than WT mice, though tracheal rings isolated from these mice are equally reactive ex vivo. Given HDM sensitized α4 KO mice also demonstrate enhanced inflammation, this suggests the heightened inflammatory state accounts for the increased in vivo airway reactivity and that the GABA-A α4 subunit plays a critical role in immune function. Thus, GABA-A α4 subunit-specific agonists have the potential to combat asthma via two mechanisms: direct ASM relaxation and inhibition of airway inflammation.

References:

1. Br J Anaesth, 2012. 109 Suppl 1: p. i17-i28.
2. Crit Care Med, 2013. 41(7): p. 1627-36.
3. Crit Care, 2010. 14(2): p. R38.
4. Amino Acids, 2013. 45(1): p. 87-94.
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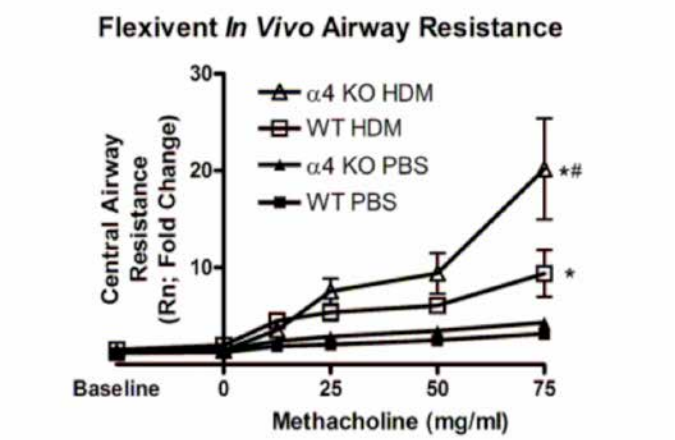

***In vivo* airway resistance during a graded methacholine challenge by Flexivent analysis.** Central airway resistances (Rn) are presented as fold change from baseline (mean +/- S.E.M.). HDM sensitization lead to a significantly increased resistance in both WT and α4 KO mice compared to their corresponding unsensitized (PBS) controls by area under curve analysis (*, $p<0.01$). Furthermore, HDM sensitized α4 KO mice were also significantly more reactive than sensitized WT mice (#, $p<0.05$). n=8.

Oral Presentations

Thursday, April 24, 1014 • 1:15pm – 3:00 pm

SAB Oral Session (Part 1)

Moderators: Max Kelz, MD, PhD; Nabil Alkayed, MD, PhD

Junior Faculty Award	**CBN 1 (116) • Inflammation Increases Brain Sensitivity to General Anesthetics** **Sinziana Avramescu, MD, PhD, FRCPC[1],** William T.H. To, MSc[2], Dian-Shi Wang, MD, PhD[2], Antonello Penna, MD, PhD[2], Irene Lecker, MSc[2], Beverley A. Orser, MD, PhD, FRCPC[3] [1]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada [2]Department of Physiology, University of Toronto, Toronto, Ontario, Canada [3]Department of Anesthesiology and Department of Physiology, University of Toronto, Toronto, Ontario, Canada *Please see page 57 for complete abstract.*
	Tox Pain 55 (53) • Increased GABA-B Receptor Inhibition Contributes to Anesthetic-Induced Depression of Synapses **Bruce M. MacIver, MSc, PhD[1]** [1]Stanford University, Stanford, California
Resident Travel Award	**CS 68 (71) • Genetic Deletion of the GABA-A ∝4 Subunit Leads to Increased Airway Resistance and Inflammation** **Gene T. Yocum, MD[1],** Damian L. Turner, PhD[1], Jennifer Danielsson, MD[1], Matthew B. Barajas, BS[1], Gregg E. Homanics, PhD[2], Charles W. Emala, MD, MS[1] [1]Columbia University, New York, New York, [2]University of Pittsburgh, Pittsburgh, Pennsylvania *Please see page 61 for complete abstract.*
	O 24 (88) • Pediatric Delirium in Infants and Preschool-Aged Children: **Validation of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)** **Heidi AB. Smith, MD, MSCI[1],** Molly Gangopadhyay, MD[1], Mary Hamilton Chestnut, NP[1], Jennifer Thompson, MPH[1], D. Catherine Fuchs, MD[1], Pratik Pandharipande, MD[1] [1]Vanderbilt University, Nashville, Tennessee
Margaret Wood Resident Research Award	**Tox Pain 59 (112) • Postoperative Dementia: Role of Anesthesia and APOE4** **Katie J. Schenning, MD, MPH[1],** Charles F Murchison, MS[1], Nora C. Mattek, MPH[1], Jeffrey A. Kaye, MD[1], Joseph F. Quinn, MD[1] [1]Oregon Health & Science University, Portland, Oregon *Please see page 59 for complete abstract.*
	CS 74 (114) • Propofol Infusion Impairs Complex 1 Activity in Human Muscle **David M. Polaner, MD[1],** Johan Van Hove, MD, PhD[1], Marissa Friedrich, PhD[1], Jeannie Zuk PhD, RN[1], Bjoern Schniewind, PhD[1], Jeffrey Galinkin, MD[1] [1]University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado
	CS 73 (100) **Pharmacogenetic Determinants of Interindividual Variability in Methadone Metabolism and Disposition:** **The Role of Cytochrome P4502B6 (CYP2B6)** **Evan D. Kharasch, MD PhD[1],** Sarah Gadel, BS[1], Amanda Crafford, BS[1], Jennifer Parchomski, RN[1], Karen Regina, MS[1], Jane Blood, RN[1] [1]Washington University in St. Louis, St. Louis, Missouri
	CS 67 (56) **Single Nucleotide Polymorphism-Specific Regulation of Matrix Metalloproteinase-9** **by Multiple Mirnas Targeting The Coding Exon** **Tyler Duellman, BS,** Jay Yangm, MD, PhD[1] [1]University of Wisconsin-Madison, Madison, Wisconsin

Tox Pain 55 (53)

Increased GABA-B receptor inhibition contributes to anesthetic-induced depression of synapses.

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GABA-A-mediated inhibition has long been recognized to contribute to the CNS depression produced by general anesthetics, however, few studies have looked at GABA-B receptor-mediated inhibition in this regard. Our lab recently found that some of the depression produced by propofol on CA1 neuron synaptic responses involved GABA-B receptor enhancement. This prompted us to study GABA-B-mediated inhibition as a target for isoflurane-induced depression of CA1 neurons. Isoflurane-induced depression of population spike recordings from the hippocampal CA1 area of rat (Long-Evans) in brain slices (400 μ) were measured. Slices were maintained in submerged chambers at 22 C and continuously perfused at 2 ml/min. Schaffer-collaterals received an electrical orthodromic stimulus to produce population spike responses recorded from the stratum oriens. Paired-pulse orthodromic responses at varying inter-pulse intervals were used to assess the degree and time course of inhibition. Isoflurane, at 0.7 rat MAC (1.0 vol%; 0.245 mM), produced about a 50% depression of CA1 neuronal population spike response amplitudes. Blocking GABA-B inhibition with CGP-55845 (100 μM) reversed 11.2% ($p<0.01$; n=5) of this propofol-induced depression. This percentage reversal was attained after inhibiting all GABA-mediated ionotropic inhibition with picrotoxin (100 μM), a GABA-A fast, slow, tonic and non-GABA chloride channel blocker. Overall, in the presence of picrotoxin and CGP-55845, the propofol-induced depression was reversed by 83.0%. Results from this study indicate that some of isoflurane's depressant effects appear to be accomplished through enhancing GABA-B-mediated inhibition. It is likely that GABA-B receptors located on CA1 neuron dendrites contribute to this effect. If GABA-B receptors on GABA nerve terminals were involved we would have expected an opposite effect, and the GABA-B effect persisted when all GABA-A inhibition was blocked. Further studies will address a possible effect of isoflurane on GABA-B receptors on glutamate nerve terminals.

O 24 (88)

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

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Introduction: Delirium is an acute state of brain dysfunction that occurs in up to 80% of critically ill adults on mechanical ventilation, associated with significantly worse outcomes such as long-term cognitive impairment and death. Advances in delirium research in children lag behind that in adults due to lack of valid and developmentally appropriate delirium monitoring instruments. Thus the true prevalence and significance of delirium in this fragile population remains unknown. The Pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU) was recently validated against formal neuropsychiatric assessments (specificity 99%; sensitivity 83%) to diagnose delirium in critically ill children over 5 years of age, adapted from the most widely used adult delirium tool called the CAM-ICU.[1] These tools are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for delirium diagnosis including: acute change or fluctuation in mental status (Feature 1), inattention (Feature 2), altered level of consciousness (Feature 3) and disorganized thinking (Feature 4). Delirium is present when patients demonstrate both features 1 and 2, and either feature 3 or 4. Children less than 5 years of age, however, pose challenges for delirium diagnosis due to vast changes in their cognitive and developmental skills from infancy to early childhood. The objective of this study was to create and validate a delirium instrument for critically ill infants and preschool-aged children, using standardized, developmentally appropriate measurements.

Methods: An interdisciplinary team comprised of pediatric anesthesiology/critical care, psychology, neurology, developmental pediatrics, and psychiatry adapted the pCAM-ICU to create the PreSchool Confusion Assessment Method for the ICU (psCAM-ICU). The psCAM-ICU is founded on the four cardinal features of delirium and adjusted using valid neurocognitive and developmental assessments for infants and toddlers. The prospective validation study of the psCAM-ICU was then conducted in critically ill patients aged 6 months to 5 years admitted to the PICU of a tertiary medical center. Patients with hearing/visual impairments, non-English speaking, moribund, or surrogate refusal of consent, were excluded. Enrolled patients were independently assessed daily by both the research team (RN or MD) using the psCAM-ICU and the reference standard, a psychiatrist using DSM-IV-TR criterion. Bootstrapping supported calculation of confidence intervals for proportions, accounting for multiple assessments on the same patient.

Results: A total of 219 blinded delirium assessments were completed on 127 enrolled patients with a median age of 21 months (IQR 11,36). Compared with the reference standard for delirium diagnosis, the psCAM-ICU demonstrated a sensitivity of 84% (95%CI 71%-92%) and specificity of 91% (95%CI 84%-95%). The psCAM-ICU performed similarly within the study cohort with a sensitivity and specificity of 85% (95%CI 71%-93%) and 91% (95%CI 82%-96%) among infants and toddlers, and 80% (95%CI 42%-96%) and 90% (95%CI 77%-96%) in children > 2 years, respectively. Among mechanically ventilated patients, the psCAM-ICU demonstrated a sensitivity of 85% (95%CI 54%-95%) and specificity of 100%. Delirium was detected in 36% of enrolled patients by the psCAM-ICU and in 29% of patients by the reference standard.

Conclusions: The psCAM-ICU is a highly valid instrument for delirium diagnosis in critically ill infants and young children. The psCAM-ICU may facilitate needed epidemiological studies on delirium among critically ill pediatric patients.

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CS 74 (114)

Propofol infusion impairs Complex 1 activity in human muscle

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Introduction: Prolonged propofol infusions have been associated with metabolic acidosis, rhabdomyolysis, dysrhythmias and cardiovascular collapse, a constellation that has been termed propofol infusion syndrome (PRIS)[1] Acid base perturbations have been described during propofol anesthetics and attributed to subclinical PRIS, although more definitive evidence is lacking[2] Previous investigations suggest that PRIS is due to impaired mitochondrial metabolism due to failure of electron transport at Complex 2.[3] We theorized that occult evidence of PRIS might be detected in children undergoing prolonged anesthesia with propofol, and that measuring respiratory chain enzyme (RC) activity might provide better insight into its causative mechanisms.

Methods: We studied 71 children with scoliosis but without mitochondrial disease undergoing posterior spinal fusion under propofol-remifentanil anesthesia (group P) and 11 controls receiving dexmedetomidine-remifentanil anesthesia (group C). Propofol and 4-OH propofol levels, blood gases, lactate, triglycerides and acylcarnitine profiles were measured hourly during the anesthetic and at 24 hours. A paraspinous muscle sample was obtained at the end of the operation to measure RC enzymes, and propofol and 4-OH propofol levels in muscle tissue. Additionally, isolated banked normal muscle tissue was incubated in vitro with varying concentrations of propofol and 4-OH propofol; drug levels and RC enzymes were assayed.

Results: The mean weight of subjects was 48.5±3.5kg. Group P subjects received an average of 21.8±2.6 mg/kg of propofol. Acid-base status was not different between groups, but 11 patients in group P had lactate levels over 3mmol/dL occurring between 3-5 hours of anesthetic time. Acylcarnitine profiles showed only non-specific mild elevations. Propofol and 4-OH propofol levels in blood averaged 3.16mcg/mL and 16.58ng/mL, respectively, but there was a pronounced non-normal distribution with significant outliers of levels up to 8-fold higher than the mode or median values. RC enzyme assays in study subjects showed mild depression of Complex 1 in group P, and no abnormalities in in Complexes 2-4, while controls showed no diminution from normal values.

When propofol and 4-OH propofol were incubated in incremental concentrations with 10 samples of banked human muscle, levels in muscle were between 2 and 40 times higher than that measured in blood (average 31.22ng/g vs 2.77ng/l). RC activity was depressed from 45-50 % in Complex 1, and unchanged in Complexes 2 - 4.

Discussion: Propofol inhibits RC enzyme activity primarily at Complex 1, not in Complex 2 as previously reported. We also believe that reported elevations in C3 acylcarnitine levels may be due to non-specific alterations in fatty acid metabolism and are not pathognomonic of PRIS. Although RC changes in muscle under our clinical conditions were modest, concentrations of propofol and 4-OH propofol in muscle are considerably higher than those measured in blood. These levels are achievable in some patients during clinically relevant propofol infusion rates. Furthermore, there are wide discrepancies between patients in the levels seen with similar infusion rates, suggesting that pharmacogenomic factors may be important in the pathogenesis of this disorder.

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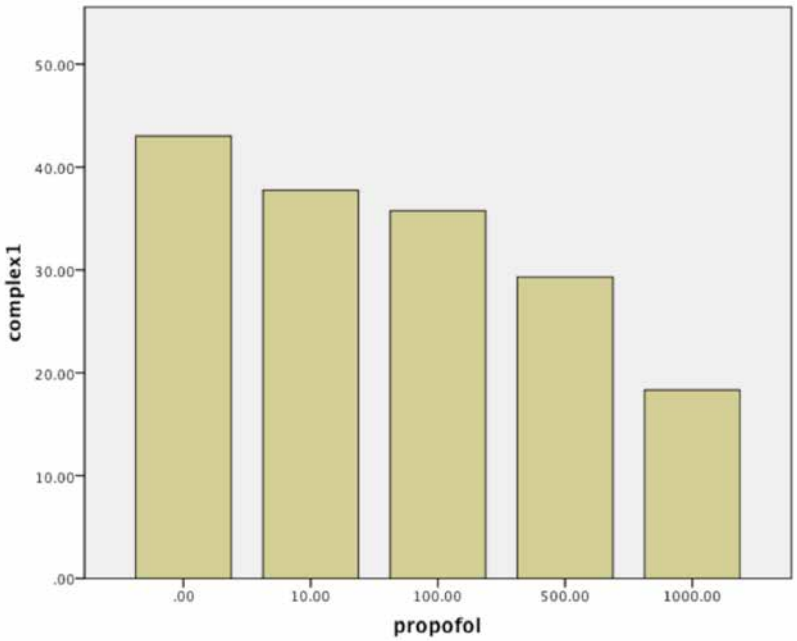

CS 73 (100)

Pharmacogenetic Determinants of Interindividual Variability in Methadone Metabolism and Disposition: The Role of Cytochrome P4502B6 (CYP2B6)

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Background: There is considerable unexplained interindividual variability in methadone clearance. Methadone N-demethylation to EDDP in vitro and in vivo, and methadone clinical clearance, are mediated mainly by hepatic CYP2B6. CYP2B6 has numerous genetic variants. Influence of CYP2B6 genetic variability on methadone metabolism and clearance is unknown. This translational investigation evaluated methadone metabolism in vitro by various human CYP2B6 allelic variants. Following identification that CYP2B6.6, the protein variant encoded by the CYP2B6*6 polymorphism, is catalytically deficient compared with wild-type CYP2B6.1, a clinical pharmacokinetic evaluation was performed to test the hypothesis that CYP2B6*6 carriers have altered methadone metabolism and clearance in vivo.

Methods: Common human CYP2B6 allelic variants (CYP2B6.1, 2B6.4, 2B6.5, and 2B6.6) were co-expressed with P450 reductase and cytochrome b5. Individual methadone enantiomers metabolism to EDDP was quantified by LC-MS-MS. Two IRB-approved clinical protocols in healthy volunteers then followed, after obtaining informed consent. Subjects (n=486) were genotyped for 516G>T, 785A>G, 983T>C, 1459C>T CYP2B6 polymorphisms, and haplotypes identified. Three CYP2B6 genotype cohorts were recruited: CYP2B6*1/*1 (n=20), CYP2B6*1/*6 (n=20), and CYP2B6*6/*6 (n=12). Subjects received 6 mg IV and 11 mg oral d5-methadone. Plasma and urine methadone and EDDP concentrations were determined by stereoselective LC-MS-MS.

Results: In vitro EDDP formation from therapeutic (0.25-1 μM) R- and S-methadone was CYP2B6.4>CYP2B6.1>CYP2B6.5>CYP2B6.6. In vitro intrinsic clearance for CYP2B6.6 was only about one-third that for wild-type CYP2B6.1; that for CYP2B6.4 was almost 2-fold greater than CYP2B6.1. Stereoselective metabolism of methadone metabolism by CYP2B6.1 (S>R) was maintained with all CYP2B6 variants. In the clinical study, in CYP2B*1/*1, *1/*6, and *6/*6 genotypes, IV R-methadone mean area under the plasma curve (AUC) was 428, 395, 718 ng-hr/ml, clearance (CL) was 6.8, 7.5, 4.6 L/hr, and EDDP/methadone AUC ratio was 0.085, 0.078, 0.068. For IV S-methadone, AUC was 447, 476, 911 ng-hr/ml, CL was 6.2, 6.6, 3.6 L/hr, and EDDP/methadone AUC ratio was 0.120, 0.099, 0.075. Oral R-methadone AUC was 563, 586, 986 ng-hr/ml, apparent oral clearance (CL/F) was 11.9, 10.4, 6.4 L/hr, and EDDP/methadone AUC ratio was 0.075, 0.068, 0.051. For oral S-methadone AUC was 599, 711, 1392 ng-hr/ml, CL/F was 11.5, 10.2, 5.1 L/hr, and EDDP/methadone AUC ratio was 0.11, 0.096, 0.055. Urine EDDP formation clearance from IV methadone in CYP2B*1/*1, *1/*6, and *6/*6 genotypes averaged 0.26, 0.21, 0.15 ml/kg/min for R-EDDP; and 0.43, 0.30, 0.20 ml/kg/min for S-EDDP.

Conclusion: Methadone N-demethylation in vitro by CYP2B6.6 was significantly less than wild-type CYP2B6.1. This predicted that clinically, CYP2B6*6 allele carriers would have impaired methadone elimination. This was confirmed. Methadone metabolism and clearance were significantly diminished in CYP2B6*6 allele carriers. There was a gene-dose effect, with CYP2B6*6 homozygotes having the lowest methadone metabolism and clearance. CYP2B6 pharmacogenetics clearly influences methadone disposition and explains, in part, interindividual variability in methadone disposition.

CS 67 (56)

Single Nucleotide Polymorphism-Specific Regulation of Matrix Metalloproteinase-9 By Multiple miRNAs Targeting the Coding Exon

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Introduction: Micro (mi)-RNAs work with exquisite specificity: they distinguish a target from a non-target based on a single nucleotide mismatch in the core nucleotide domain with a consequent reduction in the protein output upon translational inhibition and mRNA destabilization[1]. In our recent study[2] we characterized a coding exon SNP in the pro-domain of MMP-9 (N38S, rs41427445) that resulted in a profound decrease in the secreted protein. We questioned whether miRNA regulation of MMP-9 expression could occur in an SNP-specific manner, manifesting as a post-transcriptional control of expression of genetic polymorphisms in the protein coding exons.

Methods: Wt- or mutant MMP-9 cDNA were expressed in HEK293 cells by transfection and expression of mRNA and miRNA were quantified by qRT-PCR. miRNA-mimics, antagomirs, and control small synthetic RNA (mirVana, Life Technologies) specific to a given target miRNA were transfected following the manufacturer's recommended protocol. For bioinformatics analyses, we implemented a de novo search algorithm based on the report by Nicoloso et al.[3] The 1,919 mature human miRNA sequences were downloaded (July 2012) from miRBase. Annotations listing all coding exons, 5' UTRs, and 3' UTRs for each gene (refFlat.txt) were downloaded (July 2012) from the University of California-Santa Cruz. The human genome sequence for hg19 (GRCh37.1), sequences surrounding each SNP (August 2011), and the position of each SNP (August 2011) were downloaded from the National Center for Biotechnology Information (NCBI). The miRanda software was downloaded (August 2010 release) (www.microrna.org/microrna/getDownloads.do) and implemented to run on a desktop PC.

Results: Expression of an MMP-9 cDNA harboring the SNP rs41427445 resulted in a profound decrease in the secreted MMP-9 protein in the cell culture supernatant. Our initial hypothesis for the decreased protein secretion of N38S-MMP-9 was that subcellular protein mistargeting and the inability to secrete the protein were due to the loss of N-glycosylation. We tested this hypothesis through immunocytochemistry and a Western blot of the cell lysate (i.e. intracellular MMP-9) of the transfected cells expressing the wild type- or N38S-MMP-9. We expected increased retention of the mutant protein with detection of mistargeted non-secreted protein in the cells expressing the N38S-MMP-9. In contrast to our expectation, we saw no intracellular accumulation of the mistargeted N38S-MMP-9 protein, but rather a decreased intracellular protein level, confirmed by both immunocytochemistry and the Western blot of the whole cell lysate. Further analysis suggested a perplexing apparent single nucleotide-dependent difference in mRNA stability leading to a decrease in the mRNA and ultimately the intracellular and extracellular amounts of N38S-MMP-9 protein. Bioinformatics analysis identified that the presence of SNP in MMP-9 created a novel binding site for miRNA-671-3p and miR-657. Experiments with miRNA-antagomirs and –mimics confirmed that the SNP-dependent miRNA destabilization of mRNA as the likely mechanism responsible for the low level of N38S-MMP-9 protein expression. Further studies confirmed that this SNP-dependent miRNA binding can distinguish SNPs leading to a silent mutation with no amino acid changes.

Conclusions: Our results demonstrate an SNP-specific regulation of MMP-9 through miRNA targeting the coding region of the gene. Bioinformatics analysis revealed SNP-specific regulation of MMP-9 by additional miRNA targeting other SNPs, including synonymous SNPs, with no change in the coded amino acid. This discovery reveals a cellular mechanism whereby expression of a specific MMP-9 mRNA is affected by a highly selective miRNA interaction with the SNP-mRNA, most likely playing an important role in the biology of MMP-9.

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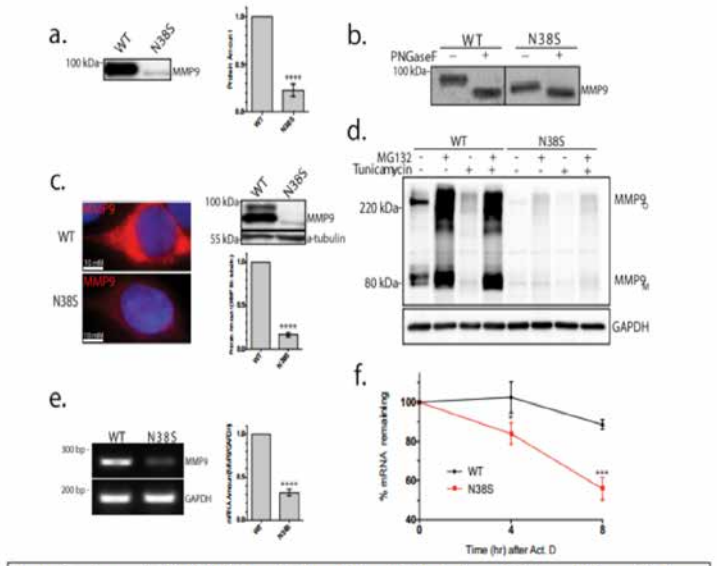

Reduction in secreted N38S-MMP-9 protein is not due solely to the loss of N-glycosylation. a. Western blot analysis of culture media (20 µL) from cells transfected with wild type- or N38S-MMP-9 probed with anti-MMP-9 antibody (left). Similar results obtained from 5 separate transfections. The MMP-9 protein amount was quantified by ELISA and averaged (mean ±S.E.M.) from 5 separate transfections shown as a bar plot (right). ****P<0.0001, t-test, n=5. **b**. Western blot of PNGase F treated cell culture media from wild type- (WT) or N38S-MMP-9 transfected cells. Note that the N38S-MMP-9 culture media was concentrated to obtain equivalent band intensity to the wild type. The observed PNGase-induced mobility shift is consistent with a loss of two N-glycosylation sites for the wild type and the loss of one remaining N-glycosylation for N38S. **c**. Anti-MMP-9 immunohistochemical staining (red) of wild type- and N38S-MMP-9 transfected cells. Nuclei were stained by Hoechst 33342 (blue) (left). Western blot analysis of total cell lysate probed with anti-MMP-9 or anti- α-tubulin antibody indicating reduced N38S-MMP-9 intracellular protein levels (right).****P<0.0001, t-test, n=5. **d**. Cells expressing WT- or N38S-MMP-9 were treated with or without MG132 (proteasome degradation inhibitor) (10 µM) or Tunicamycin (GlcNAc phosphotransferase inhibitor; selectively inhibiting N-glycosylation) (1.0 µg/ mL) both for 24 hrs and cell culture media ran on a non-reducing PAGE and was probed with anti-MMP-9- or anti-GAPDH-antibody. Note the MMP-9 monomer (MMP-9$_M$) with an apparent molecular mass near the expected ~90kDa and the larger oligomeric form (MMP$_O$). MG132 failed to rescue the N38S-MMP-9 protein amount. Tunicamycin treatment of WT mimicked the reduced N38S protein levels, but was completely rescued by MG132. Representative of 3 separate experiments. **e**. Total RNA was harvested from cells transfected with the WT- or N38S-MMP-9 plasmids, and an end point RT-PCR performed with primer pairs amplifying the MMP-9 or GAPDH mRNA. Agarose gel electrophoresis demonstrated a reduction in the amplified PCR product for N38S compared to WT. ****P<0.0001, t-test, n=3. **f**. The stability of WT- or N38S-MMP-9 mRNA was examined using qRT-PCR at the indicated time points after actinomycin D treatment (10 µg/mL). The data is normalized to the respective mRNA levels at time 0 hr. *P<0.05, ***P<0.0005, t-test, n=3.

Oral Presentations

Saturday, April 26, 1014 • 2:10 pm – 3:30 pm

SAB Oral Session (Part 2)

Moderators: Max Kelz, MD, PhD; Dean Andropoulos, MD, MHCM

Junior Faculty Award	**CBN 9 (37) • Specialized Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline** **Niccolo Terrando, BSc (hons), DIC, PhD[1],** Ting Yang, MD, PhD[1], Marta Galan, PhD[1], Ralph E. Harding, DO[2], Lars I. Eriksson, MD, PhD, FRCA[1] [1]Karolinska Institute Stockholm, Sweden, Karolinska [2]The Carl Vinson Veterans Affairs Medical Center, Dublin, Georgia *Please see page 58 for complete abstract.*
	O 28 (41) • The Usefulness of a Cognitive Screening Test in Predicting Postoperative Delirium **Lawrence S. Long, MD[1],** Jed T. Wolpaw, MD[1], Jacqueline M. Leung, MD, MPH[1] [1]University of California San Francisco, San Francisco, California
	CBN 14 (113) **Delta Opioid Receptors Presynaptically Regulate Cutaneous Mechanosensory Neuron Input to the Spinal Cord Dorsal Horn** **Vivianne L. Tawfik, MD, PhD[1],** Dong Wang, PhD[2], Scott A. Shuster, BA[2], Gregory Scherrer, PharmD, PhD[2] [1]Stanford University School of Medicine, Stanford, California [2]Stanford University, Stanford, California
	OP 76 (32) • Anesthesia-induced Neurotoxicity in the Developing Murine Retina: A Window of Opportunity? **Richard J. Levy, MD, FAAP[1],** Ying Cheng, MS[1], Linda He[1] [1]Children's National Medical Center, Washington, District of Columbia
	OP 78 (70) • Peptidylarginine Deiminase-4 Exacerbates Kidney Ischemia and Reperfusion Injury **HT Lee, MD, PHD[1],** Ahrom Ham, PhD[1], Mihwa Kim, PharmD[1], May Rabadi, PhD[1], Kyota Fukazawa, MD[1], Kevin Brown, BS[1] [1]Columbia University, New York, New York
Resident Travel Award	**CBN 12 (85) • miR-200c Contributes to Injury from Transient Cerebral Ischemia in Mice by Targeting Reelin** **Creed M. Stary, MD, PhD[1],** Lijun Xu, MD[1], Xiaoyun Sun, MD[1], Yibing Ouyang, PhD[1], Jason Leong, BS[2], Rona G. Giffard, MD, PhD[1] [1]Stanford University, Stanford, California [2]Albert Einstein College of Medicine, Bronx, New York *Please see page 60 for complete abstract.*
	OP 79 (76) **Single-Cell Deep Immune Profiling Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates** **Brice Gaudilliere, PhD, MD[1],** Gabriela K. Fragiadakis, PhD candidate[1], Robert V. Bruggner, PhD candidate[1], Wendy J. Fantl, PhD[1], Garry P. Nolan, PhD[1], Martin S. Angst, MD[1] [1]Stanford University, Palo Alto, California
	CBN 13 (91) • Deletion of CD36 Induces M2 Response to Brain Injury and Supports Ischemic Tolerance **Ines P. Koerner, MD, PhD[1],** Takeru Shimizu, MD[1], Yingxin Chen ,MD[1], Sarah Mader, BS[1] [1]Oregon Health & Science University, Portland, Oregon

O 28 (41)

The Usefulness of a Cognitive Screening Test in Predicting Postoperative Delirium

Lawrence S. Long, MD[1], Jed T. Wolpaw, MD[1], Jacqueline M. Leung, MD, MPH[1]
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Introduction: Older surgical patients with preexisting cognitive impairment are at risk for developing postoperative delirium[1]. However, screening surgical patients for cognitive impairment has yet to become routine, in part because many cognitive screens are time-intensive.

We investigated the feasibility and prognostic significance of administering a 60-second cognitive screen to older patients before surgery.

Methods: Inclusion criteria were patients >65 years of age who underwent hip, knee, or spine surgery at a university hospital over a 6-month period. Patients were screened with an animal fluency test, which has been shown to be sensitive and specific for dementia in the clinic setting[2] and takes 60 seconds to administer. It was administered before surgery and scores were recorded in the electronic medical record.

An investigator measured postoperative delirium using a chart-based tool[3] and the results were then validated by a second investigator. A third investigator determined which patients had received the cognitive screen preoperatively.

Bivariate analyses were conducted using chi-square and t-tests, and the final model was constructed using multiple logistic regression.

Results: 432 patients met the study inclusion criteria. 82 patients (19%) developed postoperative delirium and 199 patients (46%) received the screen preoperatively. The most common reason for not screening patients was clinician oversight.

Of the 199 patients who were screened, 38 (19%) became delirious postoperatively. Patients with postoperative delirium had worse clinical outcomes than non-delirious patients, including higher ICU admission rate (42% vs. 16%, p<.01), longer length of hospital stay (7.8 days vs. 5.6 days, p<.01), higher rate of institutionalization after discharge (92% vs. 43%, p<.01), and higher mortality rate (5% vs. 0.6%, p=.03).

57 patients (29%) scored low on the cognitive screen. These patients were more likely to develop postoperative delirium than other patients (54% vs. 5%, p<.01). A multiple logistic regression, with postoperative delirium as the dependent variable, identified low cognitive screening score (odds ratio 20.1, 95% CI: 7.9-51.4) and higher ASA classification (odds ratio 3.5, 95% CI: 1.3-9.2) to be the independent predictors.

Conclusions: Our study shows that older patients who scored low on a 60-second cognitive screen before surgery were more likely to become delirious afterward, and that patients who became delirious had worse clinical outcomes overall.

This study also examined the feasibility of adding a cognitive screen to the routine preoperative evaluation. Given that clinician oversight was the most common reason for not administering cognitive screen, education and reinforcement of this practice would likely improve its success.

In conclusion, a brief cognitive screen was able to identify older surgical patients at risk for developing postoperative delirium.

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CBN 14 (113)

Delta Opioid Receptors Presynaptically Regulate Cutaneous Mechanosensory Neuron Input to the Spinal Cord Dorsal Horn

Vivianne L. Tawfik, MD, PhD[1], Dong Wang, PhD[2], Scott A. Shuster, BA[2], Gregory Scherrer, PharmD, PhD[2]
[1]Stanford University School of Medicine, Stanford, California, [2]Stanford University, Stanford, California

Introduction: The cutaneous mechanosensory system is critical for the detection of innocuous and noxious mechanical stimuli that elicit sensations of touch and pain, respectively. It has been previously shown that ablation of unmyelinated nociceptors (C fibers), known to express the mu opioid receptor (MOR), does not alter injury-induced mechanical allodynia in rodents. In contrast, we have demonstrated that the delta opioid receptor (DOR) is predominantly expressed by myelinated dorsal root ganglion (DRG) neurons and that DOR-selective agonists are effective against mechanical allodynia. Further identification and characterization of the primary afferent neurons that mediate allodynia would allow for targeted therapies to treat touch-evoked pain.

Methods: All studies were performed in mice in accordance with policies set forth by the Stanford University IACUC. To characterize the DOR+ primary afferent neurons, immunohistochemistry (IHC) was performed in mice expressing the DOR as a fusion protein coupled to the reporter green fluorescent protein (DOR-GFP). In order to confirm that the DOR-GFP mouse faithfully reproduced endogenous DOR expression, in situ hybridization (ISH) was performed in wild type mice using an ultrasensitive and specific method using a probe against DOR (Oprd1) mRNA (QuantiGene ViewRNA, Panomics). For both IHC and ISH studies, mice were deeply anesthetized, transcardially perfused and lumbar DRGs and skin were dissected post-fixed, cryoprotected and cut on a cryostat. Sections were then processed for ISH followed by IHC, or IHC alone, and stained for markers of neuronal subpopulations. Confocal images were acquired using the Leica TCS SPE microscope and processed using Adobe Photoshop for cell counting.

Results: We discovered that DOR and MOR are expressed in largely non-overlapping populations of DRG neurons. In both wild type and DOR-GFP mice, ~67% of DOR+ DRG neurons expressed the marker of myelinated afferents, NF200. Furthermore, ~62% of DOR+ NF200+ neurons expressed TrkC and/or Ret, suggesting that they are cutaneous mechanoreceptors, including Aβ low-threshold mechanoreceptors (LTMRs) that encode touch. Of the DOR+ NF200- neurons, the vast majority bound the isolectin B4 (IB4), a marker of nonpeptidergic C fibers that sense acute mechanical pain. In contrast, only ~20% of MOR+ DRG neurons were NF200+ and of these, 98% expressed CGRP, a marker of nociceptive neurons. A small population of neurons (6%) were found to coexpress both receptors and 88% of these DOR+ MOR+ neurons were also NF200+. We next determined the morphology of peripheral terminals of DOR+ DRG neurons in skin using a whole-mount cleared preparation. Using this technique we found that DOR+ NF200+ axons innervate Merkel cells, hair follicles and Meissner corpuscles, to form mechanosensory organs that detect skin indentation, hair movement, and vibrations, respectively, to shape touch sensation

Conclusions: Herein, we demonstrate for the first time that the DOR is expressed in a subset of cutaneous myelinated primary afferents, including Aβ LTMRs that form the mechanosensory organs in the skin, implicating them in the modulation of innocuous touch, and touch-evoked pain. We further show that the MOR is found primarily in nociceptors, suggesting a divergence of function for the two receptors endogenously and in injury states. Together, our results define a mechanism by which opioids modulate cutaneous mechanosensation and provide a rationale for targeting DOR to alleviate injury-induced mechanical allodynia.

OP 76 (32)

Anesthesia-induced Neurotoxicity in the Developing Murine Retina: A Window of Opportunity?

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[1]Children's National Medical Center, Washington, District of Columbia

Introduction: Anesthetic agents cause widespread apoptosis in the developing brain. Vulnerability coincides with the peak in synaptogenesis and anesthesia-induced neurodegeneration has been shown to result in loss of neurons, cognitive impairment, and behavioral abnormalities in a variety of newborn animal models. However, it is unknown if anesthesia-induced neurotoxicity occurs in humans because there is currently no modality to assess for neuronal apoptosis in vivo. The retina is unique in that it is the only portion of the central nervous system that can be directly visualized by non-invasive means. As in the brain, programmed cell death occurs naturally in the developing retina and is critical for synaptogenesis and elimination of aberrant connections. Thus, we hypothesized that anesthetics can cause neurotoxicity in the developing retina. We aimed to demonstrate that isoflurane induces apoptosis in the retina following exposure. Because high resolution non-invasive methods have been developed to image single cell apoptosis within the retina in vivo, we also tested the hypothesis that a systemically injected fluorescent probe could cross the blood-retinal barrier and bind to cells undergoing programmed cell death.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. 7 day old CD-1 male mouse pups underwent 1 hour exposure to isoflurane (2%) or air. Following exposure, retina was harvested and immunohistochemistry for activated caspase-3, -9, and -8 was performed. Cytochrome c release from retinal mitochondria was assessed and steady-state levels of pro- and anti-apoptotic mediators were determined with immunoblot analysis. Significance was assessed with ANOVA and post hoc Tukey's test and significance set at $P<.05$. The types of cells undergoing apoptosis were identified with double labeling immunofluorescence. Retinal uptake and the ability of fluorescent-labeled annexin V to bind to cells undergoing natural cell death and anesthesia-induced apoptosis in the retina were determined following intraperitoneal injection.

Results: Isoflurane activated the intrinsic apoptosis pathway in the inner nuclear layer (INL) and activated both the intrinsic and extrinsic pathways in the ganglion cell layer of the retina. Immunofluorescence demonstrated that bipolar and amacrine neurons within the INL underwent physiologic cell death in air-exposed controls and were the likely targets of isoflurane-induced neurotoxicity. Following injection, fluorescent-labeled annexin V was readily detected in the INL of both air- and isoflurane-exposed mice and co-localized with activated caspase-3 positive cells.

Conclusions: These findings indicate that isoflurane-induced neurotoxicity occurs in the developing retina and lays the groundwork for development of a non-invasive imaging technique to detect anesthesia-induced neuronal apoptosis in infants and children. Thus, in future work, it may be possible to exploit neurodegeneration in the human retina as a surrogate for anesthesia-induced brain neurotoxicity.

OP 78 (70)

Peptidylarginine Deiminase-4 Exacerbates Kidney Ischemia and Reperfusion Injury

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[1]Columbia University, New York, New York

Introduction: Acute kidney injury (AKI) due to ischemia and reperfusion (IR) is a devastating clinical problem and results in renal tubular inflammation and neutrophil infiltration. Peptidylarginine deiminase-4 (PAD4) is a nuclear enzyme that catalyzes the post-translational conversion of arginine residues to citrulline. Interestingly, post-translational protein citrullination is implicated in several inflammatory autoimmune diseases including rheumatoid arthritis and multiple sclerosis[3]. However, the role for PAD4-mediated protein citrullination in renal IR injury has never been examined. Here, we tested the hypothesis that PAD4 contributes to ischemic AKI by exacerbating the inflammatory response after renal IR.

Methods: After IACUC approval, male C57BL/6 mice were subjected to 20 or 30 min renal IR injury. Mice were pretreated with vehicle (1% DMSO) or with 100 mg/kg 2-chloroamidine (a selective PAD4 inhibitor) before 30 min renal ischemia. Some mice were treated with vehicle or with 10 µg/kg recombinant PAD4 (rPAD4) before 20 min renal ischemia. In addition, cultured mouse kidney proximal tubule cells were treated with 5 µg/kg human rPAD4 for 6 hr to test whether rPAD4 directly induces neutrophil chemotactic pro-inflammatory mRNA (MIP-2 and KC) expression. Finally, we performed PAD4 immunohistochemistry in archived surgical kidney specimens from patients subjected to nephrectomy for tumor and from patients subjected to liver-related kidney transplantation (Columbia University IRB determined this as "non-human subject research" under 45CFR46).

Results: Renal IR increased PAD4 mRNA (Fig 1A), protein (Fig 1B) expression and activity (Fig 1C) in mouse kidney. In human kidneys, we found that PAD4 protein expression is localized to the nucleus in non-ischemic kidneys whereas kidneys subjected to ischemia showed cytosolic translocation of PAD4 (Figure 1D). After 30 min renal IR, vehicle-treated mice developed severe AKI with large increases in plasma Cr (Fig. 2). In contrast, mice pretreated with a PAD4 inhibitor had significantly reduced renal IR injury. Further supporting a critical role for PAD4 in generating ischemic AKI, mice pretreated with rPAD4 protein and subjected to mild (20 min) renal IR developed exacerbated ischemic AKI (Figure 2). Consistent with the hypothesis that PAD4 potentiates renal tubular inflammation after renal IR, mice treated with a PAD4 inhibitor had significantly reduced kidney proinflammatory cytokine mRNA (MIP-2, KC, MCP-1 and TNF-α) expression and neutrophil infiltration. Furthermore, mice treated with rPAD4 had significantly increased renal tubular inflammation well as secondary necrosis. Finally, cultured mouse kidney proximal tubules treated with rPAD4 had significantly increased neutrophil chemotactic MIP-2 (16±3 fold) and IL-8 (12±2 fold) mRNA expression compared to vehicle-treated cells (N=4).

Conclusions: Taken together, our studies suggest that PAD4 plays a critical role in renal IR injury most likely via increasing renal tubular cytokine synthesis and inflammatory response after renal IR. Selective inhibition of renal tubular PAD4 activity may reduce the morbidity and mortality arising from ischemic AKI.

References:

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Figure 1

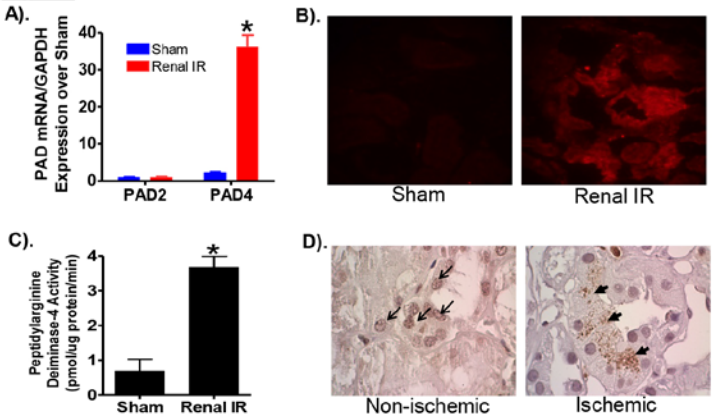

Figure 1. A. Peptidylarginine deiminase 4 (PAD4) mRNA expression increases in mouse kidney 24 hr after renal ischemia and reperfusion (IR) injury (N=4). Note the lack of increase in PAD2 mRNA after renal IR. B. Representative of 4 immunohistochemistry experiments showing increased renal tubule PAD4 protein expression (red florescence, 400X) in mouse kidney 24 hr after renal IR injury. C. Increased mouse kidney PAD4 activity 24 hr after renal IR injury (N=4). D. Representative human kidney PAD4 immunohistochemistry experiments. In kidneys not subjected to ischemia (normal kidney near a tumor), PAD4 is localized in the nucleus (thin arrows). In contrast, kidneys subjected to ~40 min of cold and warm ischemia during transplant surgery show cytosolic translocation of PAD4 (thick arrows). Biopsies taken <5 min after reperfusion (400X). Representative of 3 experiments. *P<0.05 vs. Sham group. Mean±Standard Error shown.

Figure 2

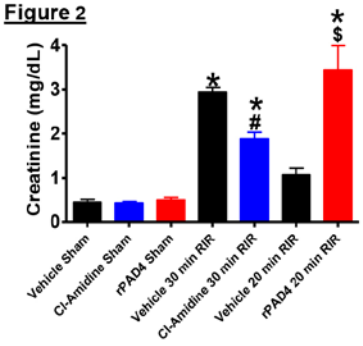

Figure 2. Peptidylarginine deiminase-4 (PAD4) plays a critical role in generating renal ischemia and reperfusion (RIR) injury. C57/BL-6 mice were subjected to sham-operation or to 20 min or 30 min RIR after pretreatment with vehicle (1% DMSO), 100mg/kg Cl-amidine (a PAD4 inhibitor) or with 10 µg recombinant PAD4 (rPAD4). Inhibition of PAD4 with Cl-amidine treatment protected against RIR. In contrast, rPAD4 exacerbated renal injury after IR. *P<0.001 vs. Vehicle Sham. #P<0.05 vs. Vehicle 30 min RIR, $P<0.001 vs. Vehicle 20 min RIR. N=5-6 per group. Data represented as mean±SEM.

OP 79 (76)

Single-Cell Deep Immune Profiling Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates

Brice Gaudilliere, PhD, MD[1], Gabriela K. Fragiadakis, PhD candidate[1], Robert V. Bruggner, PhD candidate[1], Wendy J. Fantl, PhD[1], Garry P. Nolan, PhD[1], Martin S. Angst, MD[1]
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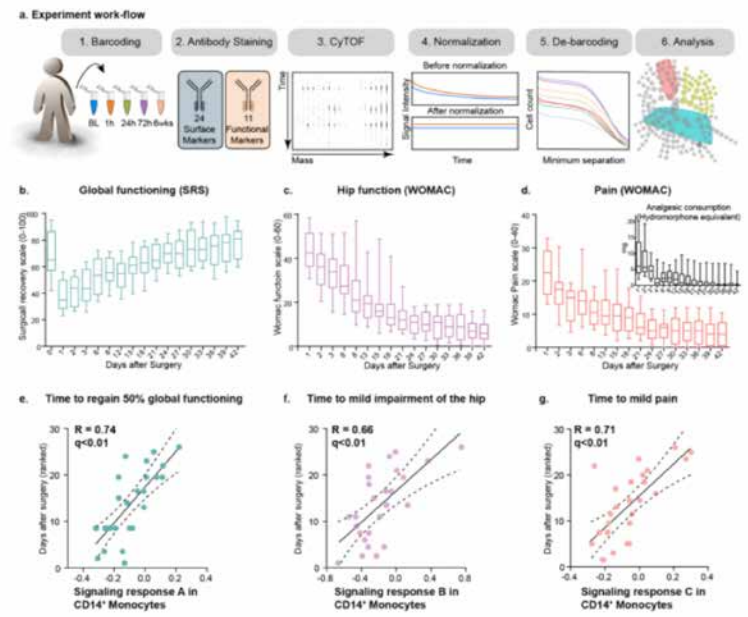
More than 100 million surgeries are performed annually in Europe and the United States[1]. This number is expected to grow as the population ages. Convalescence after surgery is highly variable, and delays in recovery result in personal suffering and societal and economic costs[2]. Perioperative care now includes enhanced-recovery protocols and evidence-based practice guidelines largely anchored in observational data[3]. The physiologic and mechanistic underpinnings of surgical recovery remain a "black box" phenomenon, however[4]. Understanding the mechanisms that drive recovery after surgery will advance therapeutic strategies and allow patient-specific tailoring of recovery protocols.

Here mass cytometry, a highly parameterized single-cell based platform that can determine functional responses in precisely phenotyped immune cell subsets[5-9], was employed to identify immune cell subsets and corresponding signaling pathways that correlate with clinical recovery. The expression levels of 35 cell-surface proteins and intracellular phospho-specific epitopes were simultaneously measured at 1 h, 24 h, 72 h, and 6 weeks after surgery in whole blood samples from 32 patients undergoing primary hip arthroplasty (20 males, 12 females, ASA 1-2, age 59 [54; 68], BMI 26.5 [24.4; 28.1]). The simultaneous analysis of 14,000 phosphorylation events across 8 immune cell subsets revealed remarkably uniform signaling responses among patients, demarcating a "trauma-specific" immune signature. When regressed against clinical parameters of surgical recovery, including functional impairment and pain, strong positive correlates were found within signaling responses of specific cell subsets rather than in frequency changes of immune cell subsets (R=0.7-0.8, False Discovery Rate < 0.01). Notably, all signaling responses correlating with clinical recovery occurred in subsets of CD14+ monocytes, underscoring a central role of these cells in processes enabling or disabling recovery from surgery.

These data provide the first set of mechanistically derived immune correlates to guide post-operative care in surgical patients. While the technology used to assess the global immune state (mass cytometry) is relatively new, the diagnostic descriptors of the outcomes can be distilled into a total of six markers that are readily adaptable to a fluorescence-based flow cytometry test. We expect the approach outlined here might eventually be used to distinguish aspects of the immune response that are misdirected or impaired after trauma and that might be targeted for the benefit of patients with predicted poor recovery.



Single-Cell Deep Immune Profiling by Mass Cytometry Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates.

a. Experimental workflow. Whole blood samples from six patients undergoing primary hip arthroplasty were collected 1 h before surgery (baseline, BL), and 1 h, 24 h, 72 h, and 6 weeks after surgery. Following red blood cell lysis, leukocyte samples from each patient were barcoded using a unique combination of palladium isotopes (*panel 1*). Barcoded samples were pooled, stained with a panel of 35 antibodies (*panel 2*), and analyzed by mass cytometry (*panel 3*). Raw mass cytometry data were normalized for signal variation over time (*panel 4*), de-barcoded (*panel 5*) and analyzed using a method for unsupervised identification of cellular responses associated with a clinical outcome (*panel 6*).

b-d. Box plots depict medians and interquartile ranges of recovery parameters (*b*) global functioning, (*c*) hip function, and (*d*) pain for individual patients over the 6-week observation period (bars indicate 10th and 90th percentiles). Global functioning was assessed with the Surgical Recovery Scale (SRS; 0-100 = worst-best function). Pain and impairment of hip function were assessed with adapted versions of the Western Ontario and McMaster Universities Arthritis Index (WOMAC, pain 0-40 = no pain-worst imaginable pain; function 0-60 = no impairment-severe functional impairment). The heat maps reflect significant variability for extent and rate of recovery across all three outcome domains. An inset graph in panel d depicts the median daily analgesic consumption expressed as the dose equivalent of intravenous hydromorphone. Graphical information regarding pain and analgesic consumption are jointly presented, as these variables are inter-dependent.

e-g. $CD45^+CD66^-$ mononuclear immune cells obtained at BL and at 1 h, 24 h, and 72 h after surgery were clustered using an unsupervised approach. Immune features, which include frequencies and signaling responses of 11 phospho-proteins, were derived for every cluster. SAM Quantitative was used to detect significant correlations between immune features and parameters of clinical recovery (False Discovery Rate, q<0.01). Cell cluster phenotypes were identified using cell surface marker expression. Significant correlations were obtained for signaling responses A, B and C with *(e)* recovery of global functioning, *(f)* function of the hip, and *(g)* resolution of pain. All signaling responses were phosphorylation events present in $CD14^+$ monocytes. Signaling responses are denoted A, B and C for technical licensing purposes. STAN-1069PRV, S13-373 Patent under review.

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CBN 13 (91)

Deletion of CD36 Induces M2 Response to Brain Injury and Supports Ischemic Tolerance

Ines P. Koerner, MD, PhD[1], Takeru Shimizu, MD[1], Yingxin Chen ,MD[1], Sarah Mader, BS[1]
[1]Oregon Health & Science University, Portland, Oregon

Introduction: Mice lacking the scavenging receptor CD36 (CD36-KO) have smaller strokes than wildtype controls and show reduced activation of pro-inflammatory transcription factor NFkB, suggesting that CD36 contributes to inflammation after stroke[1]. We hypothesized that CD36 expressed on microglia, the brain's resident immune cells, mediates the detrimental inflammatory response after stroke. We therefore tested whether transplantation of wildtype microglia with intact CD36 restores detrimental inflammation and susceptibility to stroke in CD36-KO mice.

Methods: Adult CD36-KO or C57BL/6 (wildtype, WT) mice were injected into the striatum with 20,000 microglia isolated from WT mice. After 14 days recovery, stroke was induced by 60 minutes of transient middle cerebral artery occlusion. Cerebral blood flow was monitored by laser Doppler. Infarct size was measured by TTC staining 24 hours after reperfusion and expressed as percentage of contralateral structure. Additional mice were injected with eGFP expressing microglia to allow visualization of transplanted cells. Another cohort received vehicle (culture medium) injections, and brains were harvested 1 day or 7 days later for immunohistochemistry or isolation of RNA.

Results: Infarct size after 60 min MCAO was significantly smaller in CD36-KO compared to WT mice (31±11% vs 45±8%, n=11). Transplantation of microglia moderately reduced infarct size in WT mice (35±14% vs 45±8%), but abolished infarct in CD36-KO mice (no visible infarct in 8 of 10 mice). Transplanted microglia survived and were detectable (eGFP positive) in injured brains after stroke. To determine whether transplantation-induced protection was a function of the transplanted microglia or mediated by the tissue response, we injected additional mice with astrocytes (non-immunologically active) or culture medium only (vehicle). In WT mice, protection was only achieved by microglia, but not astrocyte transplantation (42±9% infarct astrocytes vs. 31±11% microglia), suggesting that protection is a function of transplanted microglia. CD36-KO, in contrast, had smaller infarcts with vehicle injection alone (13±7% vehicle vs 24±16% no injection, n=9), suggesting that their tissue response to injury is altered. We found morphologic activation of both microglia and astrocytes in the striatum after vehicle injection of either WT or CD36-KO mice. However, while injection injury primarily induced pro-inflammatory cytokines in WT animals (TNF-α, MIP-1α), this response was shifted towards anti-inflammatory, M2 markers in CD36-KO (VEGF, IGF-1, YM1B).

Conclusions: We conclude that CD36-KO mice have an altered tissue response to injury, preferentially inducing expression of anti-inflammatory M2 markers. This causes a preconditioning-like state of ischemic tolerance and reduces infarct size after subsequent stroke. Antagonism of CD36 may therefore be a promising route to induce tolerance in states of elevated stroke risk. Transplantation of microglia induces tolerance and reduces stroke injury in WT mice, but protection is less robust than in CD36-KO.

References:

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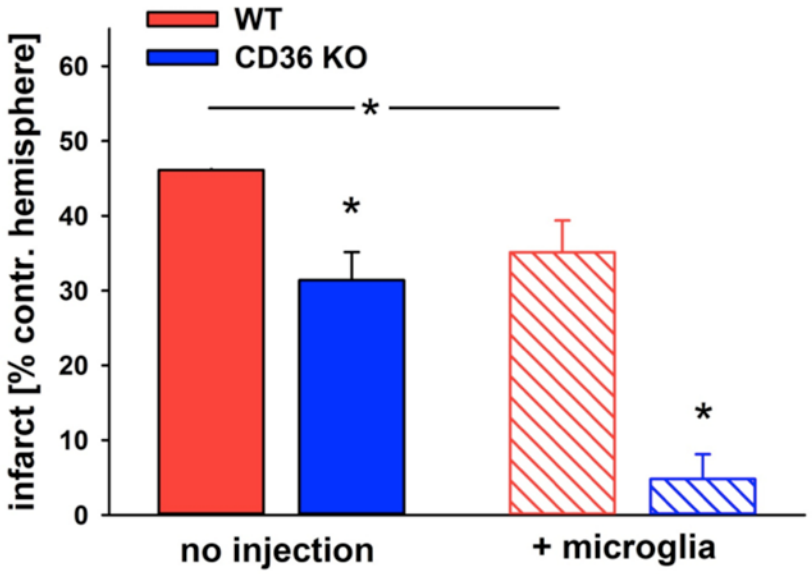

Poster Presentations Schedule

Thursday, April 24, 1014 • 3:00 pm – 4:30 pm

Moderated Poster Discussion: Anesthetic Delivery / Monitoring

Moderator: Charles Emala, MD

	ADM 36 (29) • The French Connection: T-connectors and Poiseuille's Equation. **James J. Thomas, BS, MD[1]** [1]Children's Hospital Colorado, Aurora, Colorado
	ADM 37 (36) • Comparison between Thrombelastography and Thromboelastometry in Liver Transplantation Tetsuro Sakai, MD, PhD[1], Ezeldeen Abuelkasem, MD, MSc[1], Kenichi A. Tanaka, MD, MSc[1], Raymond M. Planinsic, MD[1] [1]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
	ADM 38 (47) **Efficacy of Ventilation through a Customized Novel Cuffed Airway Exchange Catheter: a Tracheal/Lung Model Study** **Yandong Jiang, MD, PhD[1],** Yandong Jiang, MD, PhD[1], Jun Oto, MD, PhD[1], Mary Sun, MS[1], Robert M. Kacmarek, PhD[1] [1]Massachusetts General Hospital, Weston, Maryland
	ADM 39 (75) **Further In Vitro Evaluation of the "Air Test" for Perineural Catheter Tip Localization by a Novice Regional Anesthesiologist** **Jason Johns, MD[1],** T. Kyle Harrison, MD[1], Steven K. Howard, MD[2], Alex Kou Kou, BS[2], Lauren Steffel, MD[1], Edward R. Mariano, MD, MAS[2] [1]Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine Stanford, California [2]Anesthesiology and Perioperative Care Service, VA Palo Alto Health Care System, Palo Alto, California

Moderated Poster Discussion: Clinical / Basic Neuroscience

Moderators: Max Kelz, MD, PhD, Nabil Alkayed, MD, PhD

Junior Faculty Award	**CBN 1 (116) • Inflammation Increases Brain Sensitivity to General Anesthetics** **Sinziana Avramescu, MD, PhD, FRCPC[1],** William T.H. To, MSc[2], Dian-Shi Wang, MD, PhD[2], Antonello Penna, MD, PhD[2], Irene Lecker, MSc[2], Beverley A. Orser, MD, PhD, FRCPC[3] [1]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada [2]Department of Physiology, University of Toronto, Toronto, Ontario, Canada [3]Department of Anesthesiology and Department of Physiology, University of Toronto, Toronto, Ontario, Canada *Please see page 57 for complete abstract.*
	CBN 2 (81) • Inhibition of the Locus Coeruleus Impedes Emergence from Alkylphenol Hypnosis **Andrew R. McKinstry-Wu, MD[1],** Michael Chalifoux, MD[1], Jason T. Moore, PhD[1], Kellie Woll, BS[1], Roderic G. Eckenhoff, MD[1], Max B. Kelz, MD, PhD[1] [1]University of Pennsylvania, Philadelphia, Pennsylvania
	CBN 3 (84) **MicroRNAs Regulate Gene Expression in the Setting of Stroke – Protection with Post-Treatment to Reduce Levels of miR-181a** **Rona G. Giffard, MD PhD[1],** Yi-Bing Ouyang, PhD[2], Lijun Xu, MD[2] [1]Stanford University School of Medicine, Stanford, California, [2]Stanford University, Stanford, California
	CBN 4 (97) • EEG Variation During Maintenance and Emergence from General Surgical Anesthesia **Divya Chander, MD, PhD[1],** Paul S. Garcia, MD, PhD[2], Jamie W. Sleigh, MD, MBChB[3] [1]Stanford University School of Medicine, Stanford, California [2]Emory University, Atlanta, Georgia, [3]University of Auckland, Waikato Hospital, Auckland, New Zealand
	CBN 5 (117) • Disrupting NMDA Receptor-PSD-95 PDZ Domain Interactions in Neonatal Rats Impairs Hippocampal Neuronal Function, Learning, and Memory **Roger A. Johns, MD, PhD[1],** Orion Furmanski, PhD[1], Ya Yang, PhD[1], Qiang Chen, PhD[2], Pei Tang, PhD[2], Feng Tao, MD, PhD[1] [1]Johns Hopkins University School of Medicine, Baltimore, Maryland, [2]University of Pittsburgh School of Medicine, Baltimore, Maryland
	CBN 6 (119) • Hippocampal GABAergic Field Potentials: A Novel High Throughput Screen for General Anesthetics In Rodents **Boris D. Heifets, MD, PhD[1],** James Nie, BS[2], Bharat Sharma, BS[3], M. Frances Davies, PhD[1], Edward J. Bertaccini[1], MD, Bruce MacIver, MSc, PhD[1] [1]Stanford University School of Medicine, Palo Alto, California, [2]Stanford University, Palo Alto, California, [3]LSUHSC School of Medicine, Shreveport, Louisiana
	CBN 7 (120) • A Network of Discrete Metastable Activity States Mediates Recovery from Isoflurane Anesthesia **Andrew E. Hudson, MD[1],** D. P. Calderon, MD[2], D. W. Pfaff, MD[2], A. Proekt, MD[3] [1]UCLA, David Geffen School of Medicine, Los Angeles, California, [2]The Rockefeller University, New York, New York [3]The Rockefeller University & Weill Cornell Medical College, New York, New York

Poster Presentations Schedule

Thursday, April 24, 1014 • 3:00 pm – 4:30 pm

Moderated Poster Discussion: Cell Signaling
Moderators: Dolores Njoku, MD, Tim Morey, MD

	CS 67 (56) **Single nucleotide polymorphism-specific regulation of matrix metalloproteinase-9 by multiple miRNAs targeting the coding exon** **Tyler Duellman, BS,**[1] Jay Yangm, MD, PhD[1] [1]University of Wisconsin-Madison Madison, Wisconsin
Resident Travel Award	**CS 68 (71) • Genetic Deletion of the GABA-A Î±4 Subunit Leads to Increased Airway Resistance and Inflammation** **Gene T. Yocum, MD[1]**, Damian L. Turner, PhD[1], Jennifer Danielsson, MD[1], Matthew B. Barajas, BS[1], Gregg E. Homanics, PhD[2], Charles W. Emala, MD, MS[1] [1]Columbia University, New York, New York, [2]University of Pittsburgh, Pittsburgh, Pennsylvania *Please see page 61 for complete abstract.*
	CS 69 (78) **A Novel Mechanism to Impede Uterine Smooth Muscle Contractions and Treat Pre-Term Labor: Anoctamin-1 Calcium Activated Chloride Channels as Critical Mediators of Calcium Dynamics** **Kyra Bernstein, BS[1],** Jennifer Danielsson, MD[2], G. Tom Yocum, MD[2], George Gallos, MD[2] [1]Physician and Surgeons College of Medicine, New York, New York, [2]Columbia University, New York, New York
	CS 70 (87) **Antagonists of the TMEM16A Calcium-Activated Chloride Channel Relax Airway Smooth Muscle and Potentiate Î²-agonist Relaxation: Potential New Tools to Treat Bronchospasm** **Jennifer Danielsson, MD[1],** Matthew B. Barajas, BS[1], Yi Zhang, MD[1], Charles W. Emala, MD[1] [1]Columbia University, New York, New York
	CS 71 (95) **The Effect of Oxygen Tension on Reactive Oxygen Species Production in Blood Ex Vivo** **Frederic T. Billings, MD, MSc [1],**Alfiya T. Bikineyeva[1], PhD, Jorge L. Gamboa, MD, PhD[1], Sergey I. Dikalov, PhD[1] [1]Vanderbilt University, Nashville, Tennessee
	CS 72 (99) • Lavoisier's Dilemma Solved by Confirming Old Cavendish Report **John W. Severinghaus, MD[1]** [1]UCSF, Ross, California
	CS 73 (100) **Pharmacogenetic Determinants of Interindividual Variability in Methadone Metabolism and Disposition: The Role of Cytochrome P4502B6 (CYP2B6)** **Evan D. Kharasch, MD, PhD[1],** Sarah Gadel, BS[1], Amanda Crafford, BS[1], Jennifer Parchomski, RN[1], Karen Regina, MS[1], Jane Blood, RN[1] [1]Washington University in St. Louis, St. Louis, Missouri
	CS 74 (114) • Propofol Infusion Impairs Complex 1 Activity in Human Muscle **David M. Polaner, MD[1],** Johan Van Hove, MD, PhD[1], Marissa Friedrich, PhD[1], Jeannie Zuk PhD, RN[1], Bjoern Schniewind, PhD[1], Jeffrey Galinkin, MD[1] [1]University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado

Poster Presentations Schedule

Thursday, April 24, 1014 • 3:00 pm – 4:30 pm

Moderated Poster Discussion: Education
Moderators: Alex Macario, MD, Manuel Pardo, Jr., MD

EDU 41 (33) • Flipped Classroom Preferred Over Traditional Classroom in Resident Education
Amy N. DiLorenzo, MA[1], Susan M. Martinelli, MD[2], David C Mayer, MD[2], Harendra Arora, MD[2], David A. Zvara, MD[2], Randall M. Schell, MD, MACM[1], Edwin A. Bowe, MD[3]
[1]University of Kentucky Lexington, Kentucky, [2]University of North Carolina Wilmington, North Carolina, [3]Albert B. Chandler Hospital, Lexington, Kentucky

EDU 42 (89)
Performance on USMLE Step 1 but not Self-Directedness or Personality Preferences Correlate with Future Performance on In-Training Examinations During Anesthesiology Graduate Medical Education
Randall M. Schell, MD, MACM[1], Amanda Faulkner, BS[1], Woodrow Burchett, MS[1], Dominique Zephyr, MA[1], Amy N. DiLorenzo, MA[1]
[1]University of Kentucky, Lexington, Kentucky

Moderated Poster Discussion: Outcomes
Moderators: Matt Reiss, MD, PhD, Peter Nagele, MD, MSc

O 16 (65)
Tablet Based Interactive Distraction (TBID) Versus Oral Midazolam to Minimize Perioperative Anxiety in Pediatric Patients: A Non-Inferiority Randomized Trial
Samuel C. Seiden, MD[1], Susan McMullan, CRNA[2], Luis Sequera-Ramos, MD[2], Gildasio De Oliveira Jr., MD, MSCi[3], Andy Roth, MD[2], Santhanam Suresh, MD[2]
[1]Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern Feinberg School of Medicine, Chicago, Illinois
[2]Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, Illinois
[3]Northwestern University Feinberg School of Medicine, Chicago, Illinois

O 17 (90) • Utility of Electronic Management Tool in the ICU for Early Recognition and Management of Sepsis
Liza M. Weavind, MBBCh[1], Matthew W. Semler, MD[1], Arthur Wheeler, MD[1]
[1]Vanderbilt University Medical Center, Nashville, Tennessee

O 18 (34)
A Comparative Provider Workload Analysis for Femoral and Adductor Canal Catheters Following Knee Arthroplasty
Michael R. Rasmussen, MD1, Eugenia Kim, MD[2], T Edward Kim, MD[2], Steven K. Howard, MD[2], Seshadri Mudumbai, MD[2], Nicholas Giori, MD, PhD[3]
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O 19 (35)
Effect of Pre-operative ACE Inhibitor and ARB Use on Hemodynamic Variables in Pediatric Patients Undergoing Cardiopulmonary Bypass
Chinwe Ajuba-Iwuji, MD[1], Bryan G. Maxwell, MD, MPH[1], Melania Bembea, MD[1], Luca Vricella, MD[1], Eugenie Heitmiller, MD[1], Sahitya Puttreddy, MBBS[2]
[1]Johns Hopkins Hospital Baltimore, Maryland, [2]Kasturba Medical College Manipal, Karnataka, India

O 20 (44)
Impaired Red Blood Cell Deformability After Transfusion of Stored Allogeneic Blood but Not Autologous Salvaged Blood in Cardiac Surgery Patients
Steven M. Frank, MD[1], Osman N. Salaria, MD[1], Viachaslau M. Barodka, MD[1], Charles W. Hogue, MD[1], Jack O. Wasey, MD[1], Dan E. Berkowitz, MD[1]
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O 21 (57)
Establishment of Objective Criteria for Operating Room Exit is Associated with Improved Early Postoperative Outcome in Pediatric Cardiac Surgery
Brian S. Donahue, MD, PhD, Alexander K. Hughes, MD[1], Scott C. Watkins, MD[1], Gina Whitney, MD[1], Claudia Benkwitz, MD, PhD[1], Suanne M. Daves, MD[1]
[1]Vanderbilt University, Nashville, Tennessee

(continued)

Poster Presentations Schedule

Thursday, April 24, 1014 • 3:00 pm – 4:30 pm

Moderated Poster Discussion: Outcomes

Moderators: Matt Reiss, MD, PhD, Peter Nagele, MD, MSc

(continued from previous page)

	O 22 (73) • A High-Fidelity Analysis of Perioperative QTc-Prolongation in General, Regional, and Local Anesthesia Andreas Duma, MD[1], Swatilika Pal, MBBS, MS[1], Daniel Helsten, MD[1], Peter Nagele, MD, MSc[1] [1]Department of Anesthesiology, Washington University in St. Louis, St. Louis, Missouri
	O 23 (82) • Real-Time Forecasting of Pediatric Intensive Care Unit Length of Stay Using Computerized Provider Orders Daniel J. France, PhD, MPH[1], Eric T. Harley, BS[2], James C. Fackler, MD[2], Jason W. Custer, MD[3], Christoph U. Lehmann, MD[4], Scott R. Levin, PhD[2] [1]Vanderbilt University School of Medicine, Nashville, Tennessee, [2]Johns Hopkins, Baltimore, Maryland, [3]University of Maryland, Baltimore, Maryland
	O 24 (88) **Pediatric Delirium in Infants and Preschool-Aged Children:** **Validation of the PreSchool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU)** **Heidi A.B. Smith, MD, MSCI[1],** Molly Gangopadhyay, MD[1], Mary Hamilton Chestnut, NP[1], Jennifer Thompson, MPH[1], D. Catherine Fuchs, MD[1], Pratik Pandharipande, MD[1] [1]Vanderbilt University, Nashville, Tennessee
	O 25 (92) **Severity And Duration Of Metabolic Acidosis after Deep Hypothermic Circulatory Arrest for Elective Thoracic Aortic Surgery** **Kamrouz Ghadimi, MD[1],** Kirk R. Jackson, MD[1], Samuel L. Setegne, BSc[1], Albert T. Cheung, MD[1] [1]Divisions of Critical Care, Cardiovascular & Thoracic Anesthesia, Department of Anesthesiology & Critical Care, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
	O 26 (93) **Consequences of Sodium Bicarbonate Administration In Patients With Metabolic Acidosis After Deep Hypothermic Circulatory Arrest for Elective Thoracic Aortic Surgery** **Kamrouz Ghadimi, MD[1]**, Kirk R. Jackson, MD[1], Samuel L. Setegne, MD[1], Albert T. Cheung, MD[1] [1]Divisions of Critical Care, Cardiovascular & Thoracic Anesthesia, Department of Anesthesiology & Critical Care, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
	O 27 (96) • Does High-Quality Post-Acute Care Prevent Hospital Readmissions? **Mark D. Neuman, MD, MSc[1],** Rachel M. Werner, MD, PhD[1] [1]University of Pennsylvania, Philadelphia, Pennsylvania
	O 34 (115) • Patient and Surgical Factors for Predicting Perioperative Hypothermia After Abdominal Surgery **Ognjen Visnjevac, MD[1],** Remek Kocz, MD[1], Paul Kim, MD[1], Nader D. Nader, MD, PhD[1] [1]State University of New York: Buffalo, Williamsville, New York

Poster Presentations Schedule

Thursday, April 24, 1014 • 3:00 pm – 4:30 pm

Moderated Poster Discussion: Anesthetic Neurotox / Pain

Moderators: Zhongcong Xie, MD, PhD, Y.S. Prakash, MD, PhD

	Tox Pain 51 (40) **Cytotoxic Effects of Methylprednisolone Acetate with and without Preservatives on Dorsal Root Ganglion Sensory Neurons in Rats** **Nebojsa Nick Knezevic, MD, PhD[1],** Kenneth D. Candido, MD[2], Ivan Cokic, MD[3], Aleksandar Krbanjevic, MD, PhD[4], Sarah L. Berth, Ms[5], Ivana Knezevic, MD[6] [1]Department of Anesthesiology; Advocate Illinois Masonic Medical Center and University of Illinois, Chicago, Illinois, [2]Advocate Illinois Masonic Medical Center, Chicago, Illinois, [3]Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, Los Angeles, Los Angeles, California, [4]Department of Pharmacology; University of Illinois Champaign, Illinois, [5]Department of Anatomy and Cell Biology; University of Illinois, Champaign, Illinois, [6]Department of Physiology and Biophysics; University of Illinois, Champaign, Illinois
	Tox Pain 52 (86) • Nociceptive-Mediated Myocardial Infarct Size Reduction Occurs by TRPV1 In Rodents **Eric R. Gross, MD, PhD[1],** Bryce A. Small, BS[1], Anna K. Hsu, BS[2], Garrett J. Gross, PhD[2], Daria Mochly-Rosen, PhD[1] [1]Stanford University, Stanford, California, [2]Medical College of Wisconsin, Milwaukee, Wisconsin
	Tox Pain 53 (108) • The Different Effects of Local Anesthestetics on Natural Killer Cell Function **Juan P. Cata, MD[1],** Maria F Ramirez, MD[1], Vijaya Gottumukkala, MD[1], Andrea Kurz, MD[2] [1]The University of Texas – MD Anderson Cancer Center, Houston, Texas, [2]Cleveland Clinic, Cleveland, Ohio
	Tox Pain 54 (52) • Novel Molecular Targets of Dezocine, a Non-Addictive Opioid **Renyu Liu, MD, PhD[1],** Xi-Ping Huang, PhD[2], Alexei Yeliseev, PhD[3], Jin Xi, MS[1], Bryan L. Roth, MD, PhD[2] [1]University of Pennsylvania Philadelphia, Pennsylvania, [2]University of North Carolina Chapel Hill Medical School, Chapel Hill, North Carolina, [3]National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland
	Tox Pain 55 (53) • Increased GABA-B Receptor Inhibition Contributes to Anesthetic-Induced Depression of Synapses **Bruce M. MacIver, MSc, PhD[1]** [1]Stanford University, Stanford, California
	Tox Pain 56 (62) **Descending Noradrenergic Inhibition is Activated by Nociception and Responsible for Recovery from Hypersensitivity After Injury** **James C. Eisenach, MD[1],** Christopher M. Peters, PhD[1], Ken-ichiro Hayashida, DVM[1], FuZhou Wang, MD[1], Timothy T. Houle, PhD[1], Carol Aschenbrenner, MS[1] [1]Wake Forest School of Medicine, Winston Salem, North Carolina
	Tox Pain 57 (72) • Downregulation of miR-21 Mediates Propofol-Induced Neurotoxicity in Developing Human Neurons **Zeljko J. Bosnjak, PhD[1],** Danielle Twaroski, BS[1], Yasheng Yan, BS[1], Jessica Olson, MS[1], Xiaowen Bai, MD, PhD[1] [1]Medical College of Wisconsin, Milwaukee, Wisconsin
	Tox Pain 58 (80) **Ketamine Modulates DISC1 Expression in a Rat Model of Anesthetic-Induced Developmental Neuroapoptosis** **Sulpicio G. Soriano, MD[1],** Jia-Ren Liu, MD, PhD[1], Koichi Yuki, MD[1], Xiao-Hui Han, RN[2] [1]Boston Children's Hospital/Harvard Medical School, Boston, Massachusetts [2]Boston Children's Hospital, Boston, Massachusetts
Margaret Wood Resident Research Award	**Tox Pain 59 (112) • Postoperative Dementia: Role of Anesthesia and APOE4** **Katie J. Schenning, MD, MPH[1],** Charles F Murchison, MS[1], Nora C. Mattek, MPH[1], Jeffrey A. Kaye, MD[1], Joseph F. Quinn, MD[1] [1]Oregon Health & Science University, Portland, Oregon *Please see page 59 for complete abstract.*

ADM 36 (29)

The French Connection: T-connectors and Poiseuille's Equation

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Introduction: In pediatrics, the use of small-bore t-connectors is commonplace. Not only do they seem to minimize kinking, they also allow for drug administration directly at the site of connection to the angiocatheter. These t-connectors serve as a significant source of resistance to flow and may pose a problem when attempting large volume fluid resuscitation.

Materials and Methods: A standard, low resistance fluid maintenance line (Secondary medication set 37 inch, 10 drops/mL approx) was allowed to drain freely under gravity into an open burette. The burette was used as a graduated cylinder to collect and accurately measure the volume of fluid. The amount of time it took for 50mL of water to flow into the burette was measured. The experiment was repeated under identical conditions with 20 and 18 gauge angiocatheters (20GA 1.00 inch or 18GA 1.16 inch), with and without a t-connector attached to the terminal end of the infusion set. The height of the water column was kept constant for each run. The experiment was repeated five times in each group and the average for each group + standard deviation was calculated.

Results: The results are presented in Table 1. The average time for group 18-T was 60.3 + .2 seconds, The average time for group 18 was 28.4 + .1 seconds. The average time for group 20-T was 69.5 + .3 seconds. The average time for group 20 was 42.7 + 0.2 seconds.

Conclusions: We hypothesized that the t-connectors negate the high flow benefit of large bore angiocatheters for potential fluid resuscitation. Our data indicate that flow through an 18-gauge angiocatheter without the t-connector was more than two times faster, and through an 20-gauge angiocatheter without the t-connector nearly 1.5 times faster, than with the connector in place. The times to deliver 50 ml with the t-connector in place were similar with the 18 and 20 gauge cannulae, demonstrating that the t-connector acted as a restriction to flow sufficient to render the difference in flow between the two angiocatheter sizes negligible under most clinical conditions. Interestingly, the internal diameter of the t-connector is the same as the internal diameter of the 18-gauge angiocatheter. This emphasizes the importance of length as a determinant of resistance to flow, a factor which must be remembered when employing long central venous cannulae for fluid resuscitation as well. The common practice in pediatric fluid therapy of placing small bore t-connectors at the terminal end of the infusion set imposes a clinically significant reduction of fluid flow, and should be discouraged when rapid flow conditions, such as those required for fluid resuscitation during high blood losses, are necessary.

ADM 37 (36)

Comparison Between Thrombelastography and Thromboelastometry in Liver Transplantation

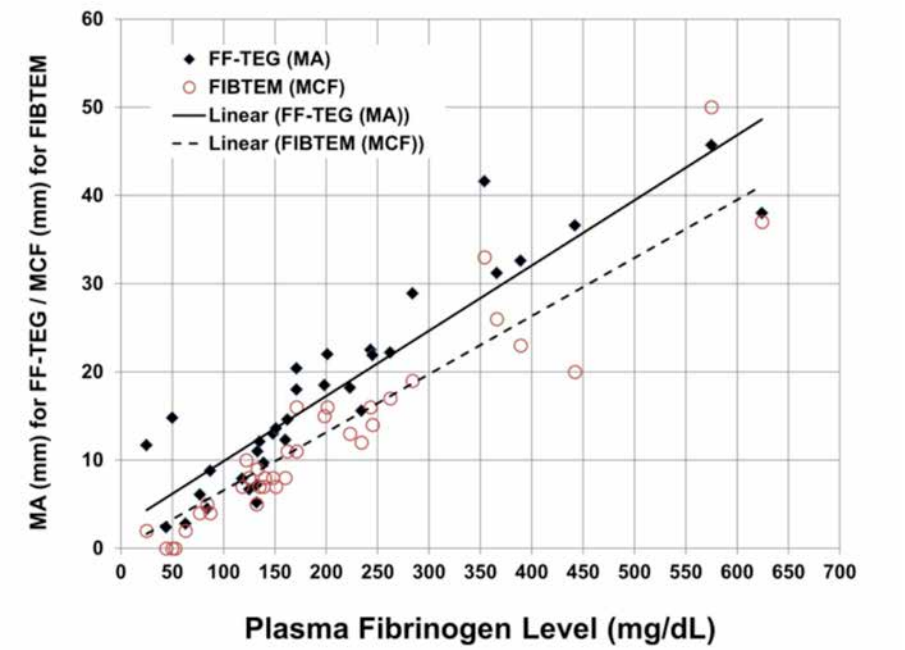
Tetsuro Sakai, MD, PhD[1], Ezeldeen Abuelkasem, MD, MSc[1], Kenichi A. Tanaka, MD, MSc[1], Raymond M. Planinsic, MD[1]
[1]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Background: Two kinds of point of care monitoring devices, thromboelastography and thromboelastometry, have widely been used for coagulation management in liver transplantation (LT). Thromboelastography has offered kaolin TEG (k-TEG), heparinase TEG, rapid TEG, and functional fibrinogen TEG (ff-TEG). Thromboelastometry has provided traditional five channels: EXTEM, INTEM, HEPTEM, FIBTEM, and APTEM. Head-to-head comparisons of thromboelastography and thromboelastometry have rarely been reported in LT.

Materials and Methods: An IRB-approved prospective study of 19 consecutive isolated LTs was conducted [median age 55 years old; 11 male (57.9%); median MELD score 19; six live donors (31.6%)]. thromboelastography and thromboelastometry were simultaneously performed including at induction of general anesthesia (baseline) and at 30 minutes after graft reperfusion (III+30). Corresponding coagulation indices between thromboelastography and thromboelastometry [maximum amplitude (MA) vs. maximum clot firmness (MCF); reaction time (R) vs. clotting time (CT); alpha angles] were compared as the percent change at III+30 from the baseline. The incidence of clot lysis (Lysis-30 >8% in thromboelastography and Maximum Lysis >15% in thromboelastometry) was also compared. The MA in functional fibrinogen TEG (ff-MA) and the MCF in FIBTEM (fib-MCF) were compared using von Clauss fibrinogen levels measured at each point. The data were described in the median with interquartile ranges. The comparison was made with Wilcoxon matched-pairs signed-rank test (or Friedman test with Dunn's multiple comparison test) with $p<0.05$ as deemed to be statistically significant.

Results: Among the corresponding coagulation indices, the only significant difference was found between R of kaolin-TEG vs. CT of INTEM (%change from the baseline of 7.9% [-11.1, 26.6] vs. 48.6% [36.0, 73.2]; $p=0.0002$). When these numbers were reanalyzed with %changes of PTT (119.1% [91.7, 225.3]), R was significantly different from PTT ($p<0.0001$) while CT was not ($p=0.43$). The incidence of clot lysis was identified in 23 measurement points (16.9% in all 136 measurement points) in thromboelastometry. Among these 23 lysis measurements, only 11 (47.8%) were detected in kaolin-TEG. ff-MA and fib-MCF were comparable in correlation with plasma fibrinogen level measurement.

Conclusion: thromboelastography and thromboelastometry were comparable in measurement of coagulation parameters in adult LT; however, thromboelastometry had a favorable correspondence with PTT and was more sensitive in identification of lysis.



Poster Presentations

ADM 38 (47)

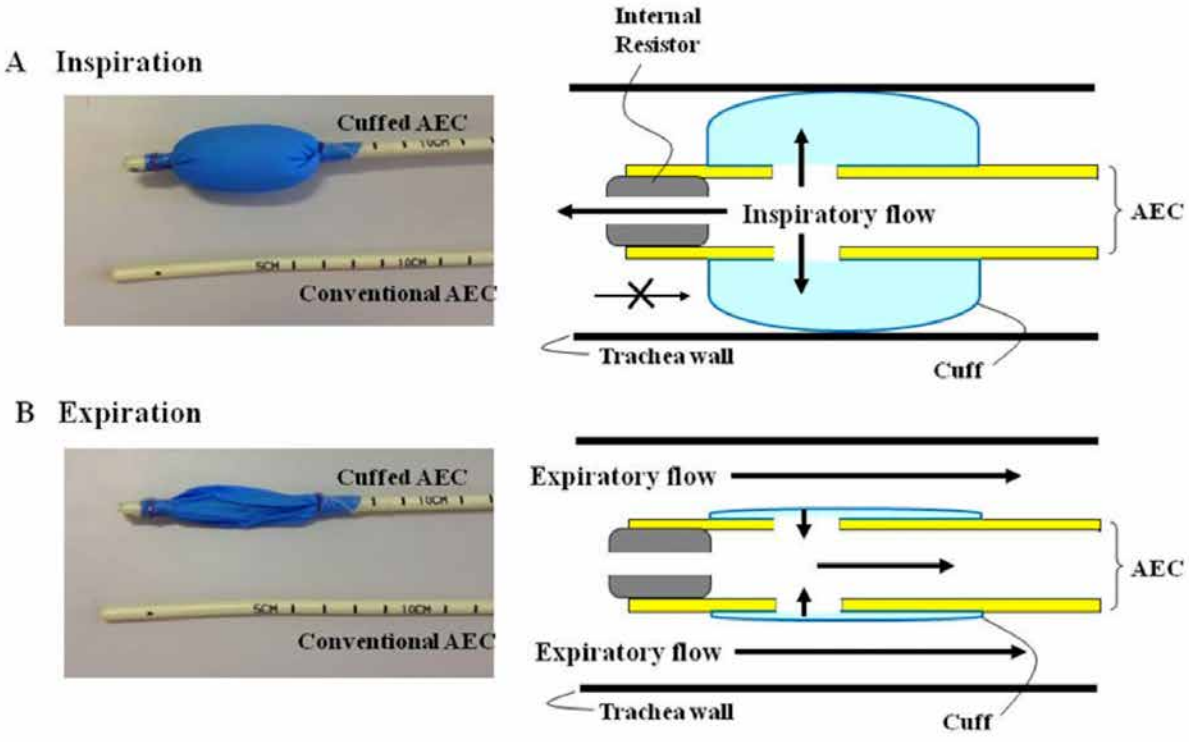
Efficacy of Ventilation Through a Customized Novel Cuffed Airway Exchange Catheter: a Tracheal/Lung Model Study

Yandong Jiang, MD, PhD[1], Yandong Jiang, MD, PhD[1], Jun Oto, MD, PhD1, Mary Sun, MS[1], Robert M. Kacmarek, PhD[1]
[1]Massachusetts General Hospital, Boston, Massachusetts

Airway exchange catheters (AECs) are commonly used in difficult airways management as a guide for re-intubation or ventilation when attached to a jet ventilator[1]. However, barotrauma resulting in pneumothorax has been a major concern when using jet ventilation with AECs[2-4]. The cause of these complications is often the excessive driving pressure with jet ventilation (15-50 psi) or airway obstruction3. Therefore, it has been suggested that minimizing intratracheal pressure and prolonging expiratory times can reduce the risk of barotrauma[4]. We propose an alternative method of ventilation via an AEC with a customized cuff (Figure). A cuffed AEC was created by placing a 5 cm long latex cuff over the distal side ports of a 14 Fr and 19 Fr AECs and inserting a 1 cm long internal resistor (14 G IV catheter for 14 Fr AEC or 11Fr Cook AEC for 19 Fr AEC) into the distal tip of each AEC (Figure). Briefly, because the lumen of the cuff freely communicated through the side ports with the lumen of the AEC, the cuff inflated during inspiration due to pressure generated by the resistor and during exhalation, the cuff deflated allowing expiratory flow around the AEC (Figure).

We evaluate the efficacy of ventilation through novel cuffed AECs using a tracheal/lung model. The lung model (Dual adult TTL training/ test lung) was connected to the distal end of a tracheal model (Airway demonstration model). The lung model was adjusted to simulate normal lung mechanics (compliance 50 mL/cmH_2O, resistance 5 cmH_2O/L/s). The proximal end was connected to an ICU ventilator set to pressure control with peak pressure 40 cmH_2O or 70 cmH_2O. Ventilation was performed at a respiratory rate of 10 breaths per minute with inspiratory: expiratory (I:E) ratios of 1:2, and 1:1. The distal tip of the AEC was placed 3 cm above the carina of the tracheal model. A flow/pressure sensor (Cardiopulmonary Management System) was placed between the distal end of the tracheal model and the model lung.

With the cuffed AEC, ICU ventilator was able to generate reasonable tidal volume (493 +/- 151 ml with 19 Fr, range: 328 ml to 694 ml and 293 +/- 103 ml with 14 Fr, range: 180 ml to 429 ml). Mean peak inspiratory airway pressure was 11.5 +/- 2.8 cmH_2O with 19 Fr (range: 8.4 cmH_2O to 15.3 cmH_2O) and 7.5 +/- 2.2 cmH_2O with 14 Fr (range: 5.0 cmH_2O to 10.4 cmH_2O). Our results indicate that cuffed AEC may enable practitioners to use ordinary ICU ventilator and achieve reasonable tidal volume and provide at least partial ventilatory support at much lower driving pressure that with the jet ventilation. The ability to ventilate patients using lower pressure settings may reduce the risk of barotraumas. Because the high resistance generated by the small inner diameter of the AEC, peak inspiratory airway pressure was within a lung protective range. In addition, ICU ventilators are much more commonly available than jet ventilator. Because this study was not conducted on patients, results from our study should be cautiously extrapolated to actual patient care until clinical studies can be conducted.



ADM 39 (75)

Further In Vitro Evaluation of the "Air Test" for Perineural Catheter Tip Localization by a Novice Regional Anesthesiologist

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Introduction: Perineural catheter visualization, specifically tip identification, remains difficult. While the "air test" may be an effective method to infer catheter location in the hands of the experienced regional anesthesiologist, its utility, sensitivity, specificity, and positive and negative predictive values for the novice regional anesthesiologist remain unknown.

Methods: An in vitro porcine-bovine model was created to simulate the clinical conditions of perineural catheter insertion as described previously. Thirty flexible epidural catheter placements were randomly assigned to either "correct" (directly below the target) or "incorrect" (beyond the target) and inserted by one expert regional anesthesiologist using a short-axis, in-plane ultrasound-guided technique with real-time visual verification by a second anesthesiologist. A CA1 anesthesiology resident without prior regional anesthesia experience and blinded to group assignment performed all catheter tip assessments utilizing ultrasound alone (pre-air) and after injection of 1 ml air via the catheter (post-air). Sensitivity, specificity, and positive and negative predictive values were calculated using the assigned procedure as the "true" value for the purpose of intent-to-treat analyses. Proportions were compared using the binomial proportion test or McNemar's test. For all comparisons, $P<0.05$ was considered statistically significant.

Results: All 30 catheters were placed according to the randomization table: 15 "correct" and 15 "incorrect." Ultrasound assessment pre-air identified proper true catheter placement 19/30 times (63%) vs. 16/30 times (53%) for ultrasound post air (p=0.606). Sensitivity, specificity, and positive and negative predictive values are presented in Table 1. The air test did not result in a difference in area under the ROC curve compared to chance (p=0.756). Following the air test, the initial assessment was changed 15 times; this change matched true catheter location 6/15 times (40%).

Conclusions: Based on this in vitro study, the air test may not aid the novice regional anesthesiologist's assessment of perineural catheter tip position. The minimum amount of experience required to utilize the air test as well as the relative benefits and drawbacks of this technique in comparison to other methods of assessing catheter location remain to be investigated.

References:

1. Korean J Anesthesiol. 2012;63:59-64;
2. Anesth Analg. 2008;106:1015-6;
3. Acta Anaesthesiol Scand. 2008;52:338-42;
4. J Ultrasound Med. 2013;32:529-33.

Table 1.

	Pre-Air	Post-Air	P-Value
Sensitivity	0.600	0.467	0.464
Specificity	0.667	0.600	>0.999
Positive Predictive Value	0.643	0.538	0.873
Negative Predictive Value	0.625	0.529	0.839

CBN 2 (81)

Inhibition of the Locus Coeruleus Impedes Emergence from Alkylphenol Hypnosis

Andrew R. McKinstry-Wu, MD[1], Michael Chalifoux, MD[1], Jason T. Moore, PhD[1], Kellie Woll, BS1, Roderic G. Eckenhoff, MD[1], Max B. Kelz, MD, PhD[1]
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Introduction: Despite extensive use over the past thirty years both to induce and maintain states of anesthesia, the neuronal mechanisms by which the prototypical alkylphenol anesthetic, propofol, works to produce hypnosis remain unknown. The locus coeruleus (LC) is a wake-active adrenergic center with widespread ascending projections to cortex and thalamus. Impairing adrenergic signaling causes hypersensitivity to anesthetic induction and has been associated with delayed emergence. LC neurons are inhibited by clinically-relevant concentrations of propofol. Using a photoreactive alkylphenol, azi-propofol-m, which covalently binds to its molecular targets in the presence of ultraviolet light (photoadduction), we test the hypothesis that prolonged inhibition of the LC slows exit from the anesthetic state.

Methods: LC neurons were identified using morphologic and electrophysiologic characteristics in intact brain slices continuously bathed in aCSF, taken from adult B6/C57 mice. After whole cell patch clamping to obtain baseline properties, the slice was bathed in 10 μM aziPm for 3 minutes followed by drug washout. After returning to a baseline rate of firing, cells were re-exposed to 10 μM aziPm for 3 minutes with UVA illumination for the final minute. 12-20 week B6/C57 male mice were implanted with chronically indwelling bilateral cannulae stereotactically targeted to the LC. After 2 weeks recovery, systemic aziPm was administered intravenously (IV) by bolus (100 mg/kg) and infusion (10 mg/kg/min over 10 minutes) with or without fiberoptically-delivered 375 nm laser light (UVA) at 5 mW/mm2 via the cannulae. After a 1-week recovery the animals were group switched and re-exposed. After another week recovery, mice were given an IV bolus and infusion of propofol (25 mg/kg followed by 2.5 g/kg/min for 10 minutes) with and without laser exposure and then group switched after another week recovery. For all experiments time to return of righting reflex was recorded. Temperature was maintained within 1.0 degrees of baseline using a heating pad and lamp, monitored via chronic subcutaneous implant. Cannula placement was confirmed histologically post-mortem.

Results: LC neurons exposed to aziPm exhibited a significant decrease in firing (38±10% of baseline) that subsequently returned to baseline within 5 minutes of washout (Figs 1A, B.) When these neurons were re-exposed to aziPm in the presence of UVA, initiating covalent binding of aziPm, ensuing inhibition did not recover over 35 minutes of recording. In intact animals, using a within-subjects randomized design, preliminary data demonstrate that mice with cannulae accurately targeting the LC exhibit a significant doubling in the duration of hypnosis upon photoadduction (aziPm + UVA: 902 ± 17 seconds) as compared to aziPm alone (aziPm + sham UVA: 457 ± 17 seconds). Moreover, accurate targeting of photoadduction centered upon the LC also significantly increased the hypnotic duration compared to mice in which photoadduction occurred through off-target cannulae (aziPm + UVA: 389 ± 36, Fig 1C.) In the placement control mice with cannulae that missed the LC, there was no effect of actual or sham UVA photoillumination on the duration of hypnosis. Finally, control studies using propofol±UVA fiberoptic targeting of the LC, demonstrate no effect of the laser itself on hypnosis (Fig 1D).

Discussion: Increased time to return of righting following alkylphenol photoadduction in the LC suggests that LC reactivation is one mechanism necessary for prompt emergence. This work also demonstrates the utility of "OptoAnesthesia" in dissecting neuronal circuits modulating hypnosis.

References:

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3. Friedman, E.B., et al. (2010). PLoS One 5, e11903.
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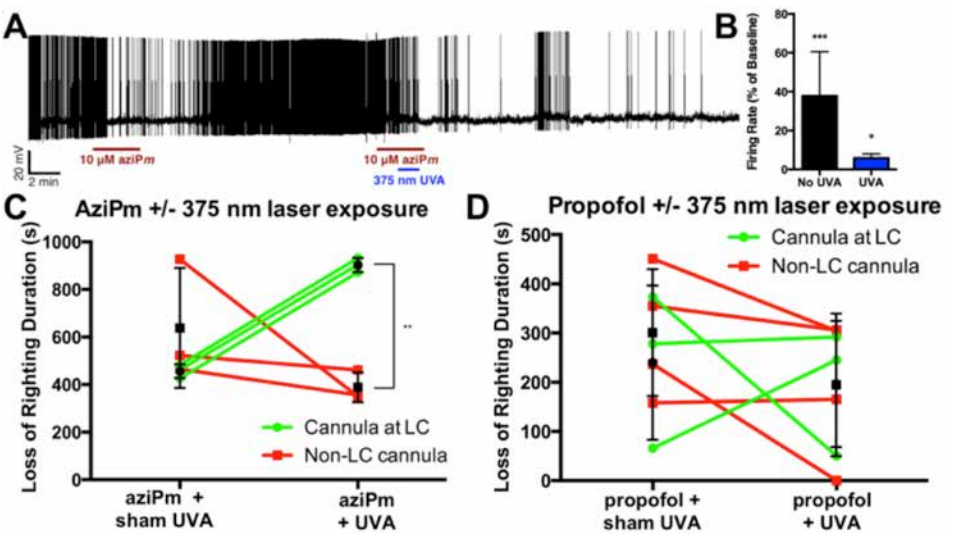

CBN 3 (84)

MicroRNAs Regulate Gene Expression in the Setting of Stroke – Protection With Post-Treatment to Reduce Levels of miR-181a

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Introduction: MicroRNAs (miRNA) are small noncoding RNAs that are now appreciated to participate in the regulation of translation of many mRNAs. Commonly this is via binding to complementary sequences in the 3' UTR of the mRNA, though other binding sites have been reported for some genes. Because the binding site is generally 5-6 nucleotides long, each miRNA can bind many mRNAs, and conversely, each mRNA may have binding sites for several different miRNAs. Recent work has shown that miRNA expression changes in response to cerebral ischemia. This led us to postulate that changes in miRNA expression could alter outcome from stroke, and that intentionally manipulating miRNAs in this setting could have therapeutic effects, by increasing expression of protective genes. We focused on regulation of the chaperone HSP70 family and the Bcl-2 apoptosis regulatory family, as we know that increasing levels of chaperones and anti-apoptotic proteins can improve outcome from stroke. MiR-181a has been shown to target GRP78, the endoplasmic reticulum chaperone, and the anti-apoptotic proteins Bcl-2 and Mcl-1. Earlier studies showed that miRNA-181a levels change in response to stroke, miR-181a levels increase in the core that is destined to die rapidly, but decrease in the penumbra where there is scattered delayed brain cell death. Pretreatment 24 hr prior to MCAO with antagomir improved outcome[1].

Methods: Stroke was induced in adult male C57BL6 mice by transiently occluding the middle cerebral artery for 1 hr with a suture (MCAO). The suture is removed to allow reperfusion and the mice are sacrificed after different durations of reperfusion. We altered levels of miR181a expression in the brain by either stereotactic intracerebroventricular infusion (ICV) or intravenous infusion of antagomir to reduce levels of miR-181a. Post-treatment at 1hr by IV infusion or 2 hr by ICV infusion with miR-181a antagomir and control mismatch was tested. miRNA levels were assessed by RT-qPCR, protein levels were assessed by western blot. Stroke outcome was assessed by histological evaluation of infarct size with triphenyltetrazolium chloride, and by assessment of neurological score. Inflammation was assessed by staining for MPO to identify infiltrating leukocytes and IBa1 to identify activated microglia/macrophages.

Results: Administration of miR181a antagomir reduces levels of miR-181a in the brain, when given by either ICV or IV infusion. Both methods of administration resulted in decreased infarct volume at 48 hr reperfusion and improved neurological score. When we evaluated the numbers of infiltrating leukocytes and activated microglia/macrophages we found these measures also reduced by post-treatment with antagomir. Of three proteins previously found to be regulated by mir-181, with post-treatment increases were seen in BCL2 and XIAP, both anti-apoptotic proteins.

Conclusions: Altering miRNA levels is a new potential treatment for stroke. Post treatment with antagomir to miR-181a at either 1 or 2 hours of reperfusion was still effective at improving short term outcome from stroke. This was associated with reduced evidence of inflammation, and increased levels of two anti-apoptotic proteins. Protection with treatment after stroke, including by IV administration, is encouraging for increased potential to translate into a clinically useful therapy. Additional studies looking at longer term survival are still needed.

Reference:

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CBN 4 (97)

EEG Variation During Maintenance and Emergence from General Surgical Anesthesia

Divya Chander, MD, PhD[1], Paul S. Garcia, MD, PhD[2], Jamie W. Sleigh, MD, MBChB[3]
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Introduction: Approximately 40 million anesthetics are delivered annually, yet the sequence by which the brain recovers conscious awareness post-surgical anesthesia is poorly understood. Although sleep and anesthesia[1-3] have been measured using the electroencephalogram (EEG) since the 1950s, a staging taxonomy based on specific EEG features has only been formalized for natural sleep[4,5]. Further, the spectral signature of anesthetic emergence has been understudied relative to induction[6]. Recent studies in which volunteers have been exposed to slowly changing doses of propofol have described spectral power changes upon emergence that appear to be the inverse of induction[7-9]. This is in contrast to the termination of natural sleep, which is typically preceded by cyclic transitions into progressively longer episodes of cortical activation[10], and recent pharmacogenetic studies which find asymmetric state transitions between anesthetic induction and emergence[11-13].

We therefore designed a study with 3 objectives. The first was to catalogue and define a standardized nomenclature for the EEG during anesthetic maintenance – analogous to that used to describe natural sleep. The second was to characterize EEG trajectories during emergence from general anesthesia, to determine if there was a single common path, or multiple pathways to re-establishing conscious awareness. Our final goal was to determine if differing emergence trajectories had any relationship to the quality of a patient's recovery.

Methods: We recorded frontal EEG from 100 patients undergoing orthopedic surgery with general volatile anesthesia, from induction through emergence. Administration of general anesthesia and adjuncts proceeded according to the clinician's judgment. Using spectral processing techniques in combination with a dynamical systems approach, we examined the EEG at the termination of anesthesia ('End Maintenance'), through the transition back to conscious awareness ('End Emergence'). Individual spectral profiles were not averaged. In the post-operative period, we used simple, heuristically derived, descriptions of level of consciousness and pain to define recovery.

Results: We were able to discriminate 4 patterns of anesthetic maintenance comprised of 2 states, 'slow-wave anesthesia' (SWA) and 'non slow-wave anesthesia' (NSWA), and 2 derivative sub-classes of the slow-wave state, 'delta-dominant' (ddSWA) and 'spindle-dominant' (sdSWA). These classes were defined by the relative contribution of delta (1-4 Hz) and spindle (alpha, 8-14 Hz) power in their spectral signatures. Emergence was defined as the period from anesthetic drug discontinuation to the subject's responsiveness to voice. During this period, most patients progressed gradually from a pattern characterized by strong delta-spindle power (SWA) to one marked by low delta-spindle power (NSWA) before awakening. These trajectories could be further characterized by the duration and rapidity of transitions amongst these slow-wave dominated brain states that preceded awakening. However, 31% of patients transitioned abruptly from SWA to waking, deviating from this canonical sequence; these subjects were also more likely to express pain in the post-operative period. These patterns reflect greater EEG heterogeneity than previously reported.

Conclusions: We present a staging nomenclature to discriminate anesthetic maintenance patterns based on the spindle and delta power in their spectral signatures. Variability in emergence trajectories suggests that the central nervous system may not always reconnect in a proscribed pattern after general anesthesia is discontinued; in some instances, uncoordinated brain arousal may precede the return of connected consciousness. We predict that these less coordinated emergence trajectories may predispose patients to undesirable wake-ups, in the same way that parasomnias are exacerbated by disrupted sleep architecture[14].

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CBN 5 (117)

Disrupting NMDA Receptor-PSD-95 PDZ Domain Interactions in Neonatal Rats Impairs Hippocampal Neuronal Function, Learning, and Memory

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Introduction: Mounting evidence from human and animal studies suggests that prolonged early postnatal anesthesia, with agents such as isoflurane (ISO), causes long-term impairment in learning and memory. These cognitive deficits in animals correlate with disruption of neuronal mitochondria, reduced neuronal branching, and hippocampal cell death. However, the mechanisms of these toxic effects of ISO are not well understood. Previously, we used NMR spectroscopy to show that ISO interacts with amino acid residues in the PDZ domains of PSD-95 that are critical for protein-protein interactions. Co-immunoprecipitation and yeast two-hybrid experiments showed that ISO inhibits NMDA receptor-PSD-95 binding in a dose dependent manner. Our data suggest that disrupting interactions between NMDA-type glutamate receptors and the PDZ domain of PSD-95 plays an important role in cognitive impairment due to early life ISO exposure.

Methods: Male Sprague-Dawley rats were exposed to vehicle air control or 3.4% ISO for 4 hours on either postnatal day (PND) 7 or 60. Animals were trained with fear conditioning to test spatial and auditory memory. Animals were sacrificed 7 days later, and brains were processed for either electron microscopy or immunofluorescence. In separate experiments, animals were exposed to air or ISO and sacrificed 7 days later for electrophysiologic experiments. Acute hippocampal slices were stimulated at the Schaffer collaterals, and activity was recorded in CA1 pyramidal neurons using whole-cell patch clamping. Finally, cultured embryonic hippocampal neurons were exposed to air or ISO for 4 hours after either 7 or 14 days in vitro (DIV). The cultures were stopped on DIV15 for immunofluorescent staining and microscopy.

Results: We now show that ISO impaired hippocampus-dependent fear memory in rats treated for 4 hours on PND7, but not in PND60 rats. ISO reduced cell proliferation in the hippocampi of rats treated on PND7, but not on PND60. Electron microscopy revealed that ISO reduced synaptic contacts and disrupted mitochondrial membranes on PND7 but not PND60. Western blotting showed that the actin-associated protein drebrin was reduced in the hippocampus after PND7 ISO treatment, suggesting impairment of synaptic spine development. To further examine the effects of disrupting NMDAR-PSD-95 interactions, recombinant PSD-95 PDZ domain 2 was conjugated to the cell-permeable Tat peptide (Tat-PDZ2). Electrophysiology showed that Tat-PDZ2 could inhibit synaptic potentiation in juvenile mouse hippocampal slices, whereas ISO in rats inhibited potentiation after PND7 treatment but not after PND60. Preliminary data suggest that ISO and/or Tat-PDZ2 treatment in cultured hippocampal neurons reduced expression of the actin-associated protein drebrin relative to the immature neuronal marker Doublecortin.

Conclusions: Taken together, these data suggest that ISO exposure during a crucial period in brain development impairs synaptic function, synaptogenesis, and neurogenesis, with long-term negative consequences for hippocampal function.

CBN 6 (119)

Hippocampal GABAergic Field Potentials: A Novel High Throughput Screen for General Anesthetics In Rodents

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Introduction: Concern for anesthetic-related cognitive dysfunction is growing. Long-lasting therapeutic effects of some anesthetic drugs have also emerged. It is vital that we develop a screen for safe, effective anesthetics with the most favorable effects on cognition. At the cellular level, anesthetics alter the behavior of neurons, often by enhancing inhibitory signals through interactions with the GABAA receptor (GABAR). We describe a novel, high throughput method to directly measure a compound's effect on aggregate GABAAR mediated inhibition within area CA1 of the rat hippocampus, an area crucial for learning and memory, without the need for disruptive whole-cell electrophysiological recordings.

We found these field inhibitory postsynaptic potentials (fIPSPs) by cutting brain slices to preserve coherent current-sources and -sinks, stimulating basket cell interneurons and recording CA1 pyramidal cell hyperpolarization. We further isolated the fIPSP using NMDA and AMPA receptor antagonists to block excitatory transmission. We validated our assay with two common GABAergic anesthetics, and have screened several compounds identified by in silico methods of molecular docking and computational chemistry for their potential as anesthetics.

Methods: 24-28 day old Sprague Dawley rats were anesthetized with isofluorane and decapitated. Brains were submerged in chilled artificial Cerebrospinal Fluid (aCSF). 400 µm thick slices were cut and placed in aCSF, and bubbled with 95% O2 and 5% CO2. Field potentials were evoked through a bipolar tungsten stimulating electrode placed in the stratum pyramidale (SP) of the CA1 region. Recordings were conducted through a glass microelectrode 250-400 µm away in the SP of CA1. fIPSPs were pharmacologically isolated with antagonists for the NMDA and AMPA type glutamate receptors. GABAergic dependence of fIPSP was confirmed by its disappearance in picrotoxin (GABAAR antagonist). The validity of the screen was tested on known anesthetics, propofol and midazolam. Benzodiazepine dependence of the fIPSP was tested with flumazenil.

Results: A significant change in the magnitude of the fIPSP is evident upon application of propofol. Application of low concentrations of propofol (1-5 um) produces a small increase in the size in the fIPSP (<5%), consistent with enhancement of phasic inhibition. Interestingly, larger doses of propofol (20 µM) decreased the fIPSP significantly (35-40%), consistent with enhanced tonic inhibition and net hyperpolarization of the slice. Midazolam, on the other hand, produced an enhancement of the fIPSP, suggesting a greater role of phasic inhibition in its anesthetic effect. Midazolam's effect was blocked by flumazenil, confirming the specificity of midazolam for the benzodiazepine binding site of the GABAAR. Several putative anesthetics were also tested, one which we identified as having significant activity at the benzodiazepine binding site of the GABAAR. In all cases, picrotoxin reduced the fIPSP to the level of background noise.

Conclusion: The isolated fIPSP gives predictable, fast results with propofol and midazolam, and exhibits sensitivity to varying concentrations of these drugs. Thus, isolated fIPSPs allow for direct measurement of an anesthetic's effect on GABAA transmission and have helped identify at least one novel anesthetic compound. Combining this fast, minimally invasive, neural population based approach affords a unique opportunity to assay multiple lead compounds for anesthetic efficacy in an intact, well characterized neural circuit with clear relevance to learning and memory.

CBN 7 (120)

A Network of Discrete Metastable Activity States Mediates Recovery from Isoflurane Anesthesia

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The process by which the brain traverses the vast space of potential neuronal activity states to recover those compatible with consciousness after a gross perturbation, such as general anesthesia, is unknown. We analyzed simultaneously recorded corticothalamic local field potential recordings of spontaneous activity from rats under isoflurane anesthesia to show that neuronal activity en route to consciousness is confined to a low dimensional subspace. Within this subspace, neuronal activity clusters into discrete metastable states that persist for minutes. Each of these metastable states has a characteristic spectral profile in the areas from which we recorded. Transitions between these metastable states are structured, such that some states form “hubs” that connect groups of otherwise disconnected “spur” states. The hubs connect to each other and to the activity state compatible with consciousness, providing a bridge between the “spur” states and the activity state compatible with consciousness. This network architecture requires that the brain must pass through one or more of the hub states en route to recovery. This hierarchical organization of metastable states within a low dimensional subspace significantly simplifies the recovery of the state consistent with wakefulness on a physiologically-relevant timescale. However, metastable intermediate states with long dwell times and structured transition probabilities imposes a tradeoff in time to recovery of consciousness; this presents a dynamical corollary to anesthetic inertia as reported by Kelz. These observations provide the beginning of an account of the intrinsic dynamics of how the brain self-tunes to allow recovery of consciousness from any large perturbation capable of inducing burst suppression, including trauma, encephalopathy, and hypothermia.

Abstract: The process by which the brain traverses the vast space of potential neuronal activity states to recover those compatible with consciousness after a gross perturbation, such as general anesthesia, is unknown. We analyzed simultaneously recorded corticothalamic local field potential recordings of spontaneous activity from rats under isoflurane anesthesia to show that neuronal activity en route to consciousness is confined to a low dimensional subspace. Within this subspace, neuronal activity clusters into discrete metastable states that persist for minutes. Each of these metastable states has a characteristic spectral profile in the areas from which we recorded. Transitions between these metastable states are structured, such that some states form “hubs” that connect groups of otherwise disconnected “spur” states. The hubs connect to each other and to the activity state compatible with consciousness, providing a bridge between the “spur” states and the activity state compatible with consciousness. This network architecture requires that the brain must pass through one or more of the hub states en route to recovery. This hierarchical organization of metastable states within a low dimensional subspace significantly simplifies the recovery of the state consistent with wakefulness on a physiologically-relevant timescale. However, metastable intermediate states with long dwell times and structured transition probabilities imposes a tradeoff in time to recovery of consciousness; this presents a dynamical corollary to anesthetic inertia as reported by Kelz. These observations provide the beginning of an account of the intrinsic dynamics of how the brain self-tunes to allow recovery of consciousness from any large perturbation capable of inducing burst suppression, including trauma, encephalopathy, and hypothermia.

CS 67 (56)

Single Nucleotide Polymorphism-Specific Regulation of Matrix Metalloproteinase-9 by Multiple MiRNAs Targeting the Coding Exon

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Introduction: Micro (mi)-RNAs work with exquisite specificity: they distinguish a target from a non-target based on a single nucleotide mismatch in the core nucleotide domain with a consequent reduction in the protein output upon translational inhibition and mRNA destabilization[1]. In our recent study[2] we characterized a coding exon SNP in the pro-domain of MMP-9 (N38S, rs41427445) that resulted in a profound decrease in the secreted protein. We questioned whether miRNA regulation of MMP-9 expression could occur in an SNP-specific manner, manifesting as a post-transcriptional control of expression of genetic polymorphisms in the protein coding exons.

Methods: Wt- or mutant MMP-9 cDNA were expressed in HEK293 cells by transfection and expression of mRNA and miRNA were quantified by qRT-PCR. miRNA-mimics, antagomirs, and control small synthetic RNA specific to a given target miRNA were transfected following the manufacturer's recommended protocol. For bioinformatics analyses, we implemented a de novo search algorithm based on the report by Nicoloso et al[3]. The 1,919 mature human miRNA sequences were downloaded (July 2012) from miRBase. Annotations listing all coding exons, 5' UTRs, and 3' UTRs for each gene (refFlat.txt) were downloaded (July 2012) from the University of California-Santa Cruz. The human genome sequence for hg19 (GRCh37.1), sequences surrounding each SNP (August 2011), and the position of each SNP (August 2011) were downloaded from the National Center for Biotechnology Information (NCBI). The miRanda software was downloaded (August 2010 release) (www.microrna.org/microrna/getDownloads.do) and implemented to run on a desktop PC.

Results: Expression of an MMP-9 cDNA harboring the SNP rs41427445 resulted in a profound decrease in the secreted MMP-9 protein in the cell culture supernatant. Our initial hypothesis for the decreased protein secretion of N38S-MMP-9 was that subcellular protein mistargeting and the inability to secrete the protein were due to the loss of N-glycosylation. We tested this hypothesis through immunocytochemistry and a Western blot of the cell lysate (i.e. intracellular MMP-9) of the transfected cells expressing the wild type- or N38S-MMP-9. We expected increased retention of the mutant protein with detection of mistargeted non-secreted protein in the cells expressing the N38S-MMP-9. In contrast to our expectation, we saw no intracellular accumulation of the mistargeted N38S-MMP-9 protein, but rather a decreased intracellular protein level, confirmed by both immunocytochemistry and the Western blot of the whole cell lysate. Further analysis suggested a perplexing apparent single nucleotide-dependent difference in mRNA stability leading to a decrease in the mRNA and ultimately the intracellular and extracellular amounts of N38S-MMP-9 protein. Bioinformatics analysis identified that the presence of SNP in MMP-9 created a novel binding site for miRNA-671-3p and miR-657. Experiments with miRNA-antagomirs and –mimics confirmed that the SNP-dependent miRNA destabilization of mRNA as the likely mechanism responsible for the low level of N38S-MMP-9 protein expression. Further studies confirmed that this SNP-dependent miRNA binding can distinguish SNPs leading to a silent mutation with no amino acid changes.

Conclusions: Our results demonstrate an SNP-specific regulation of MMP-9 through miRNA targeting the coding region of the gene. Bioinformatics analysis revealed SNP-specific regulation of MMP-9 by additional miRNA targeting other SNPs, including synonymous SNPs, with no change in the coded amino acid. This discovery reveals a cellular mechanism whereby expression of a specific MMP-9 mRNA is affected by a highly selective miRNA interaction with the SNP-mRNA, most likely playing an important role in the biology of MMP-9.

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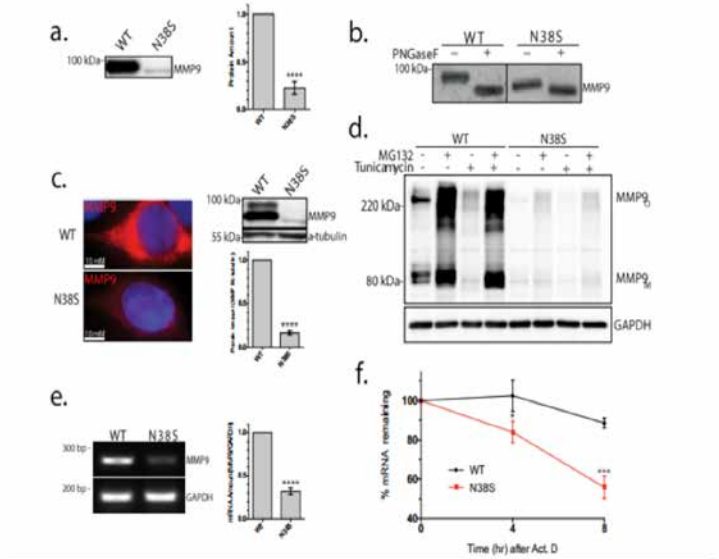

Reduction in secreted N38S-MMP-9 protein is not due solely to the loss of N-glycosylation. a. Western blot analysis of culture media (20 µL) from cells transfected with wild type- or N38S-MMP-9 probed with anti-MMP-9 antibody (left). Similar results obtained from 5 separate transfections. The MMP-9 protein amount was quantified by ELISA and averaged (mean ±S.E.M.) from 5 separate transfections shown as a bar plot (right). ****P<0.0001, t-test, n=5. **b**. Western blot of PNGase F treated cell culture media from wild type- (WT) or N38S-MMP-9 transfected cells. Note that the N38S-MMP-9 culture media was concentrated to obtain equivalent band intensity to the wild type. The observed PNGase-induced mobility shift is consistent with a loss of two N-glycosylation sites for the wild type and the loss of one remaining N-glycosylation for N38S. **c**. Anti-MMP-9 immunohistochemical staining (red) of wild type- and N38S-MMP-9 transfected cells. Nuclei were stained by Hoechst 33342 (blue) (left). Western blot analysis of total cell lysate probed with anti-MMP-9 or anti- α-tubulin antibody indicating reduced N38S-MMP-9 intracellular protein levels (right).****P<0.0001, t-test, n=5. **d**. Cells expressing WT- or N38S-MMP-9 were treated with or without MG132 (proteasome degradation inhibitor) (10 µM) or Tunicamycin (GlcNAc phosphotransferase inhibitor; selectively inhibiting N-glycosylation) (1.0 µg/ mL) both for 24 hrs and cell culture media ran on a non-reducing PAGE and was probed with anti-MMP-9- or anti-GAPDH-antibody. Note the MMP-9 monomer (MMP-9_M) with an apparent molecular mass near the expected ~90kDa and the larger oligomeric form (MMP$_O$). MG132 failed to rescue the N38S-MMP-9 protein amount. Tunicamycin treatment of WT mimicked the reduced N38S protein levels, but was completely rescued by MG132. Representative of 3 separate experiments. **e**. Total RNA was harvested from cells transfected with the WT- or N38S-MMP-9 plasmids, and an end point RT-PCR performed with primer pairs amplifying the MMP-9 or GAPDH mRNA. Agarose gel electrophoresis demonstrated a reduction in the amplified PCR product for N38S compared to WT. ****P<0.0001, t-test, *n*=3. **f.** The stability of WT- or N38S-MMP-9 mRNA was examined using qRT-PCR at the indicated time points after actinomycin D treatment (10 µg/mL). The data is normalized to the respective mRNA levels at time 0 hr. *P<0.05, ***P<0.0005, t-test, n=3.

CS 69 (78)

A Novel Mechanism to Impede Uterine Smooth Muscle Contractions and Treat Pre-Term Labor: Anoctamin-1 Calcium Activated Chloride Channels as Critical Mediators of Calcium Dynamics

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Introduction: Premature uterine contractions play a significant role in the pathogenesis of pre-term labor. Myometrial contraction is intimately dependent on calcium. In pregnancy, intracellular calcium waves are spread throughout the uterus via gap junctions to facilitate the coordination of forceful contractions. These increased calcium levels are mechanistically tied to activation of myosin light chain kinase to promote myosin-actin bridging and the cytoskeletal re-organization required for contraction. Two mechanisms govern the initial elevation in intracellular calcium: membrane depolarization and contractile agonist-induced sarcoplasmic reticulum (SR) release. Anoctamin 1 (ANO-1) is a recently discovered calcium-activated chloride channel. We have previously shown that ANO-1 antagonism potently inhibits oxytocin-induced human myometrial contractions by unclear cellular mechanisms. We hypothesize that ANO-1 channels modulate membrane potential and calcium dynamics in human myometrium. We sought to determine the role that ANO-1 plays in two integral mechanisms of intra-cellular calcium handling: cell membrane depolarization, and GPCR-mediated SR calcium release.

Methods: Immortalized human myometrial cells were grown to confluence and dynamic fluorescence was measured on a plate reader. For GPCR-mediated SR release studies, cells were loaded with two fluorescent calcium indicators to obtain differential cytosolic (Fura-2) and sarcoplasmic (Mag-Fluo-4) calcium loading. Contractile agonists (10uM bradykinin or 1uM oxytocin) were injected +/- a specific ANO-1 antagonist (10-100uM benzbromarone). For membrane potential studies, cells were loaded with the membrane potential indicator FLIPR and injected with either ANO-1 antagonist (benzbromarone 50uM), ANO-1 agonist (Eact), or K-gluconate 40mM (positive depolarizing control), or NS-1619 10uM (positive hyperpolarizaing control). Data is reported as percentage of mean inhibition compared to control or mean fluorescence (RFU) and SEM. In all cases $p<0.05$ was considered significant.

Results: The ANO-1 antagonist benzbromarone (100uM) suppressed bradykinin mediated peak Fura-2 fluorescence [Cai] by 85.1% ($p < 0.001$, N=7) and nadir Mag-Fluo-4 fluorescence [CaSR] by 92.2% ($p<0.001$, N=7); 100uM benzbromarone suppressed oxytocin mediated Fura-2 peak by 77.6% ($p<0.001$; N=5). In FLIPR studies, CaCC modulation resulted in significant changes in membrane potential. Eact significantly depolarized the membrane (25.33 + 11.68 RFU) paralleling the effect of K-gluconate (98 + 28.57 RFU) compared to vehicle control (3.2 + 0.57 RFU, $p<0.05$). Similarly, benzbromarone hyperpolarized the myometrial cell membrane (-25.67 + 4.9 RFU; $p<0.05$) paralleling the effect of NS1619 control(-39 + 1.53 RFU) compared to vehicle control.

Conclusions: ANO-1 channels are integral to two central aspects of human myometrial calcium handling: contractile agonist (e.g. oxytocin)-induced SR calcium release, and membrane potential modulation. Our results suggest the exciting possibility that ANO-1 antagonism imparts dual-modal blockade of calcium stores in human myometrial cells– a feature no other tocolytic drug class possesses. Targeting ANO-1 for the treatment of pre-term labor holds therapeutic promise.

CS 70 (87)

Antagonists of the TMEM16A Calcium-Activated Chloride Channel Relax Airway Smooth Muscle and Potentiate β-agonist Relaxation: Potential New Tools to Treat Bronchospasm

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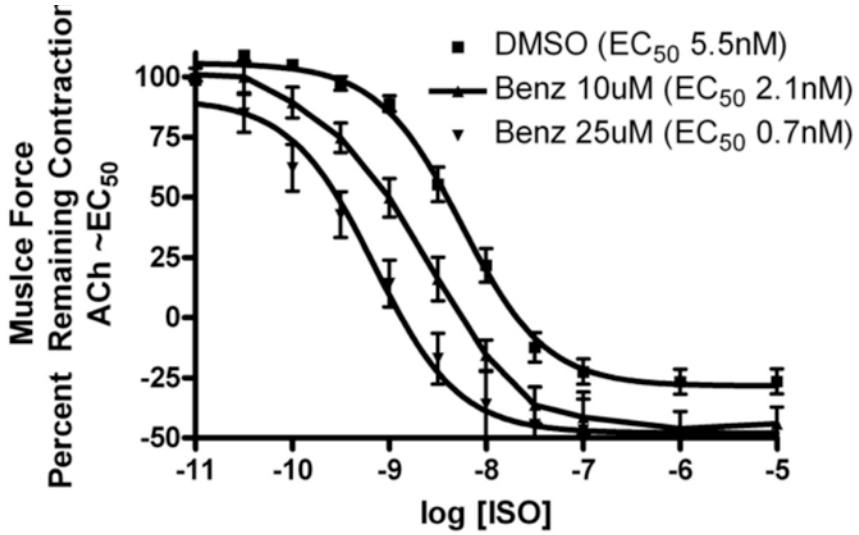
Introduction: Perioperative bronchospasm refractory to β-agonists continues to challenge anesthesiologists and intensivists. The modulation of chloride flux is a promising new target for relaxation of airway smooth muscle (ASM). Our lab has shown that blockade of the recently discovered TMEM16 family of calcium-activated chloride channels (CaCCs) modulates ASM contraction. It has been proposed that blockade of chloride flux may not only prevent depolarization of the ASM cell at the plasma membrane (PM), but may also prevent calcium release from the sarcoplasmic reticulum (SR) due to the role of chloride in balancing the charge debt created by the movement of calcium across the SR. We hypothesized that TMEM16A antagonists would relax ASM contraction from a variety of contractile mediators, relax synergistically with β-agonists, hyperpolarize ASM cells at the PM, and attenuate an increase in intracellular calcium from both the PM and SR.

Methods: Human ASM or guinea pig tracheal rings was suspended in Krebs-Henseleit buffer and contracted with EC50 dose of acetylcholine (Ach) or 20nM leukotriene D4 (LTD4). ASM was then treated with vehicle or increasing concentrations of the TMEM16A antagonists, benzbromarone or T16Ainh-A01. In separate studies, guinea pig tracheal rings were contracted with EC50 dose of Ach and then exposed to increasing doses of isoproterenol (0.01nM-10μM) ± vehicle or benzbromarone. Human ASM cells were loaded with FLIPR membrane potentiometric dye and then exposed to TMEM16A antagonists or agonists. Cells were loaded with the calcium indicator fura-2, pretreated with vehicle or benzbromarone with 0 or 2mM extracellular Ca2+, and then challenged with bradykinin or histamine.

Results: In human ASM, benzbromarone significantly relaxed both an Ach EC50 (10μM: 64.1 ± 10.5% (% relaxation at 30 minutes), $p<0.05$; 50μM: 9.6 ± 20.4%, $p<0.01$, n=8) or an LTD4 contraction (10μM: 68.5 ± 10.5%, $p<0.05$; 50μM: 36.8 ± 13.3%, $p<0.01$, n=8). Ach EC50 contraction in guinea pig tracheal rings were relaxed by T16Ainh-A01 (10μM: 78.9 ± 4.0%, $p<0.05$; 50μM: 51.8 ± 4.6%, $p<0.001$, n=6) and benzbromarone (10μM: 70.9 ± 6.7%, $p<0.01$; 50μM: -10.7 ± 3.1%, $p<0.001$, n=6). Dose response curves showed a leftward shift in isoproterenol (Iso)-induced relaxation with increasing doses of benzbromarone, indicating potentiation of β-agonist relaxation (vehicle Iso EC50 5.5nM, benzbromarone 10μM Iso EC50 2.1nM, benzbromarone 25μM Iso EC50 0.7nM, n=9, $p<0.01$). Benzbromarone hyperpolarized human ASM cells, while Eact (TMEM16A activator) depolarized cells (50μM benzbromarone -59.1 ± 6.7 RFU, 50μM Eact 115.1± 5.5 RFU, n=7, $p<0.001$). Pretreatment with benzbromarone attenuated bradykinin and histamine induced increase in intracellular calcium in either 2mM CaCl2 or 0mM CaCl2 (n=10-12, $p<0.001$).

Conclusions: TMEM16A antagonism relaxes both an Ach and LTD4 contraction in human ASM, relaxes synergistically with β-agonists, hyperpolarizes ASM cells, and attenuates increases in intracellular calcium from both the PM and SR. As TMEM16A antagonists work with first line agents for bronchospasm (β-agonists) and work through a novel pathway of interrupting ion flux both at the PM and SR, they are promising tools in the treatment of acute bronchospasm.



Benzbromarone treatment decreased the EC_{50} dose of isoproterenol required for relaxation. Benzbromarone 25μM decreased the isoproterenol EC_{50} for relaxation from 5.5 to 0.7nM, which represents a 7.9 fold difference. (n=9, $p<0.01$)

CS 71 (95)

The Effect of Oxygen Tension on Reactive Oxygen Species Production in Blood Ex Vivo

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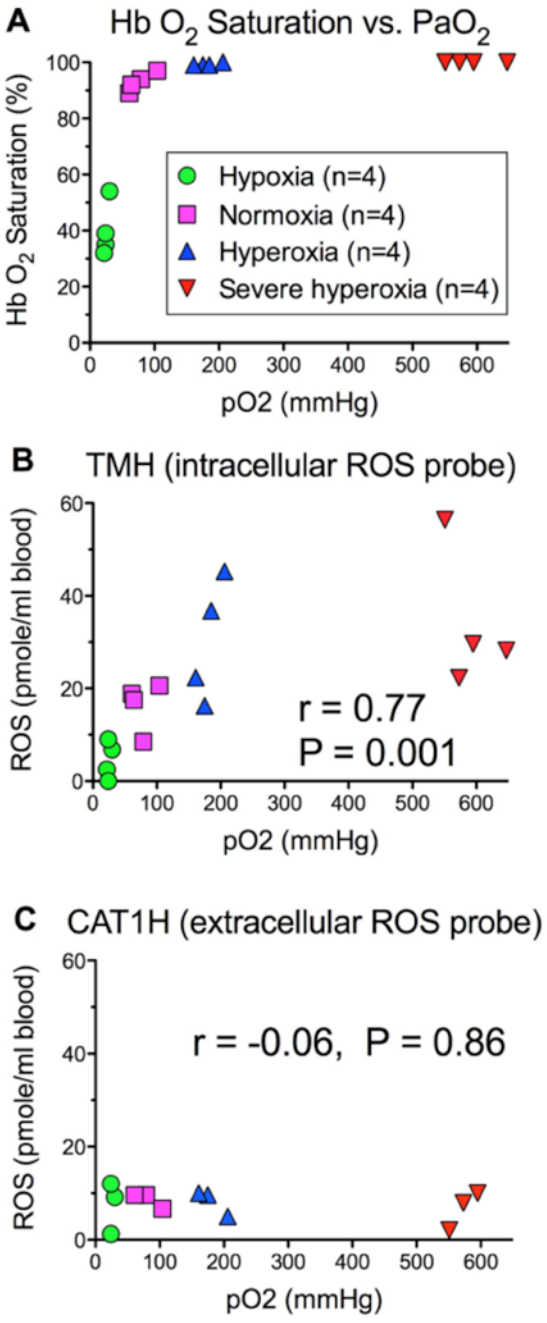
Introduction: Oxygen tension is tightly regulated in aerobic organisms, but anesthesiologists hyper-oxygenate patients during surgery. Molecular oxygen is the primary substrate for superoxide (O2-) production, the most abundant reactive oxygen species (ROS). ROS oxidize lipids and proteins, which affects cellular function and survival. Intraoperative oxidative damage causes postoperative morbidity[1]. We hypothesized that the oxygen tensions commonly observed in patients during surgery increase ROS production in blood ex vivo.

Methods: Whole blood from healthy volunteers was exposed to hypoxia (target pO2 = 30mmHg, Hb O2 sat = 50%), normoxia (80mmHg, 95% sat), hyperoxia (200mmHg, 100% sat), or severe hyperoxia (550mmHg, 100% sat) for 30 minutes at 37 degrees C. We then measured intra- and extracellular ROS production using site-specific cyclic hydroxylamine electron spin probes with and without cell impermeable superoxide dismutase (SOD). TMH is a lipophilic probe that rapidly reacts with intracellular superoxide and other ROS (2). We measured the stable nitroxide radical formed from TMH and ROS in an electron paramagnetic resonance spectrometer. CAT1H is hydrophilic probe that reacts only with extracellular superoxide, since superoxide does not readily cross bi-lipid membranes. Blood pH, pCO2, and pO2 were also measured to assess oxygenation.

Results: Target hypoxic, normoxic, and hyperoxic oxygen tensions were achieved (Figure 1A). Oxygen tension increased TMH-detected ROS production from 4.8 ± 2.1 pmol/ml blood during hypoxia to 24.8 ± 4.3 pmol/ml blood during severe hyperoxia (Rank-Sum Test P=0.03; pO2 vs. ROS Spearman correlation r=0.77, P=0.001; Figure 1B)). Oxygen tension did not affect CAT1H-detected ROS production (r=-0.06, P=0.86, Figure 1C). Extracellular elimination of superoxide with SOD did not affect TMH-detected ROS production or alter the effect of oxygen tension on TMH-detected ROS production (r=0.89, P=0.003), further suggesting that increased oxygen tension induces intracellular but not extracellular ROS production.

Conclusions: Hyperoxia increases ROS production in blood ex vivo. The source of excess ROS production appears to be intracellular, possibly from mitochondria, a common source of ROS implicated in oxidative stress. Hyperoxia does not appear to affect phagocytic NADPH oxidase (the source of neutrophils' oxidative burst) in healthy volunteer blood ex vivo, an important extracellular source of ROS. Subsequent studies will determine the cell type and molecular source of hyperoxia-induced ROS production in blood and if hyperoxia increases ROS production or oxidative damage in solid organs and in anesthetized patients.



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CS 72 (99)

Lavoisier's Dilemma Solved by Confirming Old Cavendish Report

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Ibn al Nafis 1250 Michael Servetus 1553 Michael Sendivogius 1604 John Mayow 1668 Henry Cavendish 1766 Carl W. Scheele 1771 Joseph Priestley 1774 Antoine Lavoisier 1783

During the last century, historians have discovered and published that between the 13th and 18th century at least 8 scientists discovered that the air we breathe contains something we need and use. Both Ibn al Nafis (1213-1288) in Cairo and Michael Servetus (1511-1553) in France accurately described the pulmonary circulation and its effect on blood color. Michael Sendivogius (1566–1636) in Prague identified the gas made by heating saltpetr as the part of air he named "The Food of Life". John Mayow (1641–1679) found that 1/5th of air was a special gas he named "spiritus nitro aereus" and Carl Wilhelm Scheele (1742-1786) generated "Fire Air" by heating silver carbonate. On August 1st 1774, Joseph Priestley (1733-1804) was the 6th when he discovered how to make a gas he called dephlogisticated air by heating red mercuric oxide. He found that mice lived longer breathing it than with air in a sealed bottle. He also found it made a glowing splinter burst into flame. He published his method and findings. Two months later, visiting Paris, he described his discovery to world's leading chemist, Antoine Laurent Lavoisier and other scientists. After 9 years of studying its chemistry, Lavoisier was still unable to understand the basic nature of this new gas he had labeled principe oxigen in 1777. Eight years before Priestley's discovery, in 1766, Henry Cavendish in London, a very wealthy but reclusive skilled scientist, had written that when he slowly burned "inflammable air" (later named hydrogen), pure water was deposited on the walls of his glass vessel. No one understood or believed his report because everyone had believed since antiquity that water was an element that could not be generated. In 1783, the Royal Society in London asked Cavendish to reanalyze and interpret his 17- year-old curious discovery of making water. He said he had repeated the experiment using Priestley's dephlogisticated air but still had no idea of what it meant in terms of the universally accepted phlogiston theory of life and fire. When news of the Royal Society's revisiting Cavendish's old rejected paper reached Lavoisier, he decided to repeat it himself, in the presence of several other scientists. On June 24th, 1783, he confirmed that Cavendish had generated water! He suddenly realized his (and everyone's) error about water. He announced that oxygen and inflammable air are elements and water is a compound made of them. He then named inflammable air hydrogen. This permitted him to totally revise chemistry and demolish the phlogiston theory, science's worst blunder that had lasted almost a century. I submit that Cavendish has not been sufficiently credited by science historians as having provided the key to modern chemistry.(100)

Ibn al Nafis 1250 Michael Servetus 1553 Michael Sendivogius 1604 John Mayow 1668 Henry Cavendish 1766 Carl W. Scheele 1771 Joseph Priestley 1774 Antoine Lavoisier 1783

CS 73 (100)

Pharmacogenetic Determinants of Interindividual Variability in Methadone Metabolism and Disposition: The Role of Cytochrome P4502B6 (CYP2B6)

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Background: There is considerable unexplained interindividual variability in methadone clearance. Methadone N-demethylation to EDDP in vitro and in vivo, and methadone clinical clearance, are mediated mainly by hepatic CYP2B6. CYP2B6 has numerous genetic variants. Influence of CYP2B6 genetic variability on methadone metabolism and clearance is unknown. This translational investigation evaluated methadone metabolism in vitro by various human CYP2B6 allelic variants. Following identification that CYP2B6.6, the protein variant encoded by the CYP2B6*6 polymorphism, is catalytically deficient compared with wild-type CYP2B6.1, a clinical pharmacokinetic evaluation was performed to test the hypothesis that CYP2B6*6 carriers have altered methadone metabolism and clearance in vivo.

Methods: Common human CYP2B6 allelic variants (CYP2B6.1, 2B6.4, 2B6.5, and 2B6.6) were co-expressed with P450 reductase and cytochrome b5. Individual methadone enantiomers metabolism to EDDP was quantified by LC-MS-MS. Two IRB-approved clinical protocols in healthy volunteers then followed, after obtaining informed consent. Subjects (n=486) were genotyped for 516G>T, 785A>G, 983T>C, 1459C>T CYP2B6 polymorphisms, and haplotypes identified. Three CYP2B6 genotype cohorts were recruited: CYP2B6*1/*1 (n=20), CYP2B6*1/*6 (n=20), and CYP2B6*6/*6 (n=12). Subjects received 6 mg IV and 11 mg oral d5-methadone. Plasma and urine methadone and EDDP concentrations were determined by stereoselective LC-MS-MS.

Results: In vitro EDDP formation from therapeutic (0.25-1 μM) R- and S-methadone was CYP2B6.4>CYP2B6.1>CYP2B6.5>CYP2B6.6. In vitro intrinsic clearance for CYP2B6.6 was only about one-third that for wild-type CYP2B6.1; that for CYP2B6.4 was almost 2-fold greater than CYP2B6.1. Stereoselective metabolism of methadone metabolism by CYP2B6.1 (S>R) was maintained with all CYP2B6 variants. In the clinical study, in CYP2B*1/*1, *1/*6, and *6/*6 genotypes, IV R-methadone mean area under the plasma curve (AUC) was 428, 395, 718 ng-hr/ml, clearance (CL) was 6.8, 7.5, 4.6 L/hr, and EDDP/methadone AUC ratio was 0.085, 0.078, 0.068. For IV S-methadone, AUC was 447, 476, 911 ng-hr/ml, CL was 6.2, 6.6, 3.6 L/hr, and EDDP/methadone AUC ratio was 0.120, 0.099, 0.075. Oral R-methadone AUC was 563, 586, 986 ng-hr/ml, apparent oral clearance (CL/F) was 11.9, 10.4, 6.4 L/hr, and EDDP/methadone AUC ratio was 0.075, 0.068, 0.051. For oral S-methadone AUC was 599, 711, 1392 ng-hr/ml, CL/F was 11.5, 10.2, 5.1 L/hr, and EDDP/methadone AUC ratio was 0.11, 0.096, 0.055. Urine EDDP formation clearance from IV methadone in CYP2B*1/*1, *1/*6, and *6/*6 genotypes averaged 0.26, 0.21, 0.15 ml/kg/min for R-EDDP; and 0.43, 0.30, 0.20 ml/kg/min for S-EDDP.

Conclusion: This predicted that clinically, CYP2B6*6 allele carriers would have impaired methadone elimination. This was confirmed. Methadone metabolism and clearance were significantly diminished in CYP2B6*6 allele carriers. There was a gene-dose effect, with CYP2B6*6 homozygotes having the lowest methadone metabolism and clearance. CYP2B6 pharmacogenetics clearly influences methadone disposition and explains, in part, interindividual variability in methadone disposition.

CS 74 (114)

Propofol Infusion Impairs Complex 1 Activity in Human Muscle

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Introduction: Prolonged propofol infusions have been associated with metabolic acidosis, rhabdomyolysis, dysrhythmias and cardiovascular collapse, a constellation that has been termed propofol infusion syndrome (PRIS).(1) Acid base perturbations have been described during propofol anesthetics and attributed to subclinical PRIS, although more definitive evidence is lacking.(2) Previous investigations suggest that PRIS is due to impaired mitochondrial metabolism due to failure of electron transport at Complex 2.(3) We theorized that occult evidence of PRIS might be detected in children undergoing prolonged anesthesia with propofol, and that measuring respiratory chain enzyme (RC) activity might provide better insight into its causative mechanisms.

Methods: We studied 71 children with scoliosis but without mitochondrial disease undergoing posterior spinal fusion under propofol-remifentanil anesthesia (group P) and 11 controls receiving dexmedetomidine-remifentanil anesthesia (group C). Propofol and 4-OH propofol levels, blood gases, lactate, triglycerides and acylcarnitine profiles were measured hourly during the anesthetic and at 24 hours. A paraspinous muscle sample was obtained at the end of the operation to measure RC enzymes, and propofol and 4-OH propofol levels in muscle tissue. Additionally, isolated banked normal muscle tissue was incubated in vitro with varying concentrations of propofol and 4-OH propofol; drug levels and RC enzymes were assayed.

Results: The mean weight of subjects was 48.5±3.5kg. Group P subjects received an average of 21.8±2.6 mg/kg of propofol. Acid-base status was not different between groups, but 11 patients in group P had lactate levels over 3mmol/dL occurring between 3-5 hours of anesthetic time. Acylcarnitine profiles showed only non-specific mild elevations. Propofol and 4-OH propofol levels in blood averaged 3.16mcg/mL and 16.58ng/mL, respectively, but there was a pronounced non-normal distribution with significant outliers of levels up to 8-fold higher than the mode or median values. RC enzyme assays in study subjects showed mild depression of Complex 1 in group P, and no abnormalities in in Complexes 2-4, while controls showed no diminution from normal values.

When propofol and 4-OH propofol were incubated in incremental concentrations with 10 samples of banked human muscle, levels in muscle were between 2 and 40 times higher than that measured in blood (average 31.22ng/g vs 2.77ng/l). RC activity was depressed from 45-50 % in Complex 1, and unchanged in Complexes 2 - 4.

Discussion: Propofol inhibits RC enzyme activity primarily at Complex 1, not in Complex 2 as previously reported. We also believe that reported elevations in C3 acylcarnitine levels may be due to non-specific alterations in fatty acid metabolism and are not pathognomonic of PRIS. Although RC changes in muscle under our clinical conditions were modest, concentrations of propofol and 4-OH propofol in muscle are considerably higher than those measured in blood. These levels are achievable in some patients during clinically relevant propofol infusion rates. Furthermore, there are wide discrepancies between patients in the levels seen with similar infusion rates, suggesting that pharmacogenomic factors may be important in the pathogenesis of this disorder.

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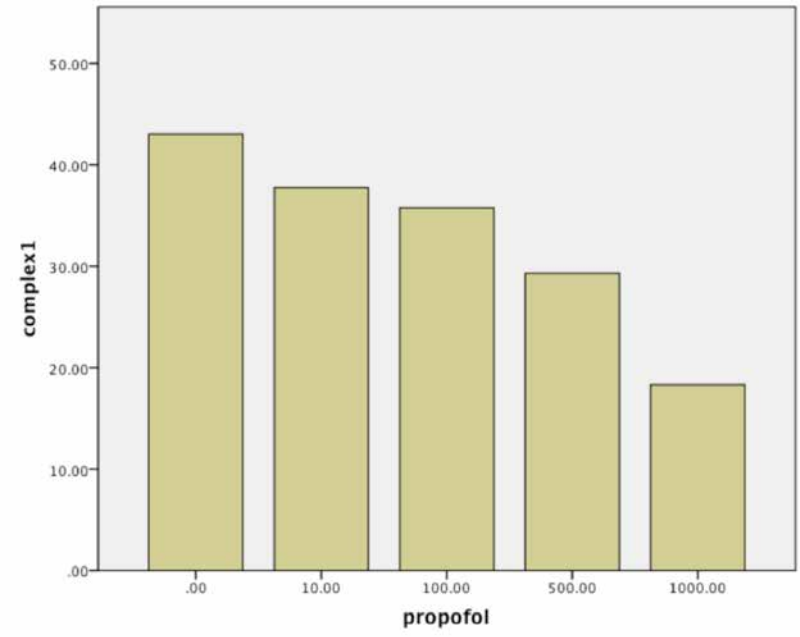

EDU 41 (33)

Flipped Classroom Preferred Over Traditional Classroom in Resident Education

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Introduction: It has been suggested that medical education should use limited face-to-face time on student-centered active learning methodologies that boost engagement and retention (1). In the "flipped classroom" model, the learner asynchronously acquires basic knowledge about a subject through short (≈15 minute) on-line videos and comes to class prepared to engage with their teacher and collaborate with their peers in active learning exercises (e.g. problems). We compared a flipped classroom approach with a traditional lecture-based classroom approach in anesthesiology residents preparing for the ABA Basic Examination.

Methods: Following IRB approval, PGY2 residents preparing for the ABA Basic Examination at two institutions (I1,I2) consented to participate. Subject material was taken from two sections (pharmacology, physics) of the ABA Basic Content Outline. Forty multiple-choice questions were developed and subjected to a rigorous content review by six experts in anesthesiology education for a pre- and post-test in each subject area. The same questions in mixed order were used for the pre- and post-test. Each subject area was taught in four classroom sessions over one month with four faculty members, two from each institution, developing and facilitating all teaching sessions. I1 taught pharmacology using flipped classroom while I2 used traditional PowerPoint lectures and the next month I1 taught physics with traditional PowerPoint lectures while I2 used flipped classroom. Residents were requested to view the 15-20 minute on-line videos before flipped classroom and to do what standard preparation they would usually do before a traditional classroom. Residents completed a pre-test at the beginning of each month and a post-test and survey questions about their preparation for classroom sessions at the end of each month. Resident and faculty surveys were used to determine preferred teaching and learning method.

Results: Demographic data (age, gender, mean USMLE scores) was similar between PGY2 residents (I1 n=14, I2 n=12) at both institutions. There was no difference in preparation time or session attendance between I1 and I2. Mean percent improvement from pre- to post-test was greater for flipped classroom than traditional classroom but did not reach statistical significance (table). A post hoc power analysis demonstrated that the n should be equal to or greater than 86 to give enough power to determine a statistical significance at the 0.05 level. Residents preferred the flipped classroom (table) and faculty "Strongly Agreed" that the flipped class teaching method engaged the learners better (4/4), provided them with more professional satisfaction (4/4), and answered yes (4/4) that they will use the flipped classroom in the future.

Discussion: There is empirical support for active learning methodology but limited data to define the benefits of the flipped classroom versus traditional classroom (2). This study demonstrated improved knowledge acquisition for both traditional and flipped classroom, and a preference by both teachers and learners for the flipped classroom.

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	Traditional	Flipped	p-value
Knowledge acquisition, % (SE)	13.4 (1.8)	16.3 (1.8)	0.28*
Preferred style (post-survey), % agree or strongly agree	5/26 (19%)	22/26 (85%)	0.008**

*p-value from a repeated measures model adjusted for study site
**Fisher exact test

EDU 42 (89)

Performance on USMLE Step 1 but Not Self-Directedness or Personality Preferences Correlate with Future Performance on In-Training Examinations During Anesthesiology Graduate Medical Education

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Background: Objective predictors of future performance in residency training have been elusive.

Objective: The research objective of this study was to explore potential predictors of future performance on the annual American Board of Anesthesiology (ABA) In-Training Examinations (ITEs) during graduate medical education in anesthesiology.

Methods: All residents in the University of Kentucky Department of Anesthesiology were asked to participate in this study following IRB approval. At the beginning of the PGY-1 year, residents were administered the Self-Directed Learning Readiness Scale (SDLRS-A) and the Myers-Briggs Type Inventory (MBTI) which were both scored electronically (www.lpasdlrs.com and www.paladinexec.com, respectively). With the use of R statistical software, SDLRS-A scores and MBTI preferences were assessed for correlation with accomplishments on the USMLE Step 1 and Step 2 CK, and SDLRS-A, MBTI preferences, and USMLE Step 1 and Step 2 assessed for correlation with annual ITE performance throughout residency training.

Results: Of 108 residents, 105 (97%) elected to participate. Data was evaluated from residents with complete data sets only (n=76); any resident 's data recorded without a USMLE Step 1 score, SDLRS score, Myers-Briggs personality preference, or at least one value for ASA/ITE score was excluded. In this cohort of anesthesiology residents, SDLRS scores were shown to have a minimal inverse correlation to future ITE accomplishments; the effect was small and not statistically significant (p=0.651). Of the Myers-Briggs personality preferences, only the MBTI extroversion/introversion binary indicator correlated with improvement throughout residency. Although introverted residents begin with lower ITE scores after the PGY-1 year, they improved more quickly over the next three years than their extroverted counterparts. Furthermore, it was also determined that the higher a resident's USMLE Step 1 score in medical school, the better the resident performed on future ITEs in residency (p=0.008); any relationship with USMLE Step 2 CK scores was proven not to be statistically significant.

Significance: MBTI personality preferences and measures of self-directedness did not correlate with future performance. However, residents with higher USMLE Step 1 scores in medical school performed better on In-Training Examinations (ITEs) during their graduate medical education in anesthesiology. Similar relationships have previously been documented in anesthesiology and in other specialties. This correlation between USMLE Step 1 scores could potentially be used to predict future performances on ABA ITEs, and to identify residents who might benefit from supplemental educational opportunities during residency.

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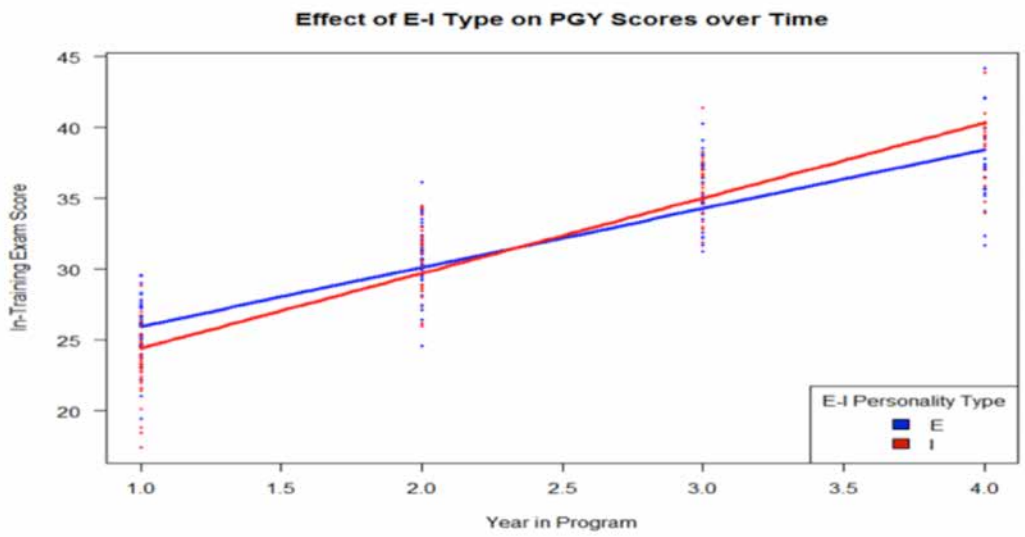
Figure 1:



O 16 (65)

Tablet Based Interactive Distraction (TBID) Versus Oral Midazolam to Minimize Perioperative Anxiety in Pediatric Patients: A Non-Inferiority Randomized Trial

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Introduction: Perioperative anxiety is a common and undesirable outcome in pediatric patients[1,2], associated with complications including worse postoperative pain,[3] and long lasting changes in sleep.[4] Benzodiazepines are commonly administered for perioperative anxiolysis, but may lead to prolonged sedation and paradoxical effects like agitation.[5,6] The use of interactive tools to minimize perioperative anxiety in children seems promising but it is vastly understudied.[7-9] Multimedia patient interaction has been shown to be beneficial for depression and anxiety disorders,[10,11] and pain perception in pediatric patients.[12,13] The main objective of this study was to compare the effects of Tablet Based Interactive Distraction (TBID) to oral midazolam on perioperative anxiety. We hypothesized that TBID was not inferior to midazolam for perioperative anxiolysis.

Methods: The investigation was a prospective and randomized study. Children ages 1-11 years, ASA-PS 1-2, presenting for first time outpatient anesthetic were recruited and randomized to oral midazolam (0.5 mg/kg orally; max 20 mg) or TBID. The primary outcome was the change in anxiety level from the baseline to parental separation and anesthesia induction measured by the Modified Yale Preoperative Anxiety Scale (mYPAS). Secondary outcomes included parental perception of child's anxiety, postoperative anesthesia emergence delirium (PAED), time to PACU discharge, and post-hospitalization behavior.

Results: 108 subjects participated in the study. Demographic and procedure characteristics were not distinct between the study groups. The mean difference (95% CI) in the increase of anxiety at parental separation between the TBID group and the midazolam group was -9 (-2.6 to - 16.4), P=0.006, where the lower limit of the confidence interval overlapped the non-inferiority boundary. In contrast, TBID was demonstrated superior to midazolam in regards to anxiety at parental separation (one sided, P =0.003). The mean difference (95%CI) in the increase of anxiety at induction between TBID and midazolam group was - 6 (1.1 to -18), where the lower limit of the confidence interval overlaps the non-inferiority boundary. Superiority of the TBID group compared to midazolam could not be established for anxiety at induction (one sided P =0.04).

The median (IQR) time to PACU discharge was 111 (75 to 197) minutes in the midazolam group and 87 (55 to 137) minutes in the TBID group, P=0.03 (see figure 1). Emergence delirium was not different in the midazolam group, 6 out of 51(12%), compared to 4 out 57 (7%) in the TBID group, P=0.51, at the threshold defining emergence delirium. However, emergence delirium scores were higher in the midazolam group relative to the TBID group. Postoperative behavior scores were not different between the groups. 43 out of 53 (81%) parents of children in the TBID group were very satisfied with their child's separation compared to 22 out of 37 (59%) in the midazolam group, P= 0.02.

Conclusions: TBID reduces both perioperative anxiety and time to PACU discharge, and increases parental satisfaction when compared to midazolam in pediatric patients undergoing ambulatory surgery.

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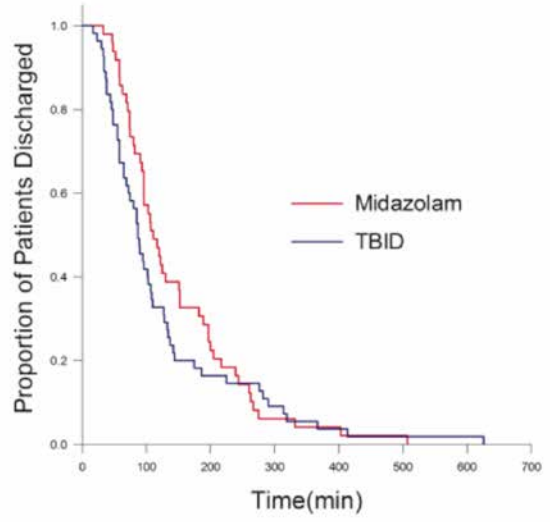
Figure 3. Kaplan-Meier plot of proportion of subjects that were discharged from PACU. TBID vs, midazolam.

The median (IQR) time to PACU discharge 111 (75 to 197) minutes in the midazolam group compared to 87 (55 to 137) minutes in the TBID group, P=0.03.



O 17 (90)

Utility of Electronic Management Tool in the ICU for Early Recognition and Management of Sepsis

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Introduction: Sepsis is common in medical and surgical ICU's with mortality rates of up to 50%. Implementation of the Surviving Sepsis Campaign's (SSC) 6-hour resuscitation bundle, which includes early recognition, antibiotic administration and resuscitation has reduced mortality rates in these patients[1,2], yet compliance rates remain low.

Hypothesis: An electronic sepsis management tool capable of sepsis detection, real time alerting, facilitated assessment, guideline-based management, and ongoing reassessment housed within the electronic medical record (EMR) will improve the time to completion of all appropriate SSC 6-hour resuscitation bundle elements.

Methods: MICU and SICU patients at a University Medical Center, with sepsis confirmed at admission or in response to an electronic alert generated when a patient met SIRS criteria, were randomized to usual care or to the sepsis management tool. We collected baseline characteristics, clinical data on sepsis management, and patient outcomes in a blinded fashion from the EMR. Patients were followed for 28 days or until hospital discharge. Tool usage data was also collected during this time. The primary endpoint was time from enrollment until completion of all indicated elements of the SSC 6-hour resuscitation bundle. Secondary end points were to evaluate the different usage of the tool in MICU and SICU.

Results: We enrolled 407 ICU patients with sepsis and randomized 189 patients to the control group and 218 to the sepsis tool group. Both groups had similar demographics, and pre-enrollment fluid and vasopressor management. Time until completion of all appropriate SSC 6-Hour resuscitation bundle elements was similar between the control and intervention group (median time 5.2 hrs. vs. 4.9 hrs. p=0.159), and so was the time until completion of each individual bundle element and the number of elements completed within 6 hours. ICU mortality was also similar between the control and intervention group (15.9% vs. 13.8%, p=0.577). In the patients randomized to the sepsis tool, providers used the tool in 126 patients (58%) and entered orders using the tool in in 63 patients (29%) with a mean of 4.1orders per usage. Significant population differences between septic patients in the MICU and the SICU were highlighted in the study. In the MICU 18% patients came from an outside hospital and 71.2% of the SICU patients were post-operative with sepsis at admission. Source of sepsis was pulmonary in 29.6% of MICU patients vs. 11.5% of SICU patients, while an abdominal source of sepsis occurred in only 13% of MICU patients but 54.1% of SICU patients. ICU mortality in septic MICU patients was 16.5% vs. 4.5% in the SICU patients.

Conclusion: In critically ill septic patients, the availability of a sepsis management tool in the EMR did not change the time to completion of all appropriate SSC 6-our resuscitation bundle elements or patient outcomes including ICU mortality. Impact of the tool was limited by low utilization, which may be reflective of the fact that the 6-hour SSC period occurred when most patients were still in the Emergency Department or Operating Room, and not in the ICU, where our intervention was focused. The tool may be more effective if were initiated in these two environments instead.

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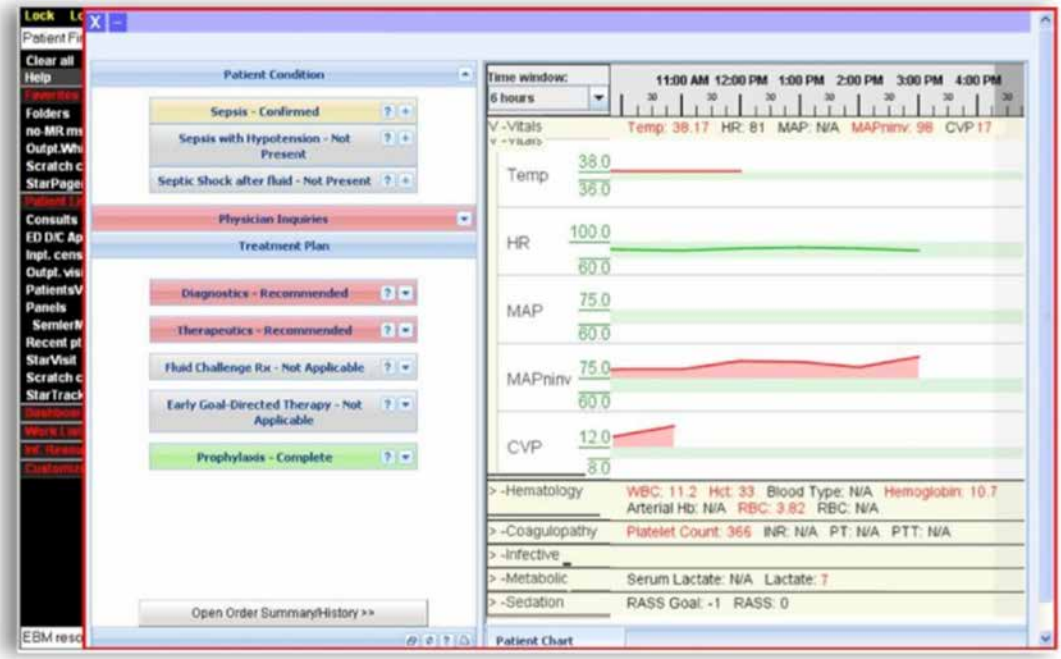

O 18 (34)

A Comparative Provider Workload Analysis for Femoral and Adductor Canal Catheters Following Knee Arthroplasty

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Background: Compared to femoral nerve catheters (FNC), adductor canal catheters (ACC) better preserve quadriceps strength and may promote greater early postoperative ambulation while providing clinically similar levels of analgesia following total knee arthroplasty (TKA). However, it is not yet known if this change in regional analgesia technique also affects system-based practice in terms of provider workload.

Methods: With IRB approval, we conducted this follow-up analysis of a database created for a previously-published study of consecutive patients who underwent primary TKA with either FNC or ACC. During the 1 year study period, only the regional analgesic technique differed; all other aspects of the clinical pathway (surgical technique, physical therapy, nursing care, multimodal analgesic regimen) remained the same. Our primary outcome was number of provider interventions recorded per patient during the postoperative perineural local anesthetic infusion. Secondary outcomes included duration of infusion (days), ambulation distance (meters) on postoperative day (POD) 1, opioid consumption (mg morphine equivalents), and hospital length of stay (days). A two-sided $p<0.05$ was considered statistically significant for the primary outcome.

Results: The database included 45 cases performed by a single orthopedic surgeon, 22 receiving FNC and 23 receiving ACC (Table 1). The ACC group required a median (10th-90th percentiles) of 0.0 (0.0-2.6) interventions while the FNC group required 1.0 (0.3-3.0) interventions ($p<0.001$). The types of interventions required are shown in Table 1. Patients in the ACC group retained their catheters for 2.0 (1.4-2.0) days vs. 1.5 (1.0-2.7) days for the FNC group ($p=0.016$). The ACC group ambulated a greater distance [mean (SD)] compared to the FNC group on POD 1 [24.5 (21.7) meters vs. 11.9 (14.6) meters, respectively; $p=0.030$) and POD 2 [44.9 (26.3) meters vs. 22.0 (22.2) meters, respectively; $p=0.003$). There was no difference in other outcomes.

Conclusion: Continuous adductor canal blocks require fewer provider interventions per patient despite a longer infusion period when compared to continuous femoral nerve blocks in the postoperative period. Prior studies have described the concept of a minimal clinically important difference (MCID), which is defined as "the smallest difference in a particular domain of interest leading to a change in treatment strategy." The results of the present study and their potential system-based implications on MCID may favor ACC over FNC for certain acute pain management practice models. Confirmation of these findings through prospective study is warranted.

Table 1: Morphometric data and procedural information

	Femoral (n=22)	Adductor Canal (n=23)
Age (yrs)	66 (52-86)	64 (55-71)
Female/Male (#)	2/20	3/20
ASA Physical Status	3 (2-3)	3 (2-3)
Height (cm)	176 (166-183)	175 (163-194)
Weight (kg)	103 (72-130)	97 (79-154)
BMI (kg/m^2)	32 (26-40)	32 (24-46)
Block Duration (min)	15 (10-20)	15 (10-20)
Length of Stay (days)	3 (2-7)	3 (2-7)

Values are reported as median (10^{th}-90^{th} percentiles) or number of subjects, as indicated; ASA = American Society of Anesthesiologists

Types of interventions required

	Femoral (n=22)	Adductor Canal (n=23)
Dressing change due to leakage	1	0
Pump replacement	1	0
Bedside evaluation due to catheter dislodgment	1	0
Catheter clamped due to weakness	3	0
Catheter removed due to weakness	1	0
Catheter clamped prior to physical therapy	20	5
Catheter unclamped due to pain	5	0
Catheter clamped at patient's request	0	2
Bolus administered via catheter	0	1
Total	**32**	**10**

O 19 (35)

Effect of Pre-operative ACE Inhibitor and ARB Use on Hemodynamic Variables in Pediatric Patients Undergoing Cardiopulmonary Bypass

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Background: Angiotensin–converting enzyme Inhibitors (ACEIs) are being utilized with increased frequency in the pediatric population.[1,2] It has been observed that children undergoing cardiac surgery whom are on pre-operative ACEIs or angiotensin II receptor blockers (ARBs) experience a greater degree of hypotension following the induction of anesthesia and also in the immediate post cardiopulmonary bypass (CPB) period.[3] The aim of this study was to examine intraoperative hemodynamics and vasopressor use in pediatric patients receiving preoperative ACEI/ARB therapy and undergoing cardiac surgery.

Methods: After obtaining Institutional Review Board approval, we carried out a retrospective cohort study of patients less than 18 years of age who underwent cardiac surgery requiring CPB between March 1, 2010, and April 1, 2011. This was a single institution study and demographic and clinical variables were collected. The primary outcome was vasoactive infusion score (VIS), a previously validated scale for assigning a composite numeric value to represent the cumulative magnitude of vasoactive support.[4] Secondary outcomes included Inotropic Score (IS) and a threshold assessment of hypotension. Cohorts were compared using Fisher's exact test for categorical variables and the Mann-Whitney-Wilcoxon test for continuous variables. Mixed effects linear modeling was used to evaluate the repeated measures nature of VIS and control for covariates. Results: There was no statistically significant difference between the ACEI/ARB group and the control group with respect to occurrence of hypotension during induction of anesthesia (P=1) or at any time point after CPB. In addition, the VIS between the two groups at 0, 30, 60, and 90 minutes following CPB did not differ significantly. Despite the absence of a statistically significant difference in VIS between the ACEI/ARB group and the control group those patients on ACEI/ARB tended to have a higher VIS than the control group and this difference became more pronounced as more time passed after CPB (Figure 1). Furthermore, patients receiving preoperative ACEI/ARB required a higher dose of epinephrine, vasopressin and phenylephrine and a lower dose of milrinone at 30, 60, and 90 minutes following termination of CPB when compared to the control group. However, none of these differences reached statistical significance.

Conclusion: Pre-operative ACEI and ARB use in pediatric patients undergoing cardiac surgery did not increase the incidence of hypotension following induction of anesthesia and did not increase vasoconstrictor requirements upon weaning from CPB. However, we observed that ACEI/ARB patients had higher VIS scores after CPB, mostly due to higher mean doses of vasoconstrictors (phenylephrine, vasopressin) and lower mean doses of milrinone, but these finding did not reach statistical significance on univariate analysis or after controlling for covariates in a mixed effects model of VIS as a repeated measures outcome. Additional prospective studies are needed.

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O 20 (44)

Impaired Red Blood Cell Deformability After Transfusion of Stored Allogeneic Blood but Not Autologous Salvaged Blood in Cardiac Surgery Patients

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Background: Both cardiopulmonary bypass (CPB)[1] and red blood cell (RBC) storage[2] are associated with detrimental changes in RBC structure and function that may adversely affect tissue oxygen delivery.[3] We tested the hypothesis that in cardiac surgery patients, RBC deformability and aggregation are minimally affected by CPB with autologous salvaged blood alone, but are negatively affected by the addition of stored allogeneic blood.

Methods: In this prospective cohort study, 32 patients undergoing cardiac surgery with CPB were divided into 3 groups by transfusion status: autologous salvaged RBCs alone (Auto; n=12), autologous salvaged RBCs + minimal (<5 units) stored allogeneic RBCs (Auto+Allo min; n=10), and autologous salvaged RBCs + moderate (≥5 units) stored allogeneic RBCs (Auto+Allo mod; n=10). Ektacytometry was used to measure RBC elongation index (deformability) and critical shear stress (aggregation) before, during, and for 3 days after surgery.

Results: Changes in RBC deformability and aggregation are shown in Figures 1 and 2, respectively. In the Auto group, RBC elongation index did not change significantly from the preoperative baseline. In the Auto+Allo min group, mean elongation index decreased from 32.31 ± 0.02 (baseline) to 30.47 ± 0.02 (nadir on postoperative day 1) (P = 0.003, representing a 6% change). In the Auto+Allo mod group, mean elongation index decreased from 32.7 ± 0.02 (baseline) to 28.14 ± 0.01 (nadir on postoperative day 1) (P = 0.0001, representing a 14% change). Deformability then dose-dependently recovered toward baseline over the first 3 postoperative days. Changes in aggregation were unrelated to transfusion (no difference between groups). For the 3 groups combined, mean critical shear stress decreased from 359 ± 174 mPa to 170 ± 141 mPa (P = 0.01, representing a 54% change), with the nadir at the end of surgery, and returned to baseline by postoperative day 1.

Conclusions: In cardiac surgery patients, transfusion with stored allogeneic RBCs, but not autologous salvaged RBCs, is associated with a decrease in RBC cell membrane deformability that is dose-dependent and may persist beyond 3 postoperative days. There were no transfusion-related adverse effects on aggregation. These findings suggest that autologous salvaged RBCs may be of higher quality than stored RBCs, since the latter are subject to the so-called "storage lesions".

Figure 1

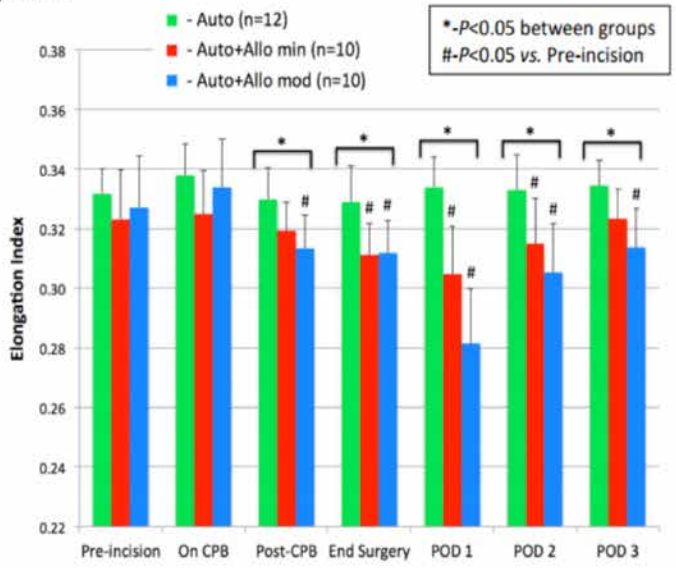
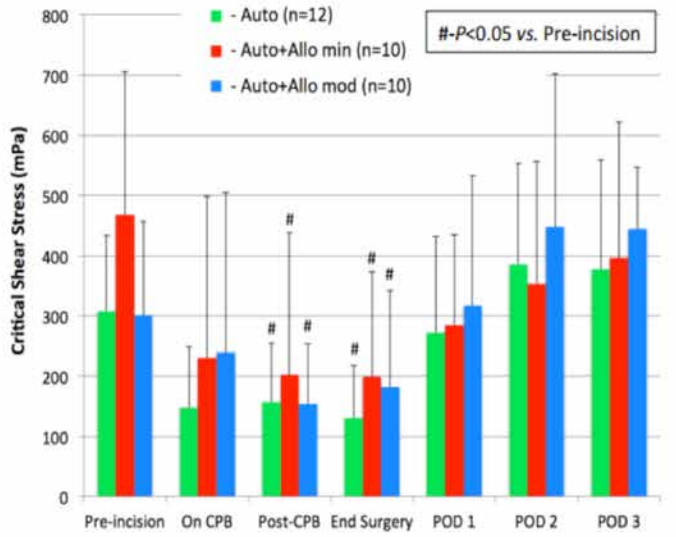


Figure 2



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O 21 (57)

Establishment of Objective Criteria for Operating Room Exit is Associated with Improved Early Postoperative Outcome in Pediatric Cardiac Surgery

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Introduction: Children undergoing surgery for correction of congenital heart defects sometimes experience complications requiring urgent intervention within the early postoperative period[1]. These complications are often associated with significant morbidity, mortality and resource utilization. In an attempt to minimize the need for urgent intervention within the first 12 postoperative hours, we developed a set of clinical criteria which must be met prior to transport of the patient from the operating room (OR) to the intensive care unit (ICU). We then implemented these criteria into practice, and compared the rates of urgent intervention with those observed before implementation of the criteria.

Methods: Personnel in the Pediatric Cardiac Anesthesia Division of the Department of Anesthesiology met over several months in 2010 and developed consensus criteria which were thought to portend a stable early postoperative course, for all pediatric patients undergoing a surgical procedure involving cardiopulmonary bypass. These consisted of laboratory values (pH > 7.30, lactate < 10mM), inotropes (epinephrine < 0.05mcg/kg/min, dopamine < 10mcg/kg/min, vasopressin < 0.06U/kg/hr), near-infrared spectroscopy (within 20% of baseline), and bleeding rate (< 10ml/kg/hr). We phased in these criteria from January to April 2011, and then gathered outcome data from 2008 through June 2013. Implementation of the criteria consisted of the following practice change: After conclusion of surgery, if a patient did not meet all criteria, a conversation was held with the surgeon regarding how to intervene: surgically, medically (change in inotropes, transfusion), continued observation, or proceed to ICU. Primary outcome data included rates of operative mortality, and mediastinal exploration (ME) and ECMO placement while undergoing CPR (ECPR) within the first 12 postoperative hours. These rates were compared with those observed prior to January 2011. Results: From 2008 through June 2013, we observed 2255 subjects. There was no identifiable shift in patient acuity or disease severity during the study interval. Following implementation of the objective criteria, rates of ME and operative mortality significantly decreased relative to pre-implementation (7.38% to 3.16% for ME, p<0.001; 9.21% to 6.66% for mortality, p=0.031). Rate of ECPR showed a trend toward decrease (1.90% to 1.01%, p=0.096). There was no significant change in hospital length of stay following implementation (p=0.54). Using process control analysis, the urgent event rate showed a significant shift downward upon implementation of the criteria (see Figure). Further statistical analysis, include regression, will be included in the poster.

Conclusions: Establishment of objective criteria, which are expected to be met prior to OR exit, is associated with a decreased rate of urgent ME within the first 12 postoperative hours, and with improved operative mortality in the pediatric cardiac surgery population. Anesthesia practices which require physiological fitness prior to case conclusion can significantly improve outcomes.

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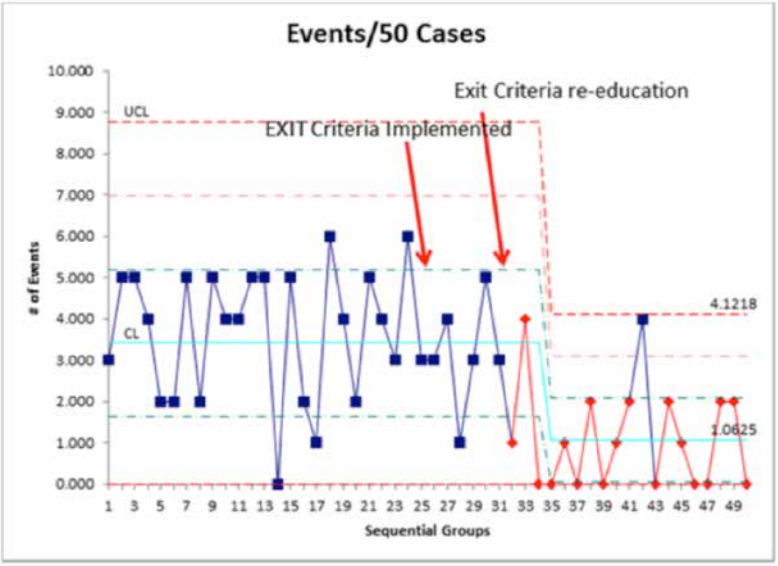

Figure: Control chart, showing urgent event rate per 50-case sequential groups, across the study interval. Broken lines indicate control limits for 1, 2, and 3 standard deviations, before and after implementation of the criteria.

O 22 (73)

A High-Fidelity Analysis of Perioperative QTc-Prolongation in General, Regional, and Local Anesthesia

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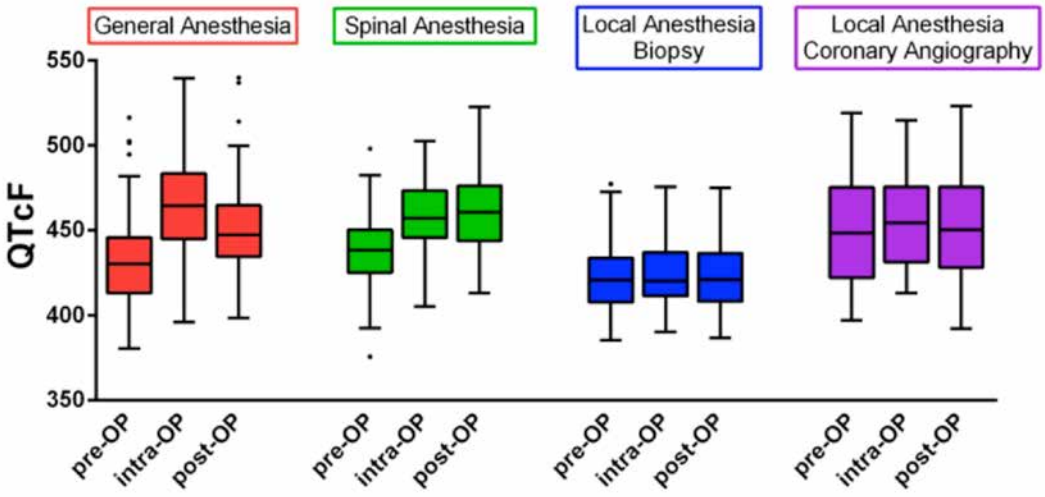
Introduction and General Purpose of the Study: QTc prolongation increases the risk of potentially life-threatening torsade de pointes. In a previous prospective study, we have shown that postoperative QTc-prolongation is very common in adult patients undergoing major non-cardiac surgery. However, it is unclear if QTc-prolongation is an isolated postoperative phenomenon or occurs regularly in the perioperative period, and if the type of anesthesia (general, regional and local) has an influence on its incidence. Here, in a prospective follow-up study, we compare QTc-duration among patients undergoing general, spinal and local anesthesia by high-fidelity beat-to-beat measurement of QT-interval duration.

Methods: Continuous 12-lead Holter ECGs were recorded in 300 evaluable patients who underwent general, or spinal anesthesia for orthopedic surgery, or local anesthesia for biopsy or diagnostic coronary angiography. We included patients who were ≥ 18 years old and scheduled for surgery or diagnostic coronary angiography. Patients were excluded who were scheduled for cardiothoracic surgery or surgery in prone position, as were those having active atrial fibrillation, a QRS > 120 ms, or a pacemaker. For the general and spinal anesthesia cohort, patients under 45 years old without cardiac risk factor were also excluded. After allocation, patients were excluded if the ECG monitor disconnected intraoperatively. ECG was recorded from 30 minutes preoperatively to up to 60 minutes postoperatively. Patients' characteristics, medical history, and home medication were noted. Time and type of anesthetic procedures (e.g.: airway management), dose, type and timing of drugs, as well as vital parameters were collected through the electronic anesthesia chart for the whole study period. Computer-derived QT calipers were manually reviewed and validated by 2 trained investigators blinded to QT duration and cohort. High interobserver agreement was achieved. QTc intervals were determined as recommended by the International Society for Computerized Electrocardiology, and were corrected by the Fredericia method. The intraoperative-to-preoperative QTc interval difference (ΔQTc) was compared between the 4 cohorts (ANOVA & post-hoc Bonferroni correction).

Results and Major Findings: In 300 patients, 57,665 minutes of ECG recordings were reviewed, and 7,563 minutes were excluded because no QT interval could be identified. QTc-interval increased markedly in the general anesthesia cohort (33 ms [22 to 46]; (median [IQR]) P<0.001), moderately in the spinal anesthesia cohort (22 [12 to 29] ms; P<0.001), and no significant increase was noted in either local anesthesia cohort (biopsy: 4 [-4 to 7] ms, coronary angiography: 6 [-5 to 16] ms; (P=0.6). Pre-, intra-, and postoperative QTc duration of each cohort is shown in Figure 1.

Conclusions: These results indicate that QTc-prolongation is not an isolated postoperative phenomenon and does occur regularly in the perioperative period. Its incidence is further influenced by the type of anesthesia.

Figure 1. Pre-, Intra-, and Postoperative QTc duration in General, Spinal, and Local Anesthesia



This figure shows Tukey boxplots of the QTc duration at the preoperative, intraoperative and postoperative period in each investigated cohort. The general anesthesia cohort (red) and the spinal anesthesia cohort developed QTc prolongation after the preoperative, baseline period. The local-anesthesia -for-biopsy cohort (blue) and the local-anesthesia -for-coronary-angiography cohort did not develop QTc prolongation during the study period. QTcF indicates QT interval duration corrected for heart rate by the Fredericia method; pre-OP, preoperative period; intra-OP, intraoperative period; post-OP, postoperative period.

O 23 (82)

Real-Time Forecasting of Pediatric Intensive Care Unit Length of Stay Using Computerized Provider Orders

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Objective: To develop a model to produce real-time, updated forecasts of patients' intensive care unit length of stay using naturally generated provider orders. The model was designed to be integrated within a computerized decision support system to improve patient flow management.

Methods: This was a retrospective cohort study of a twenty-six bed pediatric intensive care unit within an urban, academic children's hospital using a computerized order entry system. The analysis included a total of 2,178 consecutive pediatric intensive care unit admissions during a 16-month time period.

Results and Major Findings: We obtained unit length of stay measurements, time-stamped provider orders, age, admission source, and readmission status. A joint discrete-time logistic regression model was developed to produce probabilistic length of stay forecasts from continuously updated provider orders. Accuracy was assessed by comparing forecasted expected discharge time with observed discharge time, rank probability scoring, and calibration curves. Cross-validation procedures were conducted. The distribution of length of stay was heavily right-skewed with a mean of 3.5 days (95% confidence interval 0.3–19.1). Provider orders were predictive of length of stay in real-time accurately forecasting discharge within a 12-hr window: 46% for patients within 1 day of discharge, 34% for patients within 2 days of discharge, and 27% for patients within 3 days of discharge. The forecast model incorporating predictive orders demonstrated significant improvements in accuracy compared with forecasts based solely on empirical and temporal information. Seventeen predictive orders were found, grouped by medication, ventilation, laboratory, diet, activity, foreign body, and extracorporeal membrane oxygenation.

Conclusions: Provider orders reflect dynamic changes in patients' conditions, making them useful for real-time length of stay prediction and patient flow management. Patients' length of stay represent a major source of variability in intensive care unit resource utilization and if accurately predicted and communicated, may lead to proactive bed management with more efficient patient flow.

O 24 (88)

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

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Introduction: Delirium is an acute state of brain dysfunction that occurs in up to 80% of critically ill adults on mechanical ventilation, associated with significantly worse outcomes such as long-term cognitive impairment and death. Advances in delirium research in children lag behind that in adults due to lack of valid and developmentally appropriate delirium monitoring instruments. Thus the true prevalence and significance of delirium in this fragile population remains unknown. The Pediatric Confusion Assessment Method for the Intensive Care Unit (pCAM-ICU) was recently validated against formal neuropsychiatric assessments (specificity 99%; sensitivity 83%) to diagnose delirium in critically ill children over 5 years of age, adapted from the most widely used adult delirium tool called the CAM-ICU.(1) These tools are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for delirium diagnosis including: acute change or fluctuation in mental status (Feature 1), inattention (Feature 2), altered level of consciousness (Feature 3) and disorganized thinking (Feature 4). Delirium is present when patients demonstrate both features 1 and 2, and either feature 3 or 4. Children less than 5 years of age, however, pose challenges for delirium diagnosis due to vast changes in their cognitive and developmental skills from infancy to early childhood. The objective of this study was to create and validate a delirium instrument for critically ill infants and preschool-aged children, using standardized, developmentally appropriate measurements.

Methods: An interdisciplinary team comprised of pediatric anesthesiology/critical care, psychology, neurology, developmental pediatrics, and psychiatry adapted the pCAM-ICU to create the PreSchool Confusion Assessment Method for the ICU (psCAM-ICU). The psCAM-ICU is founded on the four cardinal features of delirium and adjusted using valid neurocognitive and developmental assessments for infants and toddlers. The prospective validation study of the psCAM-ICU was then conducted in critically ill patients aged 6 months to 5 years admitted to the PICU of a tertiary medical center. Patients with hearing/visual impairments, non-English speaking, moribund, or surrogate refusal of consent, were excluded. Enrolled patients were independently assessed daily by both the research team (RN or MD) using the psCAM-ICU and the reference standard, a psychiatrist using DSM-IV-TR criterion. Bootstrapping supported calculation of confidence intervals for proportions, accounting for multiple assessments on the same patient.

Results: A total of 219 blinded delirium assessments were completed on 127 enrolled patients with a median age of 21 months (IQR 11,36). Compared with the reference standard for delirium diagnosis, the psCAM-ICU demonstrated a sensitivity of 84% (95%CI 71%-92%) and specificity of 91% (95%CI 84%-95%). The psCAM-ICU performed similarly within the study cohort with a sensitivity and specificity of 85% (95%CI 71%-93%) and 91% (95%CI 82%-96%) among infants and toddlers, and 80% (95%CI 42%-96%) and 90% (95%CI 77%-96%) in children > 2 years, respectively. Among mechanically ventilated patients, the psCAM-ICU demonstrated a sensitivity of 85% (95%CI 54%-95%) and specificity of 100%. Delirium was detected in 36% of enrolled patients by the psCAM-ICU and in 29% of patients by the reference standard.

Conclusions: The psCAM-ICU is a highly valid instrument for delirium diagnosis in critically ill infants and young children. The psCAM-ICU may facilitate needed epidemiological studies on delirium among critically ill pediatric patients.

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O 25 (92)

Severity and Duration of Metabolic Acidosis After Deep Hypothermic Circulatory Arrest for Elective Thoracic Aortic Surgery

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Introduction and General Purpose of the Study: Repair of thoracic aortic aneurysms (TAA) involving the aortic arch requires temporary interruption of systemic blood flow. We hypothesize that metabolic acidosis (MA) is a consequence of deep hypothermic circulatory arrest (DHCA) and the severity of MA correlates with DHCA duration.

Methods: With IRB approval, 100 patients who underwent elective TAA repair with protocolized DHCA[1] between June 1, 2008 and December 31, 2009 were retrospectively studied. Patients with preoperative renal and hepatic dysfunction were excluded. Patients underwent retrograde cerebral perfusion (RCP) (n=91), RCP and antegrade CP (ACP) (n=8), and ACP only (n=1). Arterial blood gases were obtained every 30 minutes in the operating room and every 3 hours in the ICU until pH ≥ 7.35. Linear regression was used to determine the relationship between pH and DHCA parameters. Serum lactates were available in 39 patients. Values were reported as the mean±SD (range). Time to pH normalization was defined as the time to pH ≥ 7.35 after DHCA cessation.

Results and Major Findings: Eighty-nine patients (89%) had a minimum pH < 7.35, 62 (62%) had pH < 7.3. and 7 (7%) had pH < 7.2 after DHCA. Minimum pH averaged 7.28±0.06 (7.13-7.41). Average DHCA time (minutes) was 23.2±6.4 (13-46). Average DHCA temperature (˚C) was 17.9±2.6 (10.6-28.1). Average time to pH normalization (minutes) was 474±302 (0-1606). Maximum (max) chloride averaged 115±3 (106-124) meq/L. Max anion gap (AG) averaged 10.5±3.1 (2.6-19.8) meq/L. Max lactate averaged 7.5±4.2 (0.8-16.9) mmol/L. Minimum pH correlated with maximum lactate (r=-0.63, p<0.001). Time to pH normalization correlated with maximum AG (r=0.20, p=0.046). Minimum pH did not correlate with DHCA time (r=0.06, p=0.55), DHCA temperature (r=-0.15, p=0.14), max AG (r=-0.08, p=0.43), or max chloride (r=-0.09, p=0.37). Time to pH normalization did not correlate with max lactate (r=0.31, p=0.051), DHCA time (r=-0.02, p=0.84), DHCA temperature (r=0.16, p=0.11), or max chloride (r=0.14, p=0.16).

Conclusions: MA was common after DHCA and lasted up to 27 hours. The etiology and severity of MA after DHCA was primarily ischemia and reperfusion as indicated by increased AG and lactatemia, but the presence of hyperchloremia indicated a mixed MA. Preventing hyperchloremic acidosis could potentially reduce the severity of MA after DHCA. Lack of correlation between minimum pH and DHCA temperature or duration indicated that metabolic conditions during DHCA were optimized, or the range of DHCA durations encountered were too narrow to generate a relationship between pH and DHCA parameters.

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Table 1. DHCA and pH Parameters

	n	Mean	Range
Minimum pH	100	7.28±0.06	7.13-7.41
Minimum DHCA Temp	100	17.9±2.6 ° C	10.6-28.1
Time to pH normalization	100	474±302 minutes (7.9±5.0 hours)	0-1606 minutes (0-26.8 hours)
Maximum AG	100	10.5±3.1 meq/L	2.6-19.8 meq/L
Maximum Chloride	100	115±3 meq/L	106-124 meq/L
Maximum Lactate	39	7.5±4.2 mmol/L	0.8-16.9 mmol/L
Maximum AG (Lactate only)	39	10.8±2.9 meq/L	5.9-19.7 meq/L

O 26 (93)

Consequences of Sodium Bicarbonate Administration in Patients with Metabolic Acidosis After Deep Hypothermic Circulatory Arrest for Elective Thoracic Aortic Surgery

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Introduction and General Purpose of the Study: Management of metabolic acidosis (MA) after deep hypothermic circulatory arrest (DHCA) for thoracic aortic aneurysm (TAA) repair is not standardized. We hypothesize that the total dose of sodium bicarbonate (NaHCO3) administration is related to the severity of MA and may affect the duration of mechanical ventilator support, duration of vasoactive infusions, ICU length of stay (LOS), and hospital LOS.

Methods: With IRB approval, 100 patients were retrospectively studied who underwent elective TAA repair with protocolized DHCA between June 1, 2008 and December 31, 2009. Patients with preoperative renal and hepatic dysfunction were excluded. Patients underwent retrograde cerebral perfusion (RCP) (n=91), RCP and antegrade CP (ACP) (n=8), and ACP only (n=1). Arterial blood gases were obtained every 30 minutes in the operating room and every 3 hours in the ICU until pH ≥ 7.35. Linear regression was used to test for relationships between total NaHCO3 dose through postoperative day 2 and clinical variables. Serum lactates were available in 39 patients. Values were reported as the mean±SD (range). Time to pH normalization was defined as the time to pH ≥ 7.35 after DHCA cessation.

Results and Major Findings: Eighty-six patients (86%) received NaHCO3. NaHCO3 dose averaged 129±111 (0-535) meq per patient. Average minimum pH was 7.28±0.06 (7.13-7.41). Average time to pH normalization was 474±302 (0-1606) minutes. Average maximum (max) values for chloride was 115±3.62 (106-124) meq/L, anion gap (AG) was 10.5±3.08 (2.6-19.8) meq/L, lactate (n=39) was 7.5±4.2 (0.8-16.9) mmol/L, and sodium was 147±3.15 (138-155) meq/L. Total NaHCO3 dose correlated with minimum pH (r=-0.44, p<0.001), time to pH normalization (r=0.33, p=0.001), and max sodium (r=0.28, p=0.004). Total NaHCO3 dose did not correlate with max AG (r=0.10, p=0.30), max chloride (r=0.14, p=0.18), max lactate (r=0.31, p=0.051), ventilator days (r=-0.08, p=0.41), ICU LOS (r=-0.06, p=0.53), hospital LOS (r=-0.12, p=0.24), or duration of vasoactive infusions (r=0.11,p=0.28).

Conclusions: Routine administration of NaHCO3 was common for the treatment of MA after DHCA. The total dose of NaHCO3 was a function of the severity and duration of MA and contributed to postoperative hypernatremia. Absence of a significant relationship between the dose of NaHCO3 with clinical outcomes suggested that NaHCO3 may have attenuated the physiologic and clinical consequences of MA, or the severity of MA and its treatment with NaHCO3 did not affect clinical outcomes. Additional studies are necessary to distinguish between these two possible explanations.

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1. Perioperative Outcome in Adults Undergoing Elective Deep Hypothermic Circulatory Arrest with Retrograde Cerebral Perfusion in Proximal Aortic Arch Repair: Evaluation of Protocol-Based Care. 2006;20:3-7.

Table 1. pH Parameters and Sodium Bicarbonate Administration following DHCA

	n	Mean	Range
Minimum pH	100	7.28±0.06	7.13-7.41
Total Sodium Bicarbonate	100	129±112 meq	0-535.2 meq
Time to pH normalization	100	474±302 minutes	0-1606 minutes
Maximum AG	100	10.5±3.1 meq/L	2.6-19.8 meq/L
Maximum Lactate	39	7.5±4.2 mmol/L	0.8-16.9 mmol/L
Maximum Chloride	100	114.5±3.6 meq/L	106-124 meq/L
Maximum Sodium	100	146.5±3.2 meq/L	138-155 meq/L

O 27 (96)

Does High-Quality Post-Acute Care Prevent Hospital Readmissions?

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Introduction and Purpose: Readmissions after acute-care hospitalizations are a major health policy concern in the U.S. While one in five hospitalized Medicare beneficiaries is discharged to a skilled nursing facility (SNF), little is known regarding the association between the quality of SNF care and the risk of hospital readmission.

Methods: We analyzed data from the Medicare Provider Analysis and Review (MedPAR) file, the Minimum Data Set, and the Medicare beneficiary summary file. Our sample included all fee-for-service Medicare beneficiaries discharged alive from an acute-care hospital between October 1, 2009 and September 30, 2010, excluding admissions for psychiatric diagnoses, rehabilitation, or cancer chemotherapy. Among patients discharged to a SNF, we measured the incidence of unplanned hospital readmission or death at 30 days after discharge, employing definitions used by the Medicare Hospital Readmission Reduction Program, and evaluated rates of readmission or death across individual SNFs. We used linear probability models to estimate changes in the risk of readmission or death associated with differences in SNF quality across three domains: facility staffing, deficiencies identified during State health inspections, and performance on nine Nursing Home Compare quality measures. Within each domain, quality was measured via the Medicare Nursing Home Compare Five-Star Quality Rating System using publicly available data. Regression models adjusted for patient demographics, comorbidities, and admission diagnosis, and included hospital fixed effects to account for differences in the quality of care across hospitals.

Results: Our sample included 6,993,555 hospital discharges, 1,555,069 of which (22.2%) were to a SNF. Among patients discharged to a SNF, death or readmission occurred in 23.4% by 30 days, compared to 16.9% for all other discharges (p<0.001). Among SNFs with at least 100 admissions, the median rate of readmission or death was 23.5% (interquartile range, 19.2%, 28.0%). Higher SNF quality of care predicted a lower adjusted risk of readmission or death at 30 days across all three domains of SNF quality assessed. Patients discharged to SNFs in the highest level of staffing had an adjusted risk of readmission or death that was 1.7% lower than for patients discharged to SNFs in the lowest level (95% CI 1.4%, 2.1%, p<0.001). Better health inspection scores and higher performance on quality measures were similarly associated with a lower adjusted risk of readmission or death (health inspection scores: adjusted change in risk for highest versus lowest performance category: -1.0%, 95% CI -1.4%, -0.7%, P<0.001; quality measure performance: adjusted change in risk for highest versus lowest performance category: -1.1%, 95% CI -1.4%,-0.8%, P<0.001, see Table 1). We obtained similar findings in regressions that predicted an outcome unplanned readmission alone rather than the combined endpoint of readmission or death.

Conclusions: Hospital readmissions are common among patients discharged to SNFs. Higher SNF quality of care appears to reduce the risk of hospital readmission or death at 30 days. Hospitals may be able to reduce their readmission rates by discharging patients to higher-quality SNFs.

Table: Association of skilled nursing facility quality of care with readmission or death 30 days after hospital discharge among Medicare beneficiaries discharged to a skilled nursing facility between October 1, 2009 and September 30, 2010.[a] Nursing facility quality was measured across three domains: nursing home staffing, deficiencies identified during State health inspections, and performance on nine Nursing Home Compare (NHC) quality measures.[b] Within each domain, quality was measured via the Medicare NHC Five-Star Quality Rating System using publicly available data.

	Adjusted difference in risk (%)	95% Confidence Interval	P
Nursing home staffing levels: Five-Star Rating			
One star	Reference	N/A	N/A
Two stars	-0.317	-0.607, -0.027	0.032
Three stars	-0.378	-0.655, -0.101	0.007
Four stars	-0.745	-1.015, -0.475	<0.001
Five stars	-1.746	-2.120, -1.371	<0.001
State health inspection results: Five-Star Rating			
One star	Reference	N/A	N/A
Two stars	-0.248	-0.511, 0.015	0.064
Three stars	-0.528	-0.797, -0.259	<0.001
Four stars	-0.707	-0.985, -0.429	<0.001
Five stars	-1.016	-1.371, -0.662	<0.001
Performance on nine NHC quality measures: Five-Star rating			
One star	Reference	N/A	N/A
Two stars	-0.101	-0.353, 0.150	0.430
Three stars	-0.211	-0.468, 0.046	0.107
Four stars	-0.481	-0.741, -0.220	<0.001
Five stars	-1.101	-1.444, -0.759	<0.001

Notes: a. Regression adjusted for age, sex, admission diagnosis category, 31 comorbidities, and hospital fixed-effects; standard errors are robust and adjusted for clustering at the hospital level. b. Measures assessed included: percent of long-stay residents whose need for help with daily activities has increased; percent of high-risk long-stay residents with pressure ulcers; percent of long-stay residents who have/had a bladder catheter inserted and left in their bladder; percent of long-stay residents who were physically restrained; percent of long-stay residents with a urinary tract infection; percent of long-stay residents who self-report moderate to severe pain; percent of long-stay residents experiencing one or more falls; percent of short-stay residents with new or worsened pressure ulcers; percent of short-stay residents who report moderate to severe pain. Technical description available at: http://www.medicare.gov/NursingHomeCompare/About/Ratings.html

Tox Pain 51 (40)

Cytotoxic Effects of Methylprednisolone Acetate With and Without Preservatives on Dorsal Root Ganglion Sensory Neurons in Rats

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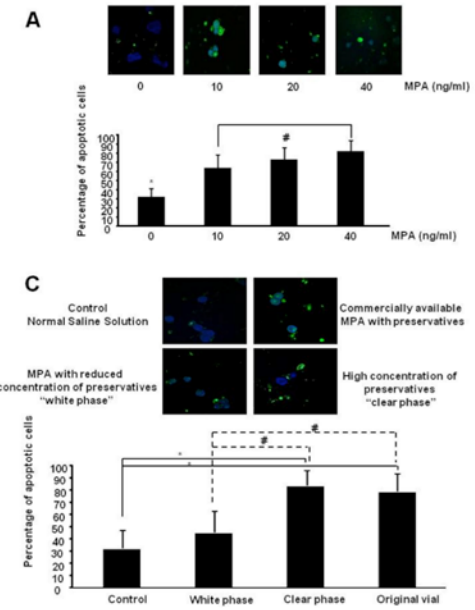
Introduction: Epidural and intrathecal injections of methylprednisolone acetate (MPA) have become the most commonly performed interventional procedures in the United States and worldwide in the last two decades. However neuraxial MPA injection has been dogged by controversy lead by presence of different additives to commercially prepared glucocorticoids. Our previous work showed that MPA could be rendered 85% free of polyethylene glycol (PEG) by simple physical separation of elements in the suspension.

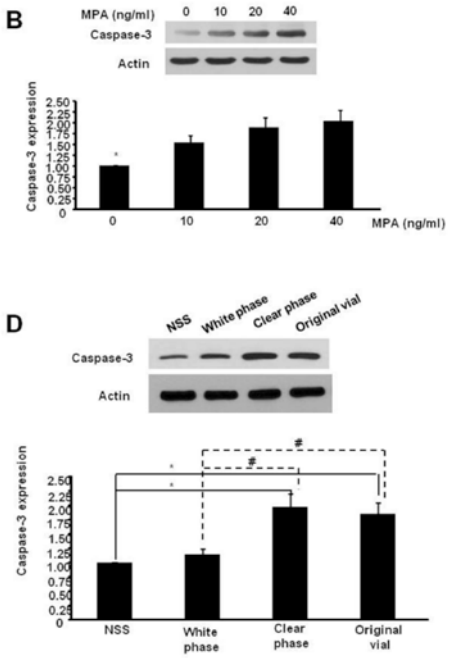
Objective: The objective of the present study was to explore possible cytotoxic effects that MPA (with intact or reduced preservatives) might have on isolated sensory neurons from rat dorsal root ganglia (DRG).

Methods: Isolated primary sensory neurons dissociated from rat DRG after differentiation on the cover slips were exposed to commercially available MPA for 24 hours with either the standard (commercial) concentration of preservatives or to different fractions after separation (MPA suspension with reduced preservative concentration or a fraction with higher concentrations of preservatives). Extent of apoptosis and DNA fragmentation was detected by labeling the terminal free ends of nucleic acids DRG using TUNEL assay kit. Cell images were taken on the confocal microscope, and the ratio was calculated using Image J software (NIH). We also detected expression of caspase-3 form the cell lysates proteins separated by electrophoresis, as another indicator of apoptosis. Statistical software SPSS was used in data analysis. Differences in percentages of apoptotic cells and differences in caspase-3 expression were analyzed using one-way Analysis of Variance (ANOVA) test.

Results: We exposed rat DRG sensory neurons to different concentrations of MPA from the original commercially prepared vial. TUNEL assay showed dose related response and increased percentage of apoptotic cells with increasing concentrations of MPA (Fig.1a). Increased concentrations of MPA caused 1.5-2 times higher caspase-3 expression in DRG sensory neurons than in control cells (ANOVA, p=0.001) (Fig.1b). Our results showed that MPA with reduced preservatives caused significantly less apoptosis observed with TUNEL assay labeling (p<0.001) (Fig.1c), and caspase-3 immunoblotting (p≤0.001) (Fig.1d) than neurons exposed to MPA from the commercially-prepared vial or "clear phase" that contained higher concentrations of preservatives. Even though MPA with reduced preservatives caused 12.5% more apoptosis in DRG sensory neurons than control cells, post hoc analysis showed no difference between these two groups.

Conclusions: The present study showed a cytotoxic effect of MPA with preservatives on rat sensory DRG neurons and no significant differences between the vehicle and MPA with reduced preservatives, confirming that either PEG or myristylgamma-picolinium chloride (MGPC) or their combination, has harmful effects on these cells. Nevertheless, the reduction of concentrations of preservatives from MPA suspension not that only makes injections of this depot steroid safer, but also may prove to be an alternative to using compounded MPA, at least for instances wherein the use of compounding is being undertaken to provide MPA without preservatives.





Tox Pain 52 (86)

Nociceptive-Mediated Myocardial Infarct Size Reduction Occurs by TRPV1 in Rodents

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Introduction: Opioids are unique in their ability to provide pain relief in addition to reducing myocardial injury during heart attacks. However, with the recent public concerns of overuse, misuse and addiction along with the heightened FDA restrictions on opioid prescribing, there is and will continue to be a shift towards clinicians prescribing non-opioid based therapeutics for pain relief[1].

This prescribing practice shift will likely lead to an increased use of non-narcotic agents, some of which may provide no benefit in reducing tissue injury from ischemia-reperfusion or even block the natural endogenous pathways of cardioprotection, as seen with cyclooxygenase-2 inhibitors[2,3]. Recently, a novel and specific peptide inhibitor was described which reduces pain-like behavior targeting the transient receptor potential vanilloid 1 (TRPV1)[4]. However, we hypothesized activating TRPV1 mediates cardioprotection and blocking TRPV1 will mitigate this natural endogenous pathway of nociceptive-mediated cardioprotection.

Methods: Eight week old male Sprague-Dawley rats were used for both in vivo and ex vivo myocardial ischemia-reperfusion protocols consisting of 30 minutes of ischemia followed by 2 hours reperfusion. Infarct size was subsequently assessed by triphenyltetrazolium chloride (TTC) staining and expressed as the percentage of infarct per area at risk. For the in vivo studies, an abdominal incision, capsaicin cream (0.1% cream) or capsaicin cream plus an abdominal incision were performed or applied to the abdomen prior to ischemia. For the isolated heart studies, the epsilon PKC activator, ΨεRACK (1μM), was infused for 10 minutes prior to ischemia. A subset of groups received either the TRPV1 inhibitor, capsazepine (3mg/kg) or a selective TRPV1 peptide inhibitor (TRP, 1mg/kg in vivo or 1μM ex vivo) for 10 minutes prior to the interventions described.

Results: An abdominal incision before ischemia reduced myocardial infarct size compared to control (44±2%*, vs. 66±1%, n=6/group, *P<0.01). Interestingly, administration of capsazepine or TRP 10 minutes prior to an abdominal incision in vivo blocked the incision-induced infarct size sparing effect. Moreover, capsaicin cream or capsaicin cream plus an abdominal incision mimicked the incision-induced protective effect (49±2%*, 40±2%*, respectively, n=6, *P<0.01 compared to control). In isolated hearts, devoid of an intact nervous system, the protective effect of ΨεRACK was also blocked by TRPV1 inhibition by TRP. Western blot and quantitative PCR also revealed the presence of a TRPV1 receptor within the heart.

Conclusions: Our data suggest TRPV1 is essential for mediating cardioprotection. Further studies are needed to discern the cross-talk existing via TRPV1 between nociception and cardioprotection, which will allow for the design of non-narcotic therapeutics to provide a dual function of analgesia and cardioprotection.

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Tox Pain 53 (108)

The Different Effects of Local Anesthestetics on Natural Killer Cell Function

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Background: Natural killer (NK) cells are key elements of the innate immune system that have the ability to kill cancer cells and viruses. At high concentrations local anesthetics (LA) appear to inhibit the function of NK cells.[1,2]

At clinically relevant plasmatic concentrations LA have shown anti-inflammatory effects, therefore, we tested the hypothesis that the function of NK cells is preserved when exposed to clinically non-toxic plasmatic concentrations.

Methods: After Institutional Review Board approval, NK cells were purified by positive magnetic isolation from buffy coats obtained from MD Anderson Cancer Center blood bank donors (n=23) and from cancer patients who underwent abdominal surgery under general balanced anesthesia (n=24). Blood from patients was collected before surgery and on postoperative day (POD) 1, 3 and 5. K562, THP-1 and OCI-AML3 cells were used as target cells. To test the effect of LA on NK cells cytotoxic (NKCC) activity against target cells, we measured the release of lactate dehydrogenase from dying target cells at an effector: target ratio of 10:1.

NK cells and target cells were co-incubated in RPMI 1640 medium with and without 0.01 μM, 0.1 μM, 1 μM, 10 μM and 50 μM of preservative free lidocaine HCl (LIDO), bupivacaine HCl (BUPI) or ropivacaine HCl (ROPI). One or two ways ANOVA followed by Dunns' or Sidak's multiple comparisons test was used in the statistical analysis. A $p<0.05$ was considered statistically significant. In figure *, ** and *** represents $p<0.05$, $p<0.01$ and $p<0.001$, respectively.

Results: The cytotoxic assays demonstrated that LIDO was able to significantly increase the NKCC activity against the 3 cancer cell lines (Figure A, B, C). In contrast, neither BUPI nor ROPI showed any effect on the NKCC activity (data not shown). To further understand the stimulatory effect of LIDO, we used a blocker of NKG2D receptor (an activating NK cell receptor) and a granzyme B (granulolytic molecule) inhibitor. Blockade of the activating receptor (Figure D) as well as inhibiting the activity of granzyme B (Figure E), reversed the effect of LIDO. To determine whether the stimulating effect of LIDO on the NKCC activity was because of its effect on voltage-sodium channel or intracellular, we conducted experiments using QX-314 (quaternary LIDO derivative without intracellular effects). QX-314 did not have an effect on NKCC activity (Figure F). LIDO has been shown to modulate several intracellular pathways and because the granulolytic pathway requires ERK activation, we decided to conduct cytotoxicity experiments in the presence of an ERK inhibitor. These experiments showed that inhibition of ERK reversed the enhancing effects of LIDO on NKCC activity (Figure G).

To translate our findings to the perioperative period, we repeated our cytotoxicity assays by treating NK cells from patients who underwent gastrointestinal cancer surgery with 0.01 μM of LIDO. We observed that the NKCC activity was significantly reduced postoperatively which was reversed by LIDO (Figure H).

Conclusion: Our investigations partially confirmed our hypothesis that at clinically relevant plasma concentrations ROPI and BUPI preserved the NKCC activity. More interestingly, we found that LIDO stimulated the function of those cells by activating the granulocytic pathway perhaps through activation of ERK. Not less important, we also found that the effect of LIDO was not target cell specific. Remarkably, LIDO also improved the NKCC activity of cells from cancer patients. Further in vitro and in vivo studies are needed to fully understand the mechanism behind our findings and to translate our results into clinical practice.

Reference:

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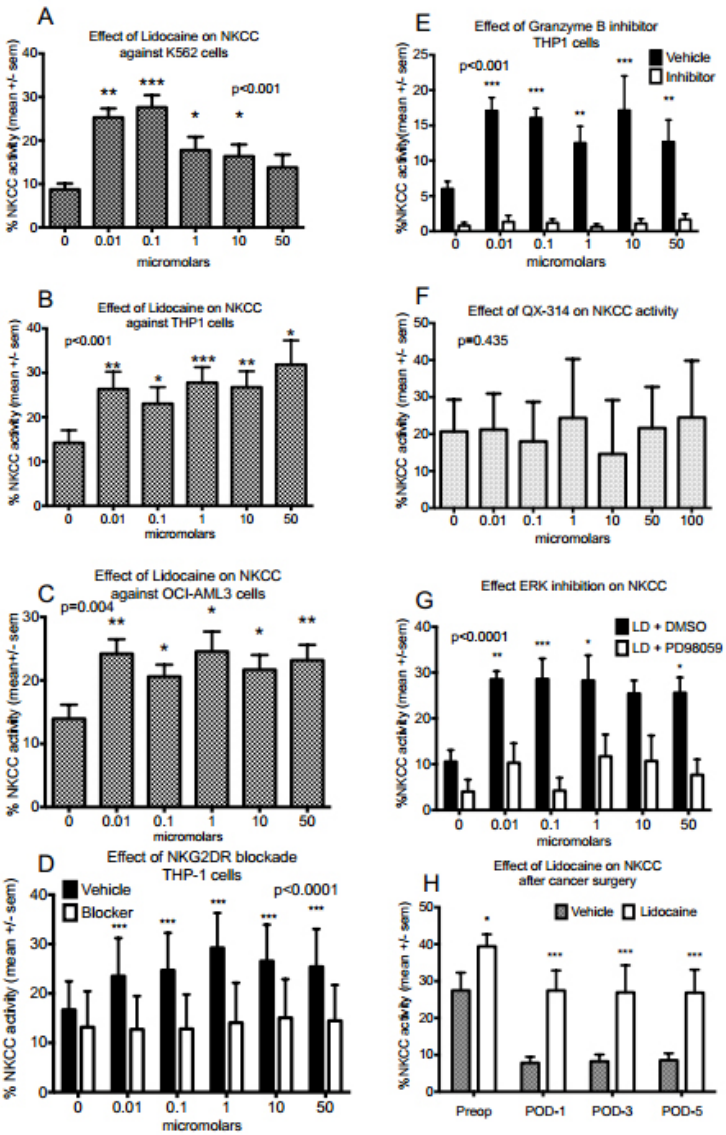

Tox Pain 54 (52)

Novel Molecular Targets of Dezocine, A Non-Addictive Opioid

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Background: While dezocine is a partial mu opioid receptor agonist, it is not a controlled substance. Thus, the characterization of the molecular targets of dezocine is critical for scientific and clinical implications. The goal of this study is to characterize molecular targets for dezocine and their implications.

Methods: A binding screen for dezocine was performed on 44 available receptors and transporter proteins. Functional assays for the novel targets were performed along with computation calculations to locate the binding site. A G protein activation study was performed for the human kappa opioid receptor to determine whether dezocine is a kappa antagonist. Data are presented as mean ± SE.

Results: The affinities for dezocine were 3.7±0.7 nM for the mu receptor, 527±70 nM for the delta receptor, and 31.9±1.9 nM for the kappa receptor. Dezocine failed to induce G protein activation with kappa opioid receptor and concentration dependently inhibited kappa agonist (salvinorin A and nalbuphine) induced receptor activation, indicating that dezocine is a kappa antagonist. Two novel molecular targets (norepinephrine transporter, NET; and serotonin transporter, SERT) were identified. Dezocine concentration-dependently inhibited norepinephrine and serotonin reuptake in vitro. The half maximal inhibitory concentrations (expressed as pIC50) were 5.68±0.11 for NET and 5.86 ± 0.17 for SERT. Dezocine occupied the binding site for known NET and SERT inhibitors.

Conclusions: The unique molecular pharmacological profile of dezocine as a partial mu receptor agonist, a kappa receptor antagonist and a norepinephrine and serotonin reuptake inhibitor (via NET and SERT) was revealed. These discoveries reveal potentially important novel clinical implications and drug interactions of dezocine.

Tox Pain 55 (53)

Increased GABA-B receptor Inhibition Contributes to Anesthetic-Induced Depression of Synapses

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GABA-A-mediated inhibition has long been recognized to contribute to the CNS depression produced by general anesthetics, however, few studies have looked at GABA-B receptor-mediated inhibition in this regard. Our lab recently found that some of the depression produced by propofol on CA1 neuron synaptic responses involved GABA-B receptor enhancement. This prompted us to study GABA-B-mediated inhibition as a target for isoflurane-induced depression of CA1 neurons. Isoflurane-induced depression of population spike recordings from the hippocampal CA1 area of rat (Long-Evans) in brain slices (400 µ) were measured. Slices were maintained in submerged chambers at 22 C and continuously perfused at 2 ml/min. Schaffer-collaterals received an electrical orthodromic stimulus to produce population spike responses recorded from the stratum oriens. Paired-pulse orthodromic responses at varying inter-pulse intervals were used to assess the degree and time course of inhibition. Isoflurane, at 0.7 rat MAC (1.0 vol%; 0.245 mM), produced about a 50% depression of CA1 neuronal population spike response amplitudes. Blocking GABA-B inhibition with CGP-55845 (100 µM) reversed 11.2% ($p<0.01$; n=5) of this propofol-induced depression. This percentage reversal was attained after inhibiting all GABA-mediated ionotropic inhibition with picrotoxin (100 µM), a GABA-A fast, slow, tonic and non-GABA chloride channel blocker. Overall, in the presence of picrotoxin and CGP-55845, the propofol-induced depression was reversed by 83.0%. Results from this study indicate that some of isoflurane's depressant effects appear to be accomplished through enhancing GABA-B-mediated inhibition. It is likely that GABA-B receptors located on CA1 neuron dendrites contribute to this effect. If GABA-B receptors on GABA nerve terminals were involved we would have expected an opposite effect, and the GABA-B effect persisted when all GABA-A inhibition was blocked. Further studies will address a possible effect of isoflurane on GABA-B receptors on glutamate nerve terminals.

Tox Pain 56 (62)

Descending Noradrenergic Inhibition is Activated by Nociception and Responsible for Recovery from Hypersensitivity After Injury

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Introduction: An acute painful stimulus engages endogenous analgesia, and the strength of this response to an experimental stimulus preoperatively correlates inversely with the likelihood of chronic pain after surgery. Whether this correlation also occurs in animals, its underlying mechanisms, and whether there is a causal link are unknown.

Methods: Noxious stimulation induced analgesia (NSIA) was produced in rats by forepaw injection of capsaicin (the conditioning stimulus) and measurement of withdrawal threshold to pressure(the test stimulus) in the hindpaw. Following NSIA testing, hypersensitivity was induced by unilateral partial spinal nerve ligation (pSNL) and withdrawal threshold tested for 10 weeks afterwards. Recovery from hypersensitivity over this period was determined using growth curve modeling. Spinally projecting noradrenergic neurons were selectively destroyed by intrathecal injection of anti-dopamine β hydroxylase saporin (DβH saporin), and spinal cord norepinephrine in microdialysates was assayed by HPLC. Glial activation was measured with GFAP and IBA1 immunohistochemistry. Studies conformed to ARRIVE guidelines.

Results: NSIA was present for 60 min after capsaicin injection, accompanied by spinal norepinephrine release and partially inhibited by intrathecal injection of an α2-adrenoceptor antagonist. Strength of this response in individual animals correlated with speed of recovery from hypersensitivity over 10 weeks after surgery(r=0.66, Figure panel A - paw pressure threshold versus slope of modeled resolution curve). Recovery was nearly abolished by destruction of spinally projecting noradrenergic neurons (Figure 1B - group means and 95% CIs), accompanied by sustained neuroinflammatory changes in the spinal cord. In animals that had recovered, injection of the anti-DβH saporin reinstated hypersensitivity.

Discussion: In animals as in humans, strength of experimental pain-induced endogenous analgesia correlates with timing of recovery from pain and hypersensitivity after surgery. In animals this involves activation of descending noradrenergic pathways which appear mechanistically linked to recovery from hypersensitivity and spinal neuroinflammation. Behavioral recovery reflects a new balance of increased noradrenergic inhibitory tone. These results have important implications for preoperative testing and treatment to speed recovery after surgery.

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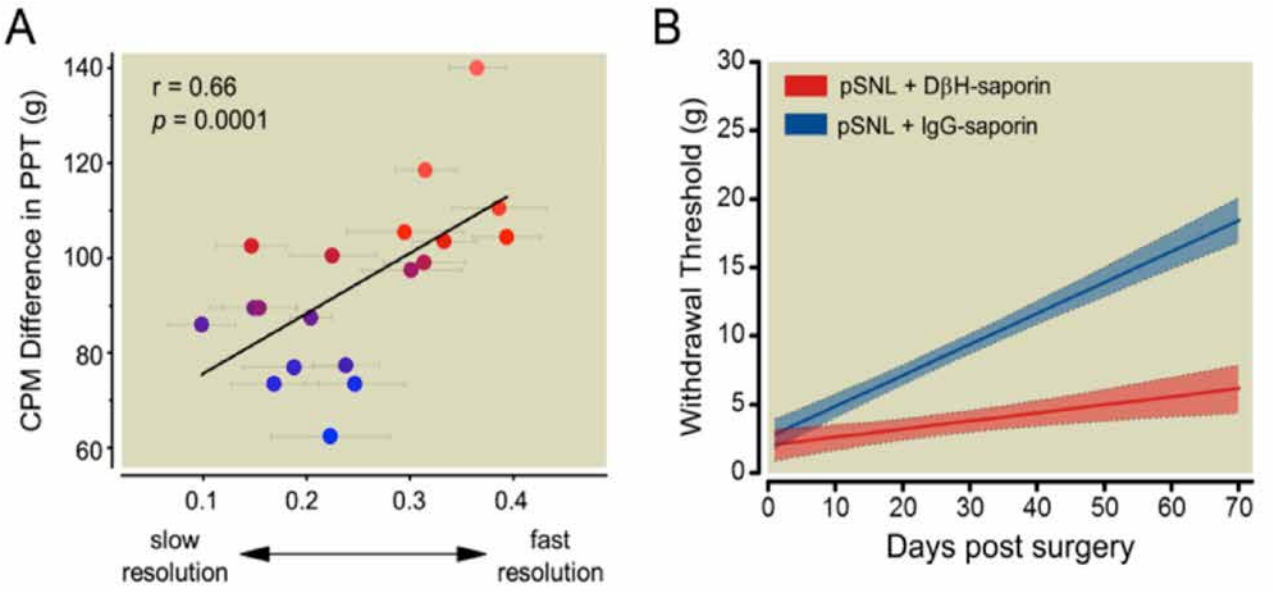

Tox Pain 57 (72)

Downregulation of miR-21 Mediates Propofol-Induced Neurotoxicity in Developing Human Neurons

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Introduction: Recent studies in various animal models have suggested that anesthetics such as propofol, when administered early in life, can lead to neurotoxicity. These studies have raised significant safety concerns regarding the use of anesthetics in the pediatric population and highlight the need for a better model by which to study anesthetic-induced neurotoxicity in humans. Human embryonic stem cells (hESCs) are capable of differentiating into any cell type and represent a promising model to study mechanisms governing anesthetic-induced neurotoxicity in humans. After screening microRNAs (miRs) and finding that miR-21 was downregulated following exposure to propofol, we hypothesized that the miR-21 signaling pathway (STAT3/Sprouty2/pAkt) plays a role in the increased cell death observed in the hESC-derived neurons following propofol administration.

Methods: To generate neurons from the hESCs, the cells were taken through a 4-step differentiation protocol as we reported. Two-week-old neurons were treated with 0, 5, 10 and 20 µg/mL propofol or equal volume of DMSO as the vehicle control in 60 mm culture dishes. Neurons were exposed to propofol for 6 hours either one time or three times (once per day for three consecutive days). Cell death was assessed using TUNEL staining and miR expression was assessed using qRT-PCR. miR-21 was overexpressed and knocked down using LNA-modified miR-21 mimics and antagomirs, respectively, and the expression of the miR-21 targets of interest was assessed by Western blot.

Results: Propofol dose- and exposure time-dependently induced significant cell death in the neurons (Fig. 1) and downregulated several microRNAs, including miR-21. Overexpression of miR-21 significantly attenuated the propofol-induced increase in TUNEL-positive cells, while miR-21 knockdown exacerbated the effects. STAT3 is a known regulator of miR-21 that has been shown to have anti-apoptotic properties. A single exposure to 6 hours of 20 µg/mL propofol significantly decreased the expression of pSTAT3, which was consistent with the miR-21 expression data. Sprouty 2 is known to be a direct target of miR-21 and exposure to propofol significantly increased the expression of Sprouty 2 which is consistent with the miR-21 expression data since microRNAs act as negative regulators of their target genes. Finally, Sprouty 2 is known to act on Akt, specifically to reduce the levels of activated/phosphorylated Akt. The expression of pAkt was significantly reduced after propofol. Since Akt is known to play an important role in survival pathways, this represents a possible pathway by which propofol induces toxicity in the hESC-derived neurons.

Conclusions: This is the first time that a role for miRs in the mechanism of anesthetic-induced neurotoxicity has been established. Our data suggest that: 1) propofol induces cell death in stem cell-derived human neurons; (2) the propofol-induced cell death occurs possibly via a STAT3/miR-21/Sprouty2-dependent mechanism; and 3) hESC-derived neurons represent a promising in vitro human model for studying anesthetic-induced neurotoxicity. The increases we observed in neuronal death following propofol exposure could possibly translate to future learning disabilities as seen in the animal studies.

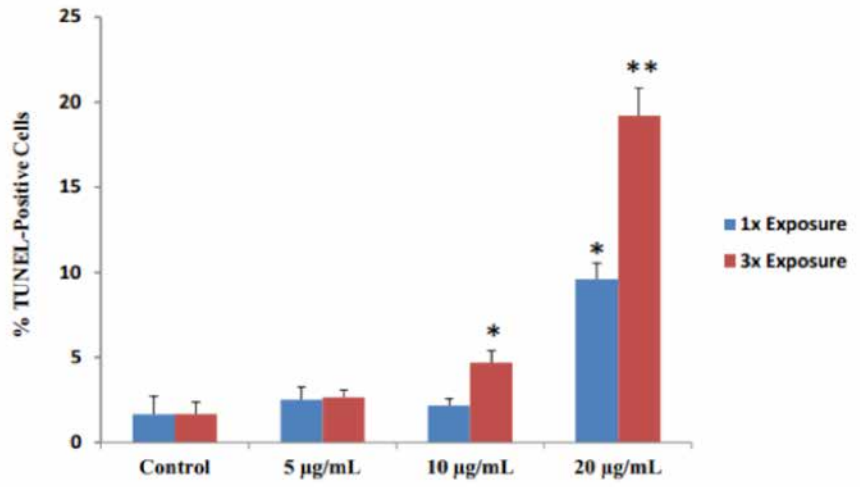

Figure 1. Quantified data from TUNEL staining images showed that cell death was significantly increased following one and three exposures to 6 hours of 20 µg/mL propofol and three exposures to 6 hours of 10 µg/mL propofol, but not after exposure to either one or three doses of 5 µg/mL propofol or one dose of 10 µg/mL propofol. (*$P < 0.05$ and **$P < 0.01$ vs. respective controls, n = 3/group). TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate in situ nick end labeling.

Tox Pain 58 (80)

Ketamine Modulates DISC1 Expression in a Rat Model of Anesthetic-Induced Developmental Neuroapoptosis

Sulpicio G. Soriano, MD[1], Jia-Ren Liu, MD, PhD[1], Koichi Yuki, MD1, Xiao-Hui Han, RN[2]
[1]Boston Children's Hospital/Harvard Medical School, Boston, Massachusetts, [2]Boston Children's Hospital, Boston, Massachusetts

Introduction: Preclinical studies clearly demonstrate that ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDA-R) antagonist, causes neuroapoptosis and other morphologic changes in the developing brain. Disrupted in schizophrenia-1 (DISC1) gene has been associated with schizophrenia, bipolar affective disorder and recurrent major depression.[1] DISC1 knockdown results in defects in migration and proliferation.[2] We previously reported that ketamine induced neuroapoptosis regulated the glycogen synthase kinase-3β (GSK-3β) pathway in the developing brain[3], which is a target of DISC1.[4] Furthermore, DISC1 has been shown to regulate NMDA-R expression and function. In the present study, we tested the hypothesis that ketamine affects DISC1 expression. We measured the impact of ketamine on DISC1 and pGSK-3β expression in this experimental paradigm.

Methods: With the approval of the local IRB, Sprague-Dawley postnatal day 7 (P7) rat pups were randomly divided to 5 (n=3 per group). Each rat pup received 4 intraperitoneal (ip) injections (10 ml/kg each) of vehicle (saline), 5, 10 and 20 mg/kg of ketamine at 90 min intervals over 6 h or 20 mg/kg for different time-points. After the treatment period, the rat pups were euthanized with pentobarbital (100 mg/kg ip). The brains from each group were rapidly isolated processed for protein analysis. Antibodies used for western blotting included rabbit antibodies to cleaved-caspase-3, total and phosphorylated GSK-3β, DISC1 and β-actin. Labeled bands from each blot were detected by enhanced chemiluminescence for visualization and quantitation. A second cohort of rat pups (n=3 per group) were euthanized and immediately perfused with saline followed by 4% paraformaldehyde. The brains were subsequently embedded in paraffin for immunohistological processing. Neurons that expressed cleaved-caspase-3 and DISC1 were labeled with neuron-specific anti-NeuN antibodies.

Results: Ketamine produced a dose- and duration-dependent increase in cleaved caspase-3 and decrease in DISC1 and pGSK-3β expression (figure). Ketamine naïve slices demonstrated co-localization of DISC1 in neurons. While the ketamine treated slices had significantly less DISC1 positive cells. Conclusion: Ketamine induces a dose- and dependent decrease in DISC1 expression, which implicates the role of DISC1 deficiency in animal models results in ketamine-induced psychosis and cognitive dysfunction. Furthermore, knockdown of DISC1 in cell cultures lead to aberrant NMDA-R currents and increased NMDA-R subunit expression.[5] This change in NMDA-R subunit density has previously been reported in ketamine treated rat pups.[6] Taken together, these findings support the DISC1-GSK-3β as another mechanistic pathway associated with ketamine-induced neuroapoptosis and neurocognitive dysfunction.

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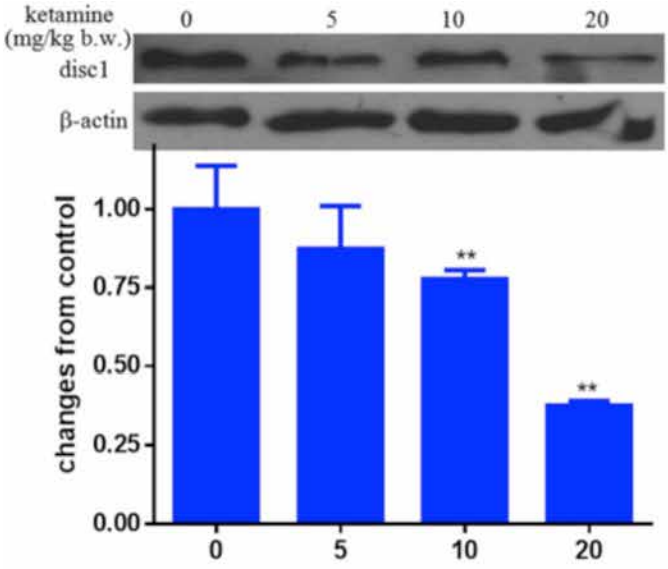
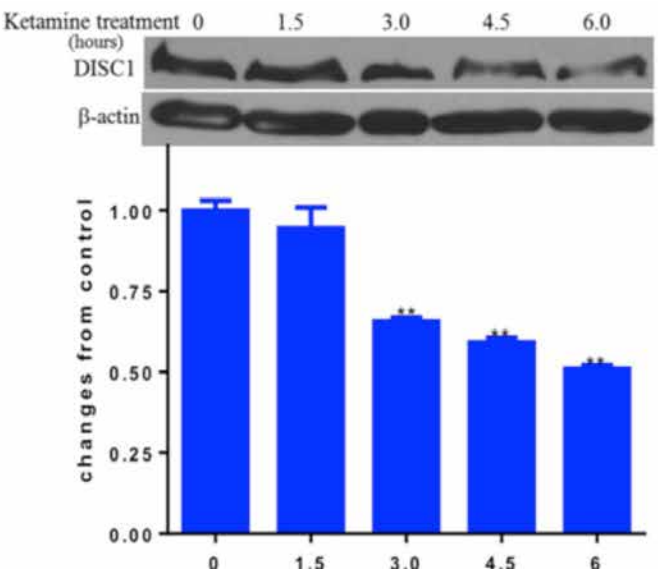
6. Han LC, et al: The effect of ketamine on N-methyl-D-aspartate receptor subunit expression in neonatal rats. Eur J Anaesthesiol 2010; 27: 181-6





Poster Presentations Schedule

Saturday, April 26, 1014 • 3:30 pm – 5:00 pm

Moderated Poster Discussion: Clinical / Basic Neuroscience

Moderator: Max Kelz, MD, PhD, Dean Andropoulos, MD, MHCM

	CBN 8 (45) • Role of Markers of Endothelial Activation and Blood Brain Barrier Injury in Acute Brain Dysfunction **Christopher G. Hughes, MD[1],** Timothy D. Girard, MD[1], Jennifer L. Thomson, MPH[1], Ayumi K.Shintani, PhD[1], E. Wesley Ely, MD[1], Pratik P. Pandharipande, MD[1] [1]Vanderbilt University School of Medicine, Nashville, Tennessee
Junior Faculty Award	**CBN 9 (37) • Specialized Pro-resolving Mediators in a Mouse Model of Postoperative Cognitive Decline** **Niccolo Terrando, BSc (hons), DIC, PhD[1],** Ting Yang, MD, PhD[1], Marta Galan, PhD[1], Ralph E. Harding, DO[2], Lars I. Eriksson, MD, PhD, FRCA[1] [1]Karolinska Institute Stockholm, Sweden, Karolinska, [2]The Carl Vinson Veterans Affairs Medical Center, Dublin, Georgia *Please see page 58 for complete abstract.*
	CBN 10 (60) • Glibenclamide and Heparin as Novel Anti-inflammatory Therapies for Subarachnoid Hemorrhage **Caron M. Hong, MD, MSc[1],** J. Marc Simard, MD, PhD[2], Volodymyr Gerzanich, MD, PhD[2], Cigdem Tosun, BS[2], David Kurland, BA[2] [1]University of Maryland School of Medicine, Baltimore, Maryland, [2]University of Maryland ,Baltimore, Maryland
	CBN 11 (74) • Fentanyl Depresses Pupillary Unrest **Michael P. Bokoch MD, PhD[1],** Andrew Neice, MD[2], Matthias Behrends, MD[1], Merlin D. Larson, MD[1] [1]University of California, San Francisco, San Francisco, California, [2]Oregon Health & Science University, Portland, Oregon
Resident Travel Award	**CBN 12 (85) • miR-200c Contributes to Injury From Transient Cerebral Ischemia in Mice by Targeting Reelin** **Creed M. Stary, MD, PhD[1],** Lijun Xu, MD[1], Xiaoyun Sun, MD[1], Yibing Ouyang, PhD[1], Jason Leong, BS[2], Rona G. Giffard, MD, PhD[1] [1]Stanford University, Stanford, California, [2]Albert Einstein College of Medicine, Bronx, New York *Please see page 60 for complete abstract.*
	CBN 13 (91) • Deletion of CD36 Induces M2 Response to Brain Injury and Supports Ischemic Tolerance **Ines P. Koerner, MD, PhD[1],** Takeru Shimizu, MD[1], Yingxin Chen ,MD[1], Sarah Mader, BS[1] [1]Oregon Health and Science University, Portland, Oregon
	CBN 14 (113) **Delta Opioid Receptors Presynaptically Regulate Cutaneous Mechanosensory Neuron Input to the Spinal Cord Dorsal Horn** **Vivianne L. Tawfik, MD, PhD[1],** Dong Wang, PhD[2], Scott A. Shuster, BA[2], Gregory Scherrer, PharmD, PhD[2] [1]Stanford University School of Medicine, Stanford, California, [2]Stanford University, Stanford, California
	CBN 15 (69) **Transfer Function Analysis of Cerebral Pressure-Flow Dynamics** **Following Aneurysmal Subarachnoid Hemorrhage: A Pilot Study** **Kevin J. Gingrich, MD, MBME[1],** Hooman Heravi, BS[2], Brett Whittemore, MD[2], Rong Zhang PhD[3], Kim Rickert MD[2] [1]Univ. of Texas Southwestern Medical Ctr, Dept Anesthesiology and Pain Management, Dallas, Texas, [2]UTSW Medical Center, Dallas, Texas, [3]Inst Exercise Environ Medicine, Dallas, Texas

Poster Presentations Schedule

Saturday, April 26, 1014 • 3:30 pm – 5:00 pm

Moderated Poster Discussion: Compliance / Outreach

Moderators: Alina Grigore, MD, Tim Morey, MD

	CO 61 (48) **Physician and Nurse Staffing Patterns in Pennsylvania Cardiac Surgery Intensive Care Units** **Meghan B. Lane-Fall, MD, MSHP[1],** Xu He, BA[2], Kelly L. Wiltse Nicely, PhD CRNA[3], Lee A. Fleisher, MD[3], Mark D. Neuman, MD, MS3 [1]University of Pennsylvania, Department of Anesthesiology and Critical Care, Philadelphia, Pennsylvania, [2]Case Western Reserve University Cleveland, Ohio, [3]University of Pennsylvania, Philadelphia, Pennsylvania
	CO 62 (54) • Needleless Connectors Substantially Reduce Flow of Crystalloid and Red Blood Cells During Rapid Infusion **Robert A. Lehn, MD[1],** Jeffrey B. Gross, MD[1], Joseph H. McIsaac, MD, MS[1], Keith E. Gipson, MD, PhD[1] [1]University of Connecticut School of Medicine, Farmington, Connecticut
	CO 63 (59) • Patient-Reported Perioperative Non-Routine Events **Matthew B. Weinger, MD, MS[1],** Jason M. Slagle, PhD[2], Eric Porterfield, MS[2], Krzysztof Dworski, BS[2], Eva Cassedy, BS[2], PCORI PNRE Project Team[2] [1]Vanderbilt University Medical Center, Nashville, Tennessee, [2]Vanderbilt University, Nashville, Tennessee
	CO 64 (63) **Engaging Students, Residents and Fellows in Global Research: An Improved Paradigm for Meeting Global Health Interests?** **Kelly McQueen, MD, MPH[1]** [1]Vanderbilt University, Nashville, Tennessee
	CO 65 (107) **Using Providers' Self-Reported Time Away Information to Predict Daily Surgical Service Volume Months in Advance** **Vikram Tiwari, PhD[1],** Warren S. Sandberg, MD, PhD[1] [1]Vanderbilt University Medical Center, Nashville, Tennessee
	CO 66 (109) • Tele-anesthesia Simulation for Martian Analogue Environments **Divya Chander, MD, PhD[1],** Matthieu Komorowski, MD[2], David Gaba, MD[3], Susan Jewell, MD[4], Yvonne Cagle, MD[5], Adrianos Golemis, MD[6] [1]Stanford University School of Medicine, International Space Surgery Consortium, Stanford, California, [2]Lille University Hospital Lille, France, [3]Stanford University, Stanford, California, [4]The Space Clinic, Houston, Texas, [5]NASA AMES, Fordham University, New York, [6]Concordia Antarctica Station/European Space Agency, Concordia, Antarctica

Poster Presentations Schedule

Saturday, April 26, 1014 • 3:30 pm – 5:00 pm

Moderated Poster Discussion: Education

Moderators: Alex Macario, MD, Manuel Pardo, Jr., MD

	EDU 43 (46) **Subsequent Research Funding Among FAER Career Development Award Recipients and Applicants** **Rebecca M. Speck, PhD, MPH[1],** Denham S. Ward, MD, PhD[2], Lee A. Fleisher, MD[1] [1]University of Pennsylvania, Philadelphia, Philadelphia, [2]University of Rochester, Rochester, New York
	EDU 44 (61) • A Pilot Study to Measure the Impact of Blended Learning on Intern Wellness and Burnout **Louise Wen, MD[1],** Emily Ratner, MD[1], Kyle Harrison, MD[2], Larry Chu, MD[1], Edward Mariano, MD[2], Ankeet Udani, MD[1] [1]Stanford University Hospital and Clinics, Palo Alto, California, [2]Veterans Affairs Palo Alto, Palo Alto, California
	EDU 45 (66) • Riding the Wave of the Future: Anesthesia Residents and Technology **Lara N. Zador, MD[1],** Harika Nagavelli, MD[1], Erica J. Zador, MLA[1], Viji Kurup, MD[1] [1]Yale University School of Medicine, New Haven, Connecticut
	EDU 46 (67) • Training Factors that Modulate Laryngoscopy Learning **Randolph H. Hastings, MD, PhD[1],** Nathan Delson, PhD[2], Steven C. Pan, BS[2], Megan A. Lida[2], Tania F. Romero[2], Timoth C. Rickard, PhD[2] [1]VA San Diego Healthcare System, San Diego, California, [2]UC San Diego, San Diego, California
	EDU 47 (94) • Simulation Model for the Pregnant Trauma Patient: A Multidisciplinary Team Training Exercise **Shobana Bharadwaj, MBBS[1],** Wendy Bernstein,MBA[2], David Schreibman, MD[2], Jessica Galey, MD[2], Peter Lax, MD[2], Jenifer Fahey, CNM, MSN, MSPH[2] [1]University of Maryland School of Medicine, Baltimore, Maryland, [2]University of Maryland, Baltimore, Maryland
	EDU 48 (98) • Assessing the Quality of Websites with Anesthesia-related Information for Patients **Viji Kurup, MD[1],** Ryan M. Chadha, MD[1], Denise Hersey, MA, MLS[1] [1]Yale University, New Haven, Connecticut
	EDU 49 (105) **Entrustable Professional Activities for Anesthesiology Residents: A Novel Approach to the Milestones Project** **Rachel M. Kacmar, MD[1],** Joy L. Hawkins, MD[1], Nathaen S. Weitzel, MD[1] [1]University of Colorado, Denver, Aurora, Colorado
	EDU 50 (121) **Improving Learning Outcomes and Resident Perceptions: The Science and Craft of Anesthesia Milestone-Specific Feedback** **Sylvia Bereknyei, DrPH, MS[1],** Alyssa Bogetz, MSW[1], Kim Walker, PhD[2], Pedro Tanaka, MD, PhD[3] [1]Stanford Center for Medical Education Research and Innovation (SCeMERI), Stanford University School of Medicine Stanford, California, Stanford, [2]Office of Graduate Medical Education, Stanford Hospital and Clinics, Stanford, California, [3]Stanford Hospital and Clinics, Stanford, California

(continued)

Poster Presentations Schedule

Saturday, April 26, 1014 • 3:30 pm – 5:00 pm

Moderated Poster Discussion: Organ Protection

Moderators: Dolores Njoku, MD, Peter Nagele, MD, MSc

	OP 75 (58) **Anesthetic Postconditioning at the Initiation of CPR Improves Myocardial and Mitochondrial Function in a Porcine Model of Prolonged Untreated Ventricular Fibrillation** **Matthias L. Riess, MD, PhD[1],** Timothy R. Matsuura, BS[2], Martin Bienengraeber, PhD[3], Mohammed Aldakkak, MD[3], Jason A. Bartos, MD, PhD[2], Demetris Yannopoulos, MD[2] [1]Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin, [2]University of Minnesota Minneapolis, Minnesota, [3]Medical College of Wisconsin, Milwaukee, Wisconsin
	OP 76 (32) • Anesthesia-induced Neurotoxicity in the Developing Murine Retina: A Window of Opportunity? **Richard J. Levy, MD, FAAP[1],** Ying Cheng, MS1, Linda He[1] [1]Children's National Medical Center, Washington, District of Columbia
	OP 77 (68) **Microvesicles Derived from Human Bone Marrow Mesenchymal Stem Cells Improve Survival in E.coli Pneumonia-Induced Acute Lung Injury in Mice and Enhance Monocyte Phagocytosis of Bacteria** **Antoine Monsel, MD1,** Ying-Gang Zhu, MD, PhD[2], Qi Hao, PhD[2], Stephane Gennai, MD, PhD[2], Michael Matthay, MD[2], Jae Woo Lee, MD[2] [1]University of California San Francisco, Department of Anesthesiology, San Francisco, California, [2]UCSF, San Francisco, California
	OP 78 (70) • Peptidylarginine Deiminase-4 Exacerbates Kidney Ischemia and Reperfusion Injury **HT Lee, MD, PHD[1],** Ahrom Ham, PhD[1], Mihwa Kim, PharmD[1], May Rabadi, PhD[1], Kyota Fukazawa, MD[1], Kevin Brown, BS[1] [1]Columbia University, New York, New York
	OP 79 (76) **Single-Cell Deep Immune Profiling Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates** **Brice Gaudilliere, PhD, MD[1],** Gabriela K. Fragiadakis, PhD candidate[1], Robert V. Bruggner, PhD candidate[1], Wendy J. Fantl, PhD[1], Garry P. Nolan, PhD[1], Martin S. Angst, MD[1] [1]Stanford University, Palo Alto, California
	OP 80 (79) **Endogenous Cardioprotection in Normothermic Isolated Hearts from Summer-Active Arctic Ground Squirrels is Enhanced by Intralipid** **Matthias L. Riess, MD, PhD[1],** Richard J. Deklotz, MD[2], Brian M. Barnes, PhD[3], Quintin J. Quinones, MD, PhD[4], Mihai V. Podgoreanu, MD[4] [1]Department of Anesthesiology, Clement J Zablocki VA Medical Center, Milwaukee, Wisconsin, [2]Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin, [3]Institute of Arctic Biology, University of Alaska Fairbanks, Fairbanks, Alaska
	OP 81 (110) • Ischemic Glomerular Endothelium May Protect Tubular Epithelial Cells from Ischemia **Michael P. Hutchens, MD, MA[1],** Sarah L. Mader, BS[1], Sharon Anderson, MD, PhD[1] [1]Oregon Health & Science University, Portland, Oregon
	OP 82 (111) • Exaggerated Acute Lung Injury in Response to Infection in the Metabolic Syndrome **Xiaomei Feng, PhD, MD[1],** Mitchell Marubayashi, BA[1], Judith Hellman, MD[1], Mervyn Maze, MB, ChB[1] [1]University of California, San Francisco, San Francisco, California

Poster Presentations Schedule

Saturday, April 26, 1014 • 3:30 pm – 5:00 pm

Moderated Poster Discussion: Outcomes

Moderators: Roy Levitt, MD, Dean Andropoulos, MD, MHCM

	O 28 (41) **The Usefulness of a Cognitive Screening Test in Predicting Postoperative Delirium** **Lawrence S. Long, MD[1],** Jed T. Wolpaw, MD[1], Jacqueline M. Leung, MD, MPH[1] [1]University of California San Francisco, San Francisco, California
	O 29 (101) **Predictors of Postoperative Opioid Use in Veterans Affairs Surgical Patients: A National Level Cross-sectional Analysis** **Seshadri C. Mudumbai, MD,MS[1,2],** Kirsten Unger Hu, MS[2], Randall Stafford, MD,PhD[1], Todd Wagner, PhD[2], Edward R. Mariano, MD,MAS[1], David Clark, MD,PhD[1] [1]Stanford University, Palo Alto, California, [2]VA Palo Alto, Palo Alto, California
	O 30 (102) **Statistical Modeling of Perioperative β-Blockade Risks Accounting for a Heterogeneous Treatment Effect: Possible Long Term Mortality Benefit with Agents other than Metoprolol** **Loren E. Smith, MD, PhD[1],** Derek K. Smith, DDS[1], Jeffrey D. Blume, PhD[1] [1]Vanderbilt University, Nashville, Tennessee
	O 31 (103) • Variations in the Risk of Acute Kidney Injury Across Intra-Abdominal Surgery Procedures **Minjae Kim, MD[1],** Joanne E. Brady, SM[2], Guohua Li, MD, DrPH[2] [1]Columbia University Medical Center, New York, New York, [2]Columbia University Medical Center and Mailman School of Public Health, New York, New York
	O 32 (104) **Decreasing Packed Red Blood Cell Utilization through Computerized Decision Support at a Large Academic Medical Center** **Suanne M. Daves, MD[1],** Gina Whitney, MD[1], Garrett S. Booth, MD[1], Pampee Young, MD[1], Tiercy K. Fortenberry, RN[1], Marcella Woods, PhD[1] [1]Vanderbilt University Medical Center, Nashville, Tennessee
	O 33 (106) **Are Hemoglobin Oximetry, Vital Signs and Laboratory Values Able to Predict Emergency Transfusion in Trauma Patients?** **Colin F. Mackenzie, MBChB[1],** Cheng Gao, PhDc[2], Peter FM, Hu PhD[3], Amechi N. Anazodi, MD[3], Shiming Wang, PhD[3], Yulei Wang, PhDc[2] [1]University of Maryland School of Medicine, Baltimore, Maryland, [2]UMBC, Baltimore, Maryland, [3]UMB, Baltimore, Maryland
	O 35 (118) **Improving Nutrition Practices at the Time of Tracheal Extubation in the ICU: The Extubation Safety Quality Improvement Project** **David Dorsey, MD[1],** Aaron Joffe, DO[1], David Yanez, PhD[1], Stephen Daniel, PhD[1], Jacob Sunshine, MD[1], Miriam Treggiari, MD[1] [1]University of Washington, Seattle, Washington

CBN 8 (45)

Role of Markers of Endothelial Activation and Blood Brain Barrier Injury in Acute Brain Dysfunction

Christopher G. Hughes, MD[1], Timothy D. Girard, MD1, Jennifer L. Thomson, MPH[1], Ayumi K. Shintani, PhD[1], E. Wesley Ely, MD[1], Pratik P. Pandharipande, MD[1]
[1]Vanderbilt University School of Medicine, Nashville, Tennessee

Introduction: Endothelial dysfunction may lead to brain dysfunction via perturbations in blood flow from impaired vascular reactivity, release of biochemical mediators from endothelial activation, or from increased permeability of the blood brain barrier (BBB). We have previously demonstrated that impaired endothelial vascular reactivity is associated with acute brain dysfunction in the ICU.[1] The role of endothelial activation and BBB injury in this acute brain dysfunction is unclear. We hypothesized that elevated markers of endothelial activation [plasminogen activator inhibitor-1 (PAI-1), E-selectin, and angiopoietin-2 (Ang-2)] and BBB injury (S100B) would be associated with acute brain dysfunction in the ICU and that BBB injury would mediate the effects of endothelial dysfunction (impaired vascular reactivity and increased activation) on this acute brain dysfunction.

Methods: In our cohort of patients with respiratory failure and/or shock with peripheral artery tonometry assessments of endothelial vascular reactivity, we further measured baseline plasma concentrations of PAI-1, E-selectin, Ang-2, and S100B. Delirium and coma were assessed daily using the CAM-ICU and RASS.[2,3] Multivariable linear regression with robust sandwich variance-covariance estimator was used to study the independent associations between endothelial activation and BBB injury with delirium/coma-free days (DCFDs) and with delirium duration in survivors, adjusting for confounders including age, comorbidities, illness severity, and sepsis. We further assessed if endothelial dysfunction (vascular reactivity and activation) correlated with BBB injury and whether BBB injury mediated the effects of endothelial dysfunction on DCFDs using multivariable regression models.

Results: Our 134-patient cohort had a median age of 57 years, median Charlson comorbidity index of 2, SOFA score of 10, and APACHE II score of 26.[4-6] Higher PAI-1 (p=0.002), E-selectin (p=0.02), and S100B (p<0.001) concentrations were independently associated with worse brain dysfunction (fewer DCFDs). Higher PAI-1 (p=0.01) and S100B (p=0.01) concentrations were also independently associated with longer duration of delirium in survivors. S100B concentration correlated with PAI-1 (p=0.01) and Ang-2 (p<0.001) but not with E-selectin or endothelial vascular reactivity. Adjusting for S100B did not affect the independent associations of endothelial vascular reactivity, PAI-1, and E-selectin with acute brain dysfunction, suggesting no mediation.

Conclusions: These pilot data support that both endothelial dysfunction and BBB injury are independently associated with acute brain dysfunction during critical illness and that BBB injury does not mediate the effects of endothelial dysfunction on acute brain dysfunction. Subsequent investigations are needed to examine whether modulation of endothelial dysfunction or BBB injury may improve patient outcomes from this costly and frequent organ dysfunction.

References:

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4. Charlson ME et al. J Chronic Dis 1987; 40:373-83.
5. Ferreira FL et al. JAMA 2001; 286:1754-8.
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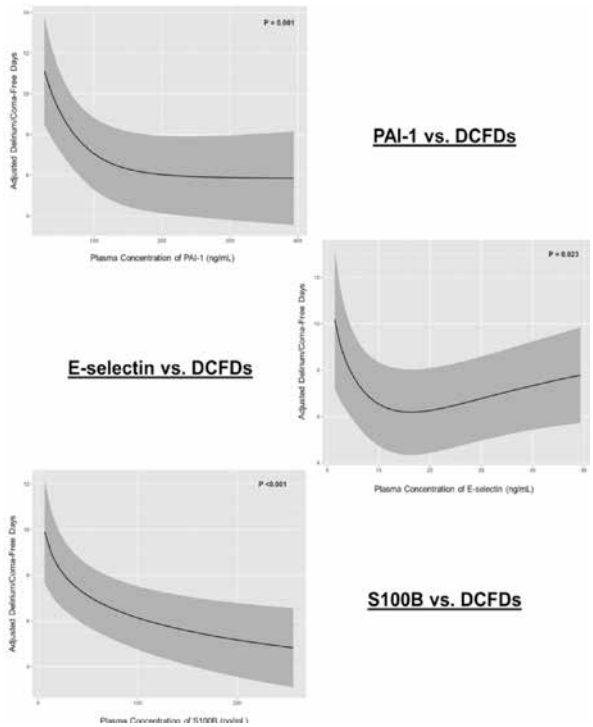

CBN 10 (60)

Glibenclamide and Heparin as Novel Anti-inflammatory Therapies for Subarachnoid Hemorrhage

Caron M. Hong, MD, MSc[1], J. Marc Simard, MD, PhD[2], Volodymyr Gerzanich, MD, PhD[2], Cigdem Tosun, BS[2], David Kurland, BA[2]
[1]University of Maryland School of Medicine, Baltimore, Maryland, [2]University of Maryland, Baltimore, Maryland

Background: Subarachnoid hemorrhage (SAH) has a high fatality rate and many survivors suffer from delayed neurological deficits (DNDs). There are many factors that may contribute to vasospasm (VSP), ischemia, stroke and ultimately DNDs. VSP research has led to surprising equivocal evidence, leading to a resurgence of interest in neuroinflammation as a primary culprit. Glibenclamide and heparin as novel anti-inflammatory therapies have demonstrated promise in improving DNDs and neurological outcome after SAH.[1] The aim of this study was to investigate glibenclamide and heparin, in parallel, to ascertain and compare their anti-inflammatory efficacy after SAH. Methods: Using an animal model of SAH devoid of ischemic injury, we evaluated the effects of glibenclamide and unfractionated heparin. SAH was performed by bilateral stereotactic injections of autologous blood into the subarachnoid space of the entorhinal cortex in adult male rats. We evaluated the effects of glibenclamide and heparin treatment after SAH on inflammation via gross histology and immunohistochemistry. Specifically, we investigated four different markers from multiple pathways of inflammation, GFAP, TNF-a (alpha), ED1 and MPO. TNF-a is an acute phase mediator, MPO is produced by PMN and macrophages during inflammation, ED1 is a microglial and macrophage marker whose increased expression occurs during phagocytic activity and GFAP is produced by astrocytes as a marker of astrocytosis during severe activation secondary to insult and inflammation. Results: Immunolabeling for ED1 and MPO-positive cells and expression of GFAP and TNF-a was significantly reduced with glibenclamide and heparin treatment when compared to non-treated SAH animals in the subpial tissues of the entorhinal cortex. Post hoc analysis also showed a significantly greater reduction of GFAP with heparin treatment when compared with glibenclamide.

Conclusion: This study demonstrates that glibenclamide and heparin are equipotent novel anti-inflammatory therapies in SAH. Although they have different mechanisms of action, glibenclamide (specific Sur1 antagonist) and heparin (non-specific anti-inflammatory) are globally equivalent in efficacy. Both glibenclamide and heparin reduces inflammation (TNF-a and MPO) and specifically neuroinflammation (ED1 and GFAP) after acute SAH. Recent translational studies have demonstrated the potential of glibenclamide and heparin as novel therapies in SAH. Simard et al1 demonstrated that Fisher grade 3 aneurysmal SAH human patients had a decreased incidence of vasospasm-related infarcts or lasting focal neurological deficits. Tosun et al2 demonstrated glibenclamide improved cognitive function after SAH, in the same animal described in this study, with improved platform search strategies and better performance on incremental and rapid spatial learning. We demonstrate the potential of glibenclamide and heparin as novel anti-inflammatory agents for SAH. Translational research investigating these two agents will potentially aid in the improvement of outcome and amelioration of DNDs after SAH.

Reference:

1. Tosun et al. Inhibiti

CBN 11 (74)

Fentanyl Depresses Pupillary Unrest

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Introduction: Opioids cause miosis through pathways that converge on the Edinger-Westphal (pupilloconstrictor) nucleus in the midbrain[1]. Aside from monotonic constriction and dilation, the pupil also undergoes random fluctuations in diameter in certain states of arousal (such as sleepiness) or in the presence of ambient light[2]. This phenomenon is known as pupillary unrest. We hypothesized that a moderate dose of fentanyl would perturb pupillary unrest in addition to causing miosis. In analogy to the electroencephalogram, measurements of pupillary unrest may provide objective data on the real-time effects of anesthetic agents on brainstem nuclei.

Methods: Following approval from the Committee on Human Research, we obtained informed consent from n = 20 patients (ASA I and II) presenting for outpatient knee procedures. Pupillary unrest was measured from the right eye with an infrared pupillometer while the left eye was illuminated with light of constant intensity. Measurements of pupil diameter versus time were obtained at baseline and following administration of fentanyl 1 mcg/kg. Measurements of recovery from fentanyl were made in the PACU upon awakening from general anesthesia and at PACU discharge.

In order to quantify pupillary unrest, we developed an algorithm to remove artifacts from the raw pupil diameter versus time data. We then computed the Fast Fourier Transform (FFT) of the data and calculated area-under-the-curve (AUC) for frequencies affected by fentanyl[3]. To compare the effect of fentanyl versus a repeat control measurement of pupillary unrest, we applied one-way ANOVA with repeated measures and Tukey's test for multiple comparisons.

Results: In outpatients presenting for knee surgery, pupillary unrest was prominent (Figure, Top) with oscillations occurring at frequencies up to 2.7 Hz, resulting in peaks in the FFT spectrum (Figure, Bottom Left). At higher frequencies the FFT amplitude was negligible, and below 0.19 Hz there was interference from artifacts such as baseline drift and blinks. We therefore considered 0.19 to 2.7 Hz as the region of interest for pupillary unrest. Pupillary unrest (AUC +/- SEM, units of mm*Hz/0.06) was significantly lower after patients received fentanyl 1 mcg/kg (0.33 +/- 0.03) as compared with replicate baseline measurements (0.62 +/- 0.13 and 0.6 +/- 0.2, $p < 0.0001$, Figure, Bottom Right). Partial recovery of pupillary unrest was observed in patients in the PACU and at the time of discharge, but residual effects of general anesthesia and administration of additional opioids in the PACU confound these measurements.

Conclusions: Fentanyl suppresses pupillary unrest, likely due to an effect on brainstem nuclei[4]. This effect can be quantified using non-invasive measurements with a portable infrared pupillometer and a simple computational algorithm. Measurements of pupillary unrest may aid rapid assessment and quantification of opioid effects on the brainstem in a variety of clinical scenarios.

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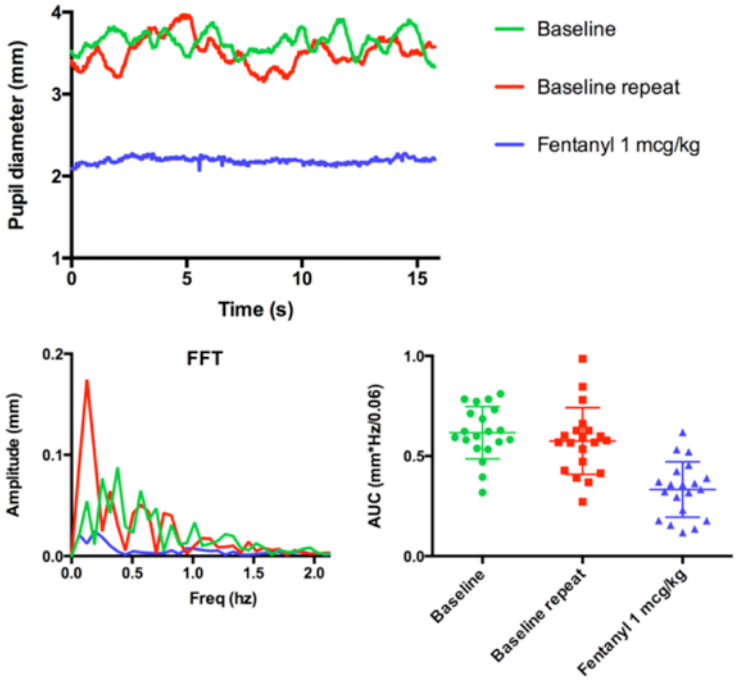

CBN 13 (91)

Deletion of CD36 Induces M2 Response to Brain Injury and Supports Ischemic Tolerance

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Introduction: Mice lacking the scavenging receptor CD36 (CD36-KO) have smaller strokes than wildtype controls and show reduced activation of pro-inflammatory transcription factor NFkB, suggesting that CD36 contributes to inflammation after stroke[1]. We hypothesized that CD36 expressed on microglia, the brain's resident immune cells, mediates the detrimental inflammatory response after stroke. We therefore tested whether transplantation of wildtype microglia with intact CD36 restores detrimental inflammation and susceptibility to stroke in CD36-KO mice.

Methods: Adult CD36-KO or C57BL/6 (wildtype, WT) mice were injected into the striatum with 20,000 microglia isolated from WT mice. After 14 days recovery, stroke was induced by 60 minutes of transient middle cerebral artery occlusion. Cerebral blood flow was monitored by laser Doppler. Infarct size was measured by TTC staining 24 hours after reperfusion and expressed as percentage of contralateral structure. Additional mice were injected with eGFP expressing microglia to allow visualization of transplanted cells. Another cohort received vehicle (culture medium) injections, and brains were harvested 1 day or 7 days later for immunohistochemistry or isolation of RNA.

Results: Infarct size after 60 min MCAO was significantly smaller in CD36-KO compared to WT mice (31±11% vs 45±8%, n=11). Transplantation of microglia moderately reduced infarct size in WT mice (35±14% vs 45±8%), but abolished infarct in CD36-KO mice (no visible infarct in 8 of 10 mice). Transplanted microglia survived and were detectable (eGFP positive) in injured brains after stroke. To determine whether transplantation-induced protection was a function of the transplanted microglia or mediated by the tissue response, we injected additional mice with astrocytes (non-immunologically active) or culture medium only (vehicle). In WT mice, protection was only achieved by microglia, but not astrocyte transplantation (42±9% infarct astrocytes vs. 31±11% microglia), suggesting that protection is a function of transplanted microglia. CD36-KO, in contrast, had smaller infarcts with vehicle injection alone (13±7% vehicle vs 24±16% no injection, n=9), suggesting that their tissue response to injury is altered. We found morphologic activation of both microglia and astrocytes in the striatum after vehicle injection of either WT or CD36-KO mice. However, while injection injury primarily induced pro-inflammatory cytokines in WT animals (TNF-α, MIP-1α), this response was shifted towards anti-inflammatory, M2 markers in CD36-KO (VEGF, IGF-1, YM1B).

Conclusions: We conclude that CD36-KO mice have an altered tissue response to injury, preferentially inducing expression of anti-inflammatory M2 markers. This causes a preconditioning-like state of ischemic tolerance and reduces infarct size after subsequent stroke. Antagonism of CD36 may therefore be a promising route to induce tolerance in states of elevated stroke risk. Transplantation of microglia induces tolerance and reduces stroke injury in WT mice, but protection is less robust than in CD36-KO.

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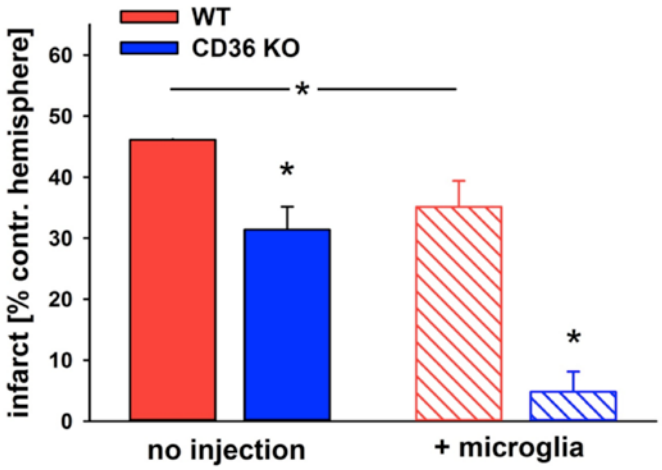

CBN 14 (113)

Delta Opioid Receptors Presynaptically Regulate Cutaneous Mechanosensory Neuron Input to the Spinal Cord Dorsal Horn

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Introduction: The cutaneous mechanosensory system is critical for the detection of innocuous and noxious mechanical stimuli that elicit sensations of touch and pain, respectively. It has been previously shown that ablation of unmyelinated nociceptors (C fibers), known to express the mu opioid receptor (MOR), does not alter injury-induced mechanical allodynia in rodents. In contrast, we have demonstrated that the delta opioid receptor (DOR) is predominantly expressed by myelinated dorsal root ganglion (DRG) neurons and that DOR-selective agonists are effective against mechanical allodynia. Further identification and characterization of the primary afferent neurons that mediate allodynia would allow for targeted therapies to treat touch-evoked pain.

Methods: All studies were performed in mice in accordance with policies set forth by the Stanford University IACUC. To characterize the DOR+ primary afferent neurons, immunohistochemistry (IHC) was performed in mice expressing the DOR as a fusion protein coupled to the reporter green fluorescent protein (DOR-GFP). In order to confirm that the DOR-GFP mouse faithfully reproduced endogenous DOR expression, in situ hybridization (ISH) was performed in wild type mice using an ultrasensitive and specific method using a probe against DOR (Oprd1) mRNA. For both IHC and ISH studies, mice were deeply anesthetized, transcardially perfused and lumbar DRGs and skin were dissected, post-fixed, cryoprotected and cut on a cryostat. Sections were then processed for ISH followed by IHC, or IHC alone, and stained for markers of neuronal subpopulations. Confocal images were acquired using a confocal microscope and processed using Adobe Photoshop for cell counting.

Results: We discovered that DOR and MOR are expressed in largely non-overlapping populations of DRG neurons. In both wild type and DOR-GFP mice, ~67% of DOR+ DRG neurons expressed the marker of myelinated afferents, NF200. Furthermore, ~62% of DOR+ NF200+ neurons expressed TrkC and/or Ret, suggesting that they are cutaneous mechanoreceptors, including Aβ low-threshold mechanoreceptors (LTMRs) that encode touch. Of the DOR+ NF200- neurons, the vast majority bound the isolectin B4 (IB4), a marker of nonpeptidergic C fibers that sense acute mechanical pain. In contrast, only ~20% of MOR+ DRG neurons were NF200+ and of these, 98% expressed CGRP, a marker of nociceptive neurons. A small population of neurons (6%) were found to coexpress both receptors and 88% of these DOR+ MOR+ neurons were also NF200+. We next determined the morphology of peripheral terminals of DOR+ DRG neurons in skin using a whole-mount cleared preparation. Using this technique we found that DOR+ NF200+ axons innervate Merkel cells, hair follicles and Meissner corpuscles, to form mechanosensory organs that detect skin indentation, hair movement, and vibrations, respectively, to shape touch sensation.

Conclusions: Herein, we demonstrate for the first time that the DOR is expressed in a subset of cutaneous myelinated primary afferents, including Aβ LTMRs that form the mechanosensory organs in the skin, implicating them in the modulation of innocuous touch, and touch-evoked pain. We further show that the MOR is found primarily in nociceptors, suggesting a divergence of function for the two receptors endogenously and in injury states. Together, our results define a mechanism by which opioids modulate cutaneous mechanosensation and provide a rationale for targeting DOR to alleviate injury-induced mechanical allodynia.

CBN 15 (69)

Transfer Function Analysis of Cerebral Pressure-Flow Dynamics Following Aneurysmal Subarachnoid Hemorrhage: A Pilot Study

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Introduction: Delayed Cerebral Ischemia (DCI) following aneurysmal subarachnoid hemorrhage (SAH) occurs in up to 30% of patients who survive the initial hemorrhage[1]. DCI results in devastating effects arising from deranged autoregulation and/or large vessel vasospasm[3]. Traditional transcranial doppler studies report flow velocities (TCDFV) in major intracranial vessels for DCI detection but lack sensitivity[2]. Transfer function analysis of cerebral pressure-flow dynamics (TFAPF) provides rich information about both cerebral autoregulation and vasculature[4]. We hypothesize that TFAPF will provide markers of cerebral circulatory dysfunction that will correlate with later development of DCI.

Methods: This was a pilot, observational, single-cohort, clinical study approved by the UT Southwestern IRB which enrolled patients with spontaneous SAH. Radial arterial blood pressure (ABP), and TCDFV waveforms were recorded, digitized (200Hz) over >300s epochs, and stored on computer. TFA was performed between input ABP and output TCDFV utilizing a cross-power spectrum technique[4]. TFAPF results reported phase shift and gain. Coherence functions were calculated to assess the linear correlation between changes in ABP and TCDFV.

Results: TFAPF at very low frequency (VLF) showed increased coherence suggesting impairment of dynamic autoregulation compared to historical controls (see Fig.). TFAPF changes at low frequencies (LF) and high frequencies (HF) suggest alterations in large and small vessel resistance and compliance in light of a Windkessel model[5]. Figure shows representative TFACPFD responses in control (left) and SAH (right) where data with low coherence (<0.5) were excluded from analysis (dashed lines drawn by hand for comparison). Conclusions: TFAPF demonstrated alterations of dynamic autoregulation, and vessel resistance and compliance in subjects with SAH. Quantitative analysis of these changes will provide new insights to pathophysiological mechanisms underlying DCI which may yield early markers of DCI.

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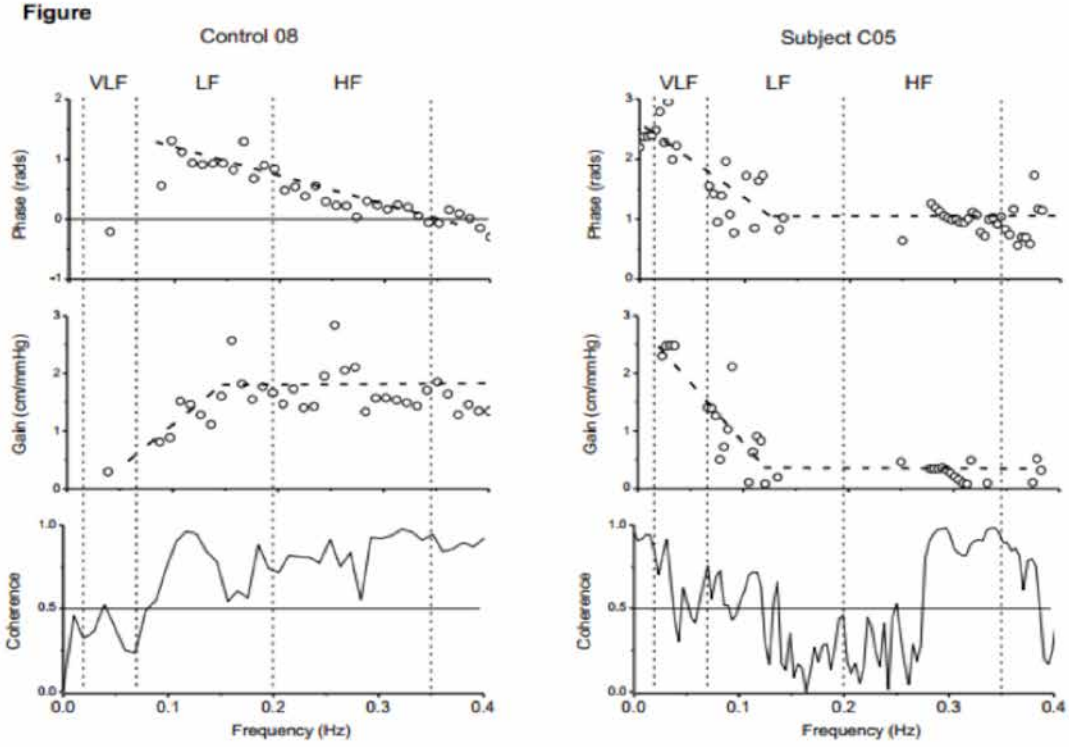
Figure



CO 61 (48)

Physician and Nurse Staffing Patterns in Pennsylvania Cardiac Surgery Intensive Care Units

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Introduction and General Purpose: In the intensive care unit (ICU), physician and nurse staffing have been independently linked to patient outcomes. However, no studies have simultaneously evaluated physician and nurse staffing since the advent of the Leapfrog Group standards for physician intensivist staffing. The purpose of the current study was to characterize physician and nurse staffing patterns in Pennsylvania cardiac surgery ICUs, including variation in physician presence and nurse characteristics on night and weekend shifts compared with weekday shifts.

Methods: Telephone and mail survey of all Pennsylvania cardiac surgery ICU nurse managers. Published instruments were adapted using clinician experts. Hospitals performing cardiac surgery in Pennsylvania were identified from the most recent statewide cardiac surgery report issued by the Pennsylvania Health Care Cost Containment Council (PHC4). The nurse manager of each hospital's cardiac surgery ICU was contacted using public hospital directory information. Participants completed a 60-item questionnaire regarding physician and nurse staffing. We compared responders and non-responders with respect to facility-level characteristics using univariate hypothesis tests. Descriptive statistics were used to characterize responding ICUs' staffing patterns and care practices.

Results and Major Findings: 61 hospitals were identified from PHC4 data. Three hospitals no longer performed cardiac surgery. From the remaining 58 hospitals, 48 nurse managers were contacted; 44 completed the survey and 4 declined. The final response rate was 44/58, or 75.9%. There were no significant differences between responders and non-responders with respect to bed size, urban versus rural locality, academic affiliation, or Hospital Safety Score(SM). Magnet® status had been achieved by more of the respondents' hospitals (15/44, 34.1%) than the non-respondents' hospitals (1/14, 7.1%, p=0.05). In the survey hospitals, 37 ICUs (84.1%) employed nurse practitioners (NPs) or physician assistants (PAs); housestaff (residents or fellows) provided care in 10 ICUs (22.7%). In 5 ICUs (11.4%), neither NPs/PAs nor housestaff provided patient care. Nighttime clinician staffing was variable: Attending physicians were present at night in 26/44 (59.0%) and no physicians were present at night in 16 units (36.4%). Neither physicians nor NPs/PAs were present at night in 11/44 (25.0%) ICUs. On weekends, attendings were present in 30/44 (68.1%) units, and no weekend physicians were available in 12/44 (27.3%) ICUs. Neither physicians nor NPs/PAs were present on weekends in 5/44 ICUs (11.4%). Registered nurse characteristics in some ICUs changed according to time of day and on weekends: 6 ICUs (13.6%) had less experienced nurses on nights/weekends and 4 ICUs (9.1%) had a higher proportion of RNs with a BSN degree on nights/weekends.

Conclusions: Pennsylvania cardiac surgery ICUs employ a variety of physician, advanced practitioner and registered nurse staffing schemes, with variation apparent in weekday versus nighttime and weekend coverage for all provider types. Additional work is needed to establish whether these staffing models are associated with differential patient outcomes.

CO 62 (54)

Needleless Connectors Substantially Reduce Flow of Crystalloid and Red Blood Cells During Rapid Infusion

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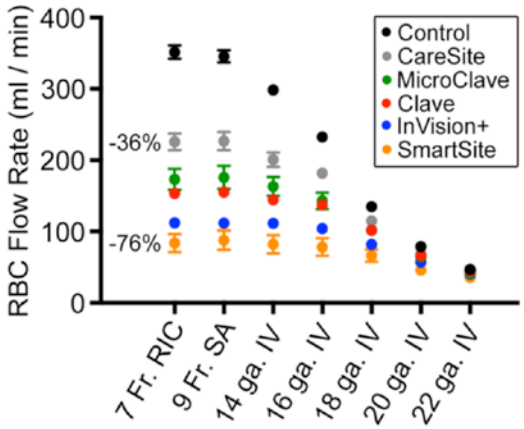
Background: Needleless connectors are frequently used at intravenous (IV) access points in the perioperative setting despite their potential to slow delivery of IV fluids. Although patient safety may depend on IV flow rates during certain surgeries, the flow restriction attributable to needleless connectors during rapid infusion of crystalloid and red blood cells (RBC) has not been thoroughly studied.

Methods: We examined flow characteristics of five needleless connector models during pressurized delivery of Lactated Ringer's solution and banked RBCs from a Level 1® warmer through a variety of IV catheters. We measured flow rates by timed fluid delivery into a graduated cylinder without (control) and with 5 samples of each in-line needleless connector for each fluid type. Flow rate differences from control were tested for each fluid and IV catheter type using a one-way analysis of variance with post-hoc Dunnett's test.

Results: While there were performance differences among needleless connector models, all tested models substantially reduced flows of both crystalloid and RBCs. Crystalloid flow reductions from control ranged from 49–84% (9 French introducer, all $p<0.05$), 51–85% (7 French rapid infusion catheter, all $p<0.05$), 39–81% (14 gauge IV, all $p<0.05$), 29–75% (16 gauge IV, all $p<0.05$), 13–60% (18 gauge IV, some $p<0.05$), 7–42% (20 gauge IV, some $p<0.05$), and 6–34% (22 gauge IV, some $p<0.05$). RBC flow reductions from control ranged from 34–75% (9 French introducer, all $p<0.05$), 36–76% (7 French rapid infusion catheter, all $p<0.05$), 33–72% (14 gauge IV, all $p<0.05$), 22–66% (16 gauge IV, all $p<0.05$), 15–51% (18 gauge IV, all $p<0.05$), 14–42% (20 gauge IV, all $p<0.05$), and 3–24% (22 gauge IV, some $p<0.05$).

Conclusions: Needleless connectors greatly reduce flows of crystalloid and RBC through large-bore IV catheters during rapid infusion. We suggest that institutions consider flow properties when choosing needleless connectors for the perioperative setting, and that practitioners consider eliminating needleless connectors altogether when large bore IV catheters are inserted in anticipation of rapid fluid administration.



Needleless Connectors Reduce RBC Flow Rates. Pressurized fluid delivery from a Level 1® warmer with no needleless connector (control) or five models of in-line needleless connector. Each data point represents n = 5 trials employing 5 different needleless connectors of a given model. Fr. = French; ga. = gauge; RIC = Rapid Infusion Catheter®; SA = introducer side arm; IV = intravenous catheter. Data are mean ± SEM.

CO 63 (59)

Patient-Reported Perioperative Non-Routine Events

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Introduction: We've previously described the "non-routine event" (NRE), defined as any event that is perceived by clinicians or skilled observers to deviate from ideal care for that specific patient in that specific clinical situation[1]. We have shown that NREs: 1) can be reliably collected prospectively from physicians and nurses in various care settings[2,3]; 2) are frequent (from 15% to 50%) (1-3); 3) are often associated with patient impact or injury[2,4]; and 4) provide data about the nature and severity of process deficiencies that could cause future patient injury[2]. In this study, we concurrently collected NREs from patients and their perioperative clinicians.

Methods: We refined our previous NRE collection tool, the Comprehensive Open-ended Non-routine Event Survey (CONES),[2] for use with patients based on a thematic analysis of patient/caregiver focus groups, input from our team's patient representatives, and pilot testing. Preoperatively, we obtained patient written consent and demographic data. Postoperatively, trained investigators collected NREs from elective ambulatory surgery (discharged within 23-hours) patients and from the anesthesia providers, surgeons and nurses caring for them. Patients were surveyed prior to discharge and were phoned approximately one-week later.

Results: For the 140 patients studied to date (age 58±14 yrs, 54% male), there were a total of 160 clinician-reported NREs and 87 patient-reported NREs. Eighty-two cases (59%) contained clinician-reported NREs while 57 cases (41%) contained patient-reported NREs. Both the patients and at least one clinician reported an NRE in 39 cases (28%) although they rarely were about the same event. CRNA's were most likely to report an NRE (69% of completed CONES), OR nurses and surgeons reported NREs in 53% and 55%, respectively, while anesthesia residents reported least often (34%). The themes of the patient reported NREs are shown in Table 1.

Conclusions: In this preliminary study, we show that 40% of ambulatory surgery patients report NREs which include clinical events, communication failures, and service deficiencies. Patient NREs rarely overlapped with clinician NREs. The NRE approach appears promising for studying to best to create patient-centered perioperative processes.

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Table 1. Key Themes from Focus Groups & their Occurrence in Patient Reported NREs.

Key Non-Routine Event Theme	Patient NREs in this Theme # (%)
Diagnostic and therapeutic issues (unfamiliarity with the patient's condition, mistakes and errors, diagnostic delays or misdiagnoses) ["I couldn't breathe when I woke up from surgery"]	43 (63%)
Health care process deficiencies (e.g., unexpected care, failure to get access, delays in treatment, care disruptions or variability) ["I was dumped on sidewalk before I was ready to go home"]	35 (51%)
Communication of health information (e.g., getting the wrong amount of information, its content, or when information is provided, etc.) ["infrequent inadequate information provided to the family while patient in surgery"]	32 (47%)
Concerns about the environment of care (available food choices, incorrect diet, cleanliness) ["The lights and noise disrupted my sleep"]	17 (25%)
Problems related to patient-provider relationships (dismissal of patient concerns, not talking with or listening to patients, being rude or inflexible, etc.) ["(Clinician Name or Role) was condescending and didn't listen"]	15 (22%)

CO 64 (63)

Engaging Students, Residents and Fellows in Global Research: An Improved Paradigm for Meeting Global Health Interests?

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Introduction: Growing numbers of students, residents and fellows express interest in global experiences during medical school and training. Providing meaningful and ethical experiences is a challenge when only clinical opportunities are considered. Global research projects allow for meaningful exchange, insight into the local healthcare system and its limitations, and collection of data that may impact the population in need without compromising international ethical standards of care.

Methods: Students, residents and fellows engaged in an IRB approved survey of surgical and anesthesia infrastructure in a low-income country and were interviewed upon return from time abroad. Attitudes and perceptions about their global experience were assessed from an electronic survey.

Results: Eight groups of student and post-graduate trainees were evaluated upon returning from a global research elective. All participants were interviewed in follow up to the research project and 91% completed an electronic survey. Interviews and survey responses indicate that students, residents and fellows valued their global research experience and that the experience provided real cultural exchange and insight into local health care that was similar to experiences gained from global clinical rotations. A majority (90%) of those responding to the survey indicated that they would pursue a similar project in the future or recommend the experience to a colleague, and a majority (90%) also indicated that the experience was worth the sacrifices involved. Local challenges were identified and categorized. A majority (80%) of participants went on to publish the data collected during their research experiences.

Conclusions: Participating in a global research project may offer students, residents and fellows an alternative to clinical rotations abroad without sacrificing the potential benefits of an international elective. When carefully constructed, research projects offer similar exposure to local health care systems, related patient outcomes, and the challenges faced by local physicians. Both global clinical and research electives have the potential to impact career choices for students, residents and fellows.

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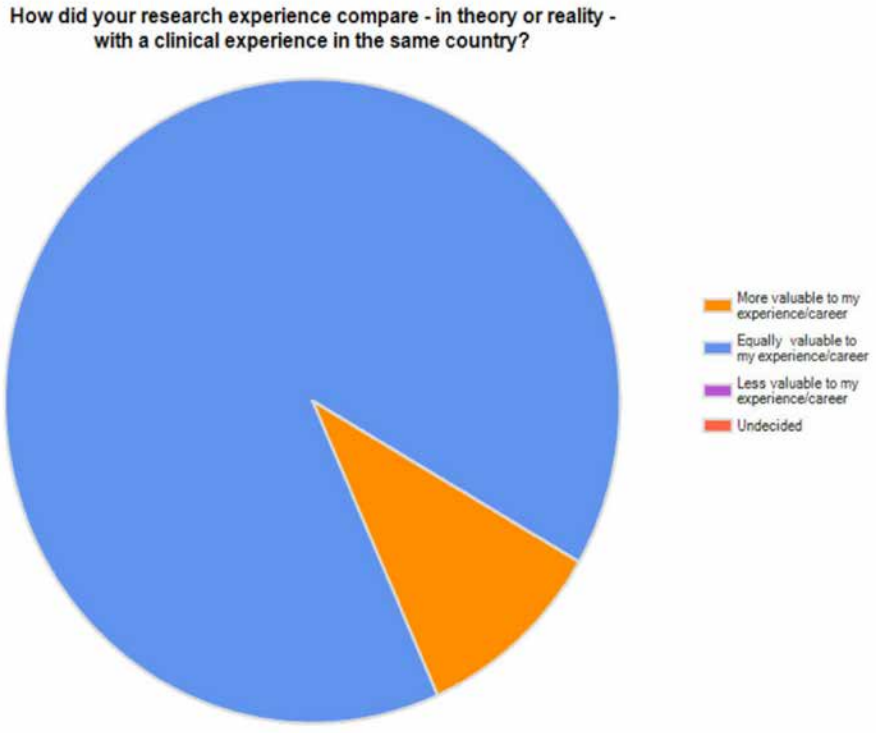

CO 65 (107)

Using Providers' Self-Reported Time Away Information to Predict Daily Surgical Service Volume Months in Advance

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Introduction: Declining reimbursements force medical centers to maximize use of expensive resources, such as operating rooms (OR). OR capacity is perishable1, and unused OR block time is a lost revenue opportunity. Execution on policies temporarily reallocating a service's unused block time to another service requires a reliable mechanism to capture and predict, months in advance, the anticipated block redirection opportunity when a service has people away from clinical work. This long time frame is required to allow other services to rearrange clinic and lab days to use released time. Our institution tracks time away from service using a mandatory, prospective reporting tool. We hypothesized that the time-away data could be used to predict a service's daily surgical volume months in advance.

Methods: We extracted and scrubbed 13 months of data from the surgeon-time-away tool for a specific high volume service. All 19 surgeons in this service appeared to consistently use the tool to indicate, at least 7 weeks in advance, their days away from the OR. We used two techniques to predict daily case counts from time-away information,[1] expected case volume for any day is the sum of the average case volume, by day of the week, of those surgeons that are present, and,[2] to account for variability in a surgeon's daily case volume, we used Monte Carlo simulation to generate a surgeon's anticipated volume based on his/her historical probability distribution of case counts by day of the week. This was then multiplied by the probability of the surgeon performing a surgery on that day of the week. We used MS-Excel and Palisade Corporation's @Risk for Excel add-in to do 10 simulation runs, each with 100 iterations for each of the 268 days in the dataset.

Results: The test service has an average daily case volume of 14 cases. The first method (average available surgeon daily volume by day of the week) predicts the daily case volume with a mean absolute error of 3.6 cases/day (28.66% mean absolute percentage error). The second method – using simulation to generate the anticipated case volume of surgeons that are not away, further improves predictability. Using the 95th percentile of the simulation output, the mean absolute error is 2.6cases/day (24.16% mean absolute percentage error) – Figure 1. The simulation method outperforms the monthly budget estimate (which is based on historical surgeon case volume). As shown in Figure 2, the simulation method had lower prediction error in 9 of the 13 months.

Discussion: Our proposed simulation methodology predicts daily case volume for each surgeon, and the entire service, by using historical case volume probability distributions and information about surgeon availability. Available block time can be identified up to 7 weeks in advance and dynamically reallocated to services that can rearrange their schedules to use it for scheduled full day blocks of additional elective cases.

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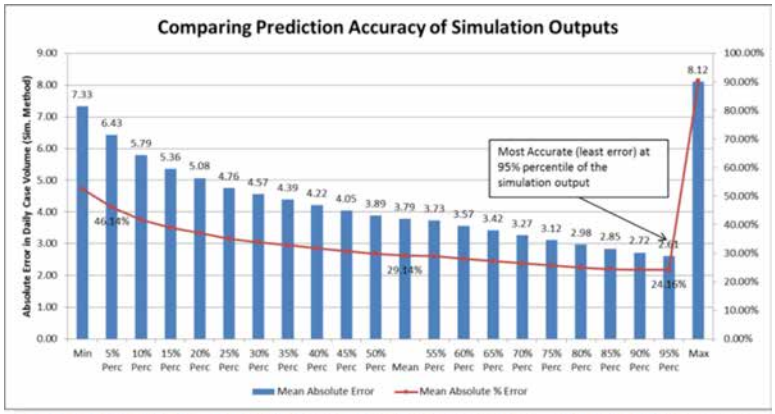

Figure 1: Using the 95th percentile from the simulation output proves the least prediction error (2.61 cases/ day)

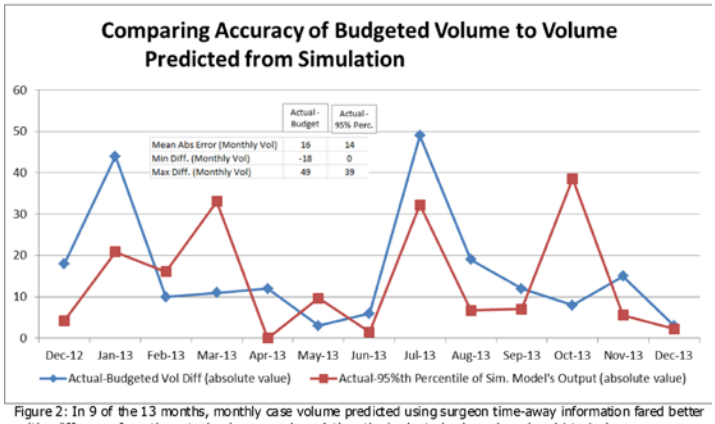

Figure 2: In 9 of the 13 months, monthly case volume predicted using surgeon time-away information fared better (the difference from the actual volume was lower) than the budgeted volume based on historical surgeon case volume alone.

CO 66 (109)

Tele-Anesthesia Simulation for Martian Analogue Environments

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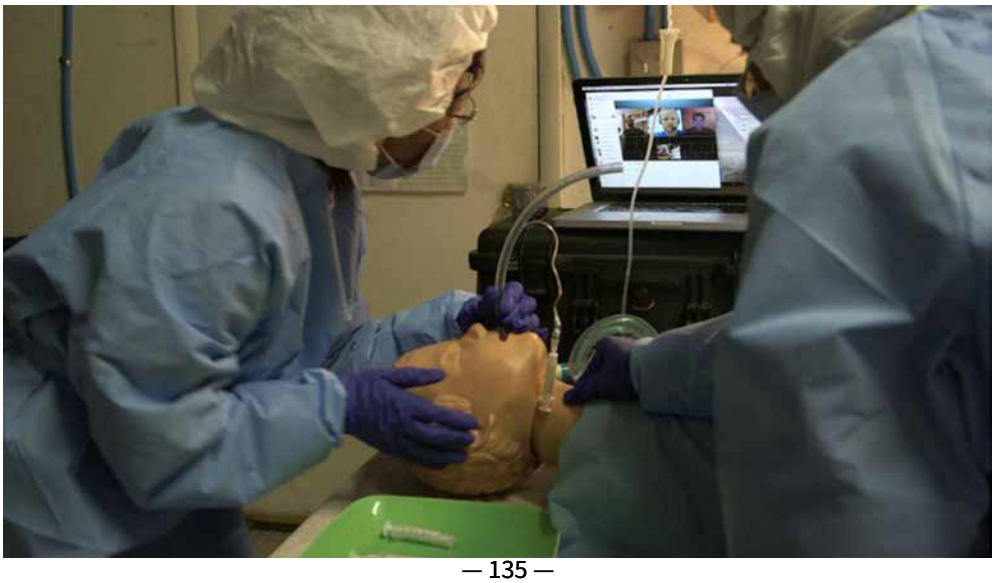
Current medical capabilities of human space ventures (e.g. International Space Station) are inadequate to sustain or stabilize the life of a crewmember in the event of a medical crisis. Further, with the birth of several private space companies (e.g. SpaceX, Bigelow), and the nascent development of a commercial astronaut work-force (e.g. 'Astronauts for Hire'), there is critical need to develop more sophisticated delivery of medical care in space. Although the exploration of Mars is a future goal, it is not too early to consider medical issues for such a distant location. Research has been done on elements needed for space medicine (e.g. miniaturized sensors, telerobotics), but these have not been brought together in a way that can serve these diverse platforms. We have recently founded a collaboration of specialists, the International Space Surgery Consortium (ISSC), in complementary disciplines such as anesthesia/critical care, surgery, and remote medicine, to develop the knowledge base, tools, and protocols for space-based medical delivery platforms. ISSC's first mission was to conduct a pilot project to assess the ability of minimally trained non-medical personnel to deal with a simulated medical crisis while receiving remote guidance from trained anesthesiologists and surgeons in a Mars analogue environment.

Mars Desert Research Station (MDRS) Crew 134 spent 2 weeks immersed in a simulated habitat in remote desert Utah, developing capabilities for future human missions to Mars. A medical scenario was developed requiring rescue and stabilization of a deconditioned astronaut suffering from hemorrhagic shock after limb trauma on the Martian surface. Non-medical crewmembers managed resuscitation, general anesthesia (with RSI intubation), and surgical stabilization of the injured astronaut (torso-mannequin/plus MUSE simulation software). A laptop-based anesthesia protocol was prepared in advance for the crew members to follow. Telementoring support was provided using video-Skype via satellite; this simulated a Martian surface (or Mars orbit) medical crew since an Earth-Mars time delay was not included in this first simulation. The scenario was run twice. During the 2nd run, we collaborated with a team from the European Space Agency sponsored Concordia Station in Antarctica and included a 3 minute delay. The pilot simulations were evaluated via video review (including OSAT-type assessment instruments) and participant debriefing.

Between simulations, anesthesia protocols were refined to accommodate international differences, and the novice crew's limited clinical abilities. Shortcomings included clinical observation and technical skills, and the inability to find and identify instruments. Several cognitive and communication problems occurred due to time delays and bandwidth limitations. Video resolution was sometimes insufficient for the medical team to properly direct the Mars crew. Finally, crew fatigue, psychological stress, and retention were major factors limiting their ability to implement remote medical advice.

ISSC, in collaboration with Concordia Antarctic base, developed a list of lessons learned and techniques to be evolved. Better assessment tools should help to evaluate the deployable clinical knowledge of crew, medical/technical performance, communication, and crisis resource management. The conduct of simulations in academic simulation centers with varied crew complements, equipment and resource availability, and differing levels of remote mentoring can complement simulations in analogue environments. Medical simulations can also be incorporated into long duration analogue missions (i.e. HI-SEAS, FMARS).

ISSC intends to become an international leader in developing and testing such medical capabilities, and facilitating their integration in public and private platforms for space exploration.



EDU 43 (46)

Subsequent Research Funding Among FAER Career Development Award Recipients and Applicants

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Introduction: Understanding the effect of career development awards on the future success and productivity of academic anesthesiologists is of interest to the Foundation for Anesthesia Education and Research (FAER). In 1995, FAER surveyed recipients of FAER funding from 1973-1995 about their subsequent research funding, career progress, and publications. Despite the supportive evidence gathered via the survey, a major limitation was that no data was collected from individuals that applied for, but did not receive funding. Our work addresses that limitation by including both FAER funding recipients and applicants.

Methods: An investigator-designed web-based survey was sent to 830 individuals that applied for FAER career development funding between January 1973-February 2013. The survey included 59-items on demographics, subsequent research funding, leadership positions, mentoring, and career satisfaction. Participants were also asked to upload their curriculum vitae. The primary outcome of interest for the present analysis is subsequent research funding. The Chi square test and Student t-tests were used to compare key variables among FAER grant recipients and applicants.

Results: The overall survey response rate was 38% (N=318), with response rates of 49% and 22% among recipients and applicants, respectively (p<0.001). The majority of applicants and recipients were male (77%) and of white race (74%). A greater proportion of recipients compared to applicants held PhDs in addition to their MD (31% vs. 15%, p=0.01); the two groups did not differ in Masters degree status. FAER grant recipients compared to applicants were significantly more likely to apply for NIH funding (62% vs. 43%, p=0.006), but not other federal, foundation, or commercial/industry funding. With the exception of NIH program project grants, receipt of subsequent research funding as the PI or Co-I of an NIH grant (R01, R21, R03, other R awards, K awards, and other NIH awards) did not differ among FAER grant recipients and applicants. 10% of FAER recipients received an NIH program project grant as compared to 2% of applicants (p=0.04). The proportion of FAER recipients and applicants that received subsequent funding from the federal government (e.g., NSF, DOD, CDC, PCORI, VA, EPA, AHRQ, FDA) did not differ, nor did the receipt of research funding from foundations (32% of recipients vs. 39% of applicants, p=0.30), or commercial/industry (28% of recipients vs. 21% of applicants, p=0.32).

Conclusions: Roughly half of both FAER grant recipients and applicants apply for external grant funding, suggesting that this group is intent in pursuing an academic career. The process of applying for FAER career development funding and receiving feedback may be beneficial to one's early academic career. Though not statistically significant across external funding sources, the greater proportion of FAER recipients that apply for and receive external grant funding could indicate that the receipt of FAER grant funding provides resources and experience that support one to continue to apply for funding. While this study had a strong response rate, the lower response rate from the applicants could indicate that this group contains notable biases, particularly response bias and information bias. Overall, it is encouraging for the field of academic anesthesiologists to note that over 30% of both applicants and recipients subsequently received external grant funding.

	FAER grant recipient	FAER grant applicant	P-value
Male	185 (79.1)	41 (69.5)	0.19
Age	50.3 (9.9)	47.0 (8.4)	0.03
Caucasian	177 (76.0)	38 (65.5)	0.11
MD or equivalent	235 (100)	60 (100)	-
PhD or equivalent	72 (30.6)	9 (14.8)	0.01
MBA	10 (4.3)	1 (1.6)	0.47
MPH	5 (2.1)	4 (6.6)	0.09
MS	30 (12.8)	9 (14.8)	0.68
Other Masters	16 (6.8)	9 (14.8)	0.047
R01 recipient	74 (31.5)	13 (21.3)	0.12
R21 recipient	25 (10.6)	2 (3.3)	0.08
R03 recipient	11 (4.7)	1 (1.6)	0.47
Other "R" grant[a]	15 (6.4)	2 (3.3)	0.54
"K" grant	53 (22.6)	11 (18.0)	0.45
Program project	24 (10.2)	1 (1.6)	0.036
Other NIH grant[b]	16 (6.8)	2 (3.3)	0.38
Foundation funding	76 (32.3)	76 (32.3)	0.30
Other federal funding[c]	35 (14.9)	9 (14.8)	0.98
Commercial/industry	65 (27.7)	13 (21.3)	0.32

[a]Other "R" grant = Small Business Innovative Research (R43/R44), Small Business Technology Transfer (R41/R42)
[b]Other NIH grant = Clinical and Translational Science Award (CTSA), Research Project Cooperative Agreements (U01, U50), Institutional Training Grant (T32)
[c]Other federal funding = NSF, DOD, CDC, PCORI, VA, EPA, AHRQ, FDA

EDU 44 (61)

A Pilot Study to Measure the Impact of Blended Learning on Intern Wellness and Burnout

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Background/Introduction: The incidence of intern burnout approaches 75% [1]. Recognition of the serious issue of intern burnout has catalyzed the development of wellness programs that have shown increases in self-reported well-being [2].

ImPRINT, a yearlong blended curriculum for interns matriculating into anesthesiology residency includes monthly courses based on the "flipped classroom." Assigned didactics are viewed from home, and classroom time is reserved for interactive discussions, part task training, and high-fidelity case simulations. We hypothesized that such a course would promote intern wellness.

Methods: After IRB approval, all anesthesiology interns were invited to participate. A learning management system (Moodle, Perth, Australia) organized the online curriculum. All interns completed a modified Maslach Burnout Inventory in their first and last months of internship. Additionally, for each module, responses to the following statement were recorded: "We define wellbeing as a sense of wholeness and balance (of mind, body, and spirit) that creates an inner resilience to meet the challenges of living without being overwhelmed. On a scale of 1 to 100, please score your wellbeing at this particular moment: 100 being the most and 1 being the least."

Our primary outcome and hypothesis is that higher rates of burnout would be present at the end of intern year and that participation in ImPRINT would be a protective factor. For the primary outcome, we case matched students by gender and age. Our secondary outcome and hypothesis is that participation in the monthly modules would promote an improvement in reported well-being through facilitating a sense of community.

Normality of distribution was determined using the Kolmogorov-Smirnov test. Primary outcome data were normally distributed and were compared using Student's t test. Secondary outcome data, pre- and post- scores for each module, were compared using repeated measures ANOVA with post-hoc Tukey-Kramer multiple comparisons testing. A two-side $p<0.05$ was considered statistically-significant for all analyses.

Results: All 22 anesthesia interns consented and were enrolled in our study. For the primary outcome, a control group of 5 interns did not participate in ImPRINT (group 1) and were case-matched to the interns that did participate in ImPRINT (group 2).

Primary outcome: Mean[SD] score on modified MBI of 2.2[2.9] vs. 2.8[2.8] for groups 1 and 2, respectively ($p=0.749$).

Secondary Outcome: Within module pre- vs. post- scores were not statistically-significant.

Post-hoc power calculation revealed that the sample size of 5 subjects per group had 6% power to detect the 0.6 difference between means at a 0.05 significance level, and a sample size of 34 per group would have been required to achieve 80% power.

Conclusion: Based on this pilot study, a blended learning curriculum did not show a significant impact on intern wellness or burnout. Scores greater than 4 on the MBI suggest a high risk of burnout and the rationale for our post-hoc power calculation. In theory, utilizing classroom time for interactive learning activities promotes socializing and peer-to-peer support. Future research should focus on disseminating a similar curriculum to other institutions and promote multi-center prospective study to further elucidate of the impact of blended learning on physician wellness.

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EDU 45 (66)

Riding the Wave of the Future: Anesthesia Residents and Technology

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Background: The field of anesthesiology has been at the forefront in integrating technology in education[1-3]. The widespread use of mobile technologies has created new platforms in anesthesia education. Limited data exists on how residents in anesthesia use electronic resources for learning and how residents perceive the usefulness of technology in education.

Objective: Our objective was to evaluate the importance of electronic media in resident education among current and incoming anesthesia residents at a major academic institution. Methods: After IRB approval, an email with a survey link was sent to all current (54) and incoming (38) anesthesia residents in the program. The survey contained 10 questions designed to obtain demographic information and use of technological tools, preferred method of study, and interest in being involved in creation of multimedia learning objects. The survey is currently ongoing, so results presented are preliminary. As the survey will be opened to additional incoming PGY1 residents matched into the anesthesia program, an increase in response rate is anticipated.

Results: 47 residents responded and completed the survey, out of a total of 92 residents who were sent the survey for a response rate of 51%. The majority of those who completed the survey were between the ages of 25-35 (94%). The survey results demonstrated that 94% (44/47) of residents currently use smart phones or personal tablet/computers for learning. Of the respondents, only 36% (17/47) stated that they currently use electronic textbooks and videos for learning. However 98% (46/47) of residents stated that if available, they would choose to use videos to learn procedures and anesthesia setups; 78% (36/47) indicated that they would be interested in actively being involved in the making of media related educational materials. To the question regarding what topics the anesthesia residents would like to see in video format, there were over 25 various responses ranging from case specific OR setups to advanced line placement to TEE imaging and regional blocks.

Conclusion: To optimize use of technology in resident education, an understanding of how the learners use electronic media is paramount. The results of this survey demonstrate that the vast majority of residents seek and attempt to utilize electronic media for learning and there is a strong interest for not only for viewing, but also to participate in creating electronic resources for education.

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EDU 46 (67)

Training Factors that Modulate Laryngoscopy Learning

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Introduction: Anesthesiologists must perform direct laryngoscopy and endotracheal intubation in patients with a wide range of anatomies and varying degrees of difficulty. We have developed an airway mannequin that simulates human variability with discrete adjustments in face and jaw length, mouth opening and tongue size (Reference 1). The mannequin can transform into over 500 configurations and take on Cormack and Lehane grade 1, 2, 3 and 4 laryngeal views. In this project, we tested the hypothesis that laryngeal view was a dominant factor in learning efficacy, specifically that mastering intubation on one mannequin with a grade 3 view (only epiglottis visible) would enable intubation of other grade 3 view configurations, regardless of anatomy.

Methods: Subjects, 30 UC San Diego undergraduate students without laryngoscopy or intubation experience, gave written informed consent for the IRB-approved project. Half the subjects practiced laryngoscopy with a Macintosh 3 blade with the mannequin set first to grade 1 view (full glottis available), then to grade 2 (best view cuneiform cartilages). Grade increased when the subject intubated successfully in 30 seconds or less with no procedural faults (excessive force, rocking on teeth, laryngoscope mal-positioned). The second subject group followed this scheme with an added grade 3 configuration. One week after training, subjects performed laryngoscopies on four different grade 3 configurations. The configurations rotated in succession for three rounds, 12 laryngoscopies total. Observations were duration, intubation success and occurrence of procedural faults. Continuous data were analyzed by ANOVA, and ordinal data by non-parametric methods.

Results: In the training phase, laryngoscopy duration decreased progressively with successive trials at each grade level and increased when grade stepped to the next level (Figure). The curves were similar for the two experimental groups at grade 1 and grade 2. Surprisingly, curves for the two groups overlapped in the grade 3 testing phase, even though one group had already been exposed to grade 3 and demonstrated successful intubation at that grade. Furthermore, the performance was worse compared to performance on grade 3 in the training phase and improvement was slower. Specifically, subjects took a greater number of trials to achieve the target duration of 30 seconds, median (interquartile gap) 11 (7-12) compared to 5 (2-6) during training ($P = 0.0005$). This pattern was generally consistent with observations for intubation success curves and error curves (data not shown), i.e. the groups performed worse in the testing session and had slower rate of improvement.

Conclusions: Training on a mannequin with a grade 3 view does not equip trainees to handle any grade 3 view. Thus, all grade 3 views are not equivalent and laryngoscopy skills must depend on the underlying anatomy. Training pattern is also important for laryngoscopy learning, since the rate of improvement slowed when subjects were exposed to several configurations in succession, rather than practicing with just one anatomy.

Reference:

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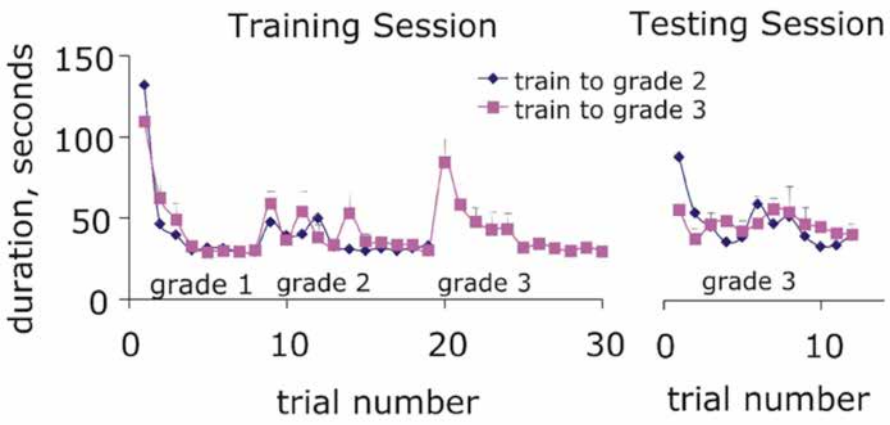

EDU 47 (94)

Simulation Model for the Pregnant Trauma Patient: A Multidisciplinary Team Training Exercise

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A simulation-based inter-professional module was developed for the management of an obstetric trauma patient with the goal of sharing knowledge, increasing respect for each other's professional roles and improving the quality of care delivery.

The multidisciplinary team training scenario was developed using a high fidelity mannequin and fetal monitor. The multidisciplinary team consisted of anesthesiology residents, anesthesia technician, trauma nurse, trauma surgeon, obstetrician and emergency medical personnel (EMR confederate). Anesthesiology residents were STAT paged to a simulated trauma bay where they received report on a patient who was extricated after a head-on collision. The Spanish speaking patient with a gravid uterus modification was awake, alert and communicative, despite suffering an occult pelvic fracture. Learners' ability and skills to communicate with both EMR personnel and the patient that was necessary to obtain pertinent information, complete imaging studies, obtain timely obstetric and trauma surgery consults, displace the uterus despite placement on a backboard, interpret the non-reassuring electronic fetal monitoring, recognize ongoing bleeding despite multiple confounding factors and timely transfusion, management of the airway with a potential cervical injury, placement of invasive lines, and ACLS skills in a pregnant patient were also studied. All sessions were videotaped and analyzed during the post scenario debriefing. Commonly occurring mistakes were detected and addressed. We believe that this simulation unit helped the anesthesiology residents to gain experience in management of patients in an emergency outside of the operating rooms.

EDU 48 (98)

Assessing the Quality of Websites with Anesthesia-related Information for Patients

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Introduction and Purpose: Patients and caregivers are increasingly turning to the Internet for health-related information. Surveys show that majority of patients would look at information on a website if directed to appropriate ones by their anesthesiologist[1]. However, accuracy and reliability of information found on the Internet is questionable. A study by Corcoran et al. established a distinct technical scoring system to help better evaluate websites for anesthesia[2]. The goal of the study was to find good quality websites from unbiased sources to direct patients for information on anesthesia related topics.

Methods: Using Google as a search engine, we used 'Anesthesia Information For Patients' as a search term. We limited our search to the first 250 websites that appeared. We focused on sites with general background information for patients. Websites were eliminated if they referenced each other via hyperlinks and if they were affiliated with any academic institution or any private anesthesia firm. Using Corcoran's technical criteria[2], we assigned scores to each website, with a finalized rating score for each site.

Results: Using the criteria described, we selected eight websites to evaluate.
1. Medline
2. American Society for Anesthesiology/ASA
3. American Association of Nurse Anesthestists/AANA
4. WebMD
5. Society for Ambulatory Anesthesia/SAMBA
6. American Society for PeriAnesthesia Nurses/ASPA
7. Encyclopedia
8. Royal College of Anesthetists/RCA

Overall, websites did poorly in giving background information about anesthesia. Most websites had information regarding complications and procedure (Figure 1). Scoring of websites revealed one that reached an 'excellent' rating, two websites scored a 'very good' rating, and remaining five scored a 'fair or poor' rating.

Conclusions: Based on our findings, we can recommend one website to patient and caregivers for education on anesthesia. Yet, due to the poor scoring of majority of the websites, this review shows that significant work needs to be done on establishing Internet based anesthesia education resources for patients.

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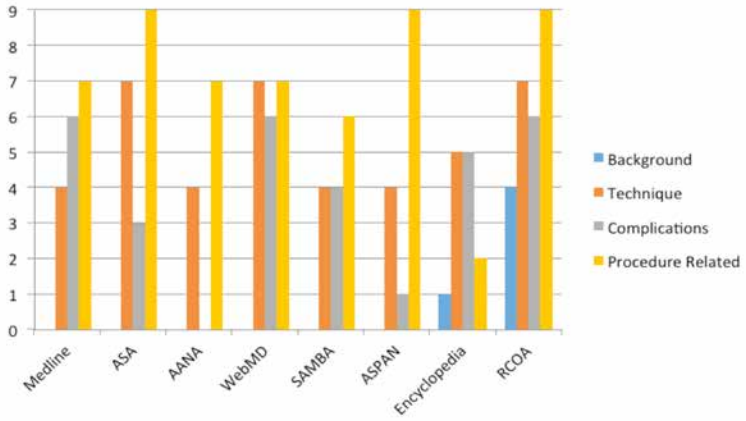

Figure 1: This table represents the technical scoring of the selected websites using the Cocoran criteria. The scoring is as follows with 1 point for each aspect of the criteria, and a bonus point if all aspects are mentioned. The criteria are as follows: 1) BACKGROUND: History/Classification/Biological Explanation (Max Score 4); 2) TECHNIQUE: Sedation/General/Gas Agents/IV Agents/Regional & Blocks/Local Agents (Max Score 7); 3) COMPLICATIONS: PONV/Shivering/Pain/Sore Throat/Hypotension/Awareness/Injury to Teeth/Injury to Nerves/Aspiration/Malignant Hyperthermia/Prolonged Paralysis (Max Score 11, deduction of 1 each if not mentioning aspiration or awareness), and 4) PROCEDURE RELATED: Anesthesia Preop/Medical History/Allergies/Fasting/Monitoring/Canula/Anesthesia Presence/Recovery Area (Max Score 9).

EDU 49 (105)

Entrustable Professional Activities for Anesthesiology Residents: A Novel Approach to the Milestones Project

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Introduction: On July 1, 2014, all Anesthesiology training programs will be expected to utilize performance milestones to evaluate and ultimately deem residents fit to practice independently following graduation. A consensus list of 25 Anesthesiology Milestones was created by an expert taskforce, but little to no instruction has been given on how to use the milestones for meaningful evaluation. To our knowledge there are no publications or described tools related to the use of residency milestones in the anesthesiology literature. Thus, we share our experience in developing a milestone-based evaluation instrument for anesthesiology residents, with the aim of providing ideas for other programs currently still developing their own assessment system.

Methods: Evaluation in our specialty has long been based on direct supervision of clinical activities, both technical and non-technical. Entrustable Professional Activities (EPAs) are critical, observable, everyday clinical activities, that can be used to operationalize competencies and milestones in the context of clinical work, and that reflect both patients' and supervisors' trust in a trainee's ability to competently provide aspects of care. We chose EPAs as the base of our Milestone assessment tools to improve not only resident evaluation, but also to increase directed feedback from faculty and provide goals for resident progression over time.

Results: A general assessment tool for the CA1 year was drafted utilizing EPAs as "Curricular Milestones" and each Curricular Milestone was matched to one of more of the ACGME Milestones (Figure 1). An average anticipated level of supervision, similar to the performance levels described in the ACGME document, was assigned to several time points spread over the CA1 year with progressively decreasing supervision necessary over time. This tool then went through a modified Delphi review, revision and approval process by a taskforce representing junior and senior faculty members from a cross-section of training sites and subspecialties. Similarly structured assessment tools for each subspecialty rotation are currently in development.

Conclusions: The new ACGME system allows programs demonstrating high quality educational outcomes to initiate innovative educational and evaluative freedom outside of specified formal standards. Such liberation also provides opportunity for individual programs to creatively adapt tools for the milestones project. Implementing the ACGME Milestones for Anesthesiology is not as simple as merely creating and using a resident evaluation tool. Curricular changes and intensive faculty development will be necessary to meet the goals of meaningful formative and summative feedback for trainees. The specifics will vary by department and institution, but the common theme should be longitudinal preparation of residents to not only adequately complete rotations and pass board exams, but also to graduate as competent independent physicians. By sharing our experiences with this new system, as a specialty we can create more effective evaluation tools, stronger residency curriculum and ultimately more accomplished graduating anesthesiologists.

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Curricular Milestones	ACGME Reporting Milestones					
	PC	MK[€]	ICS	P	PBLI	SBP
Prepare anesthesia work station for basic OR case						
1. Complete Machine Check	1. PC-9			1. P-1		
2. Prepare standard monitors	2. PC-9					
3. Prepare standard emergency drugs	3. PC-1,5					
4. Set up for case on time	4. PC-1			4. P-1		
Perform pre-operative assessment for ASA 1 & 2 patients receiving monitored anesthesia care or general anesthesia						
1. Adequate presentation to supervisor			1. ICS-2	1. P-1		
2. Obtain relevant medical history and medication lists including previous anesthetics	2. PC-1		2. ICS-1			
	3. PC-1					
3. Perform relevant physical exam including airway exam	4. PC-1		4. ICS-1			
4. Summarize pertinent patient diagnostic data	5. PC-1					
5. Determine if additional diagnostic tests are needed and order/ interpret as appropriate						
6. Understand ASA classification system and assign the appropriate class	6. PC-1					
7. Consent patient for monitored anesthesia care and/or general anesthesia	7. PC-1,2		7. ICS-1	7. P-1,2	7. PBLI-4	
8. Identify potential ethical issues (e.g. Blood transfusion refusal, Do Not Resuscitate, etc.)			8. ICS-1	8. P-3	8. PBLI-4	
9. Include or rely on family members or medical power of attorney in pre-operative discussion and consent process as appropriate	9. PC-1,2		9. ICS-1	9. P-1,2	9. PBLI-4	9. SBP-1

PC = Patient Care; MK = Medical Knowledge; ICS = Interpersonal and Communication Skills; P = Professionalism; PBLI = Practiced-based Learning and Improvement; SBP = Systems-based Practice. Numbers align with specific ACGME Milestones.

€ Medical Knowledge, although an integral part of clinical interactions and care, will be mainly assessed with the In-Training Exam, Anesthesia Knowledge Test, and written board exam.

EDU 50 (121)

Improving Learning Outcomes and Resident Perceptions: The Science and Craft of Anesthesia Milestone-Specific Feedback

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Introduction and General Purpose: While program directors, key faculty and GME administrators have become fully engaged in creating the infrastructure to support the systemic shift to milestones, the level of involvement and input into the process by clinical educators and the residents has been limited. How well evaluation tools are adopted and valued by both the assessors and assesses might be partly influenced by the role they play in the creation of these tools. In addition, residents' perceptions of the quality of feedback the tools can provide to direct the teaching and learning experience will be vital to achieving the intended goals of milestones.

Methods: We describe how a qualitative inquiry to determine resident perceptions of how feedback is currently provided led to the development of a milestones-based feedback and assessment tool. We asked anesthesia residents participating in focus groups about how feedback is currently provided, how is it done well and can be improved, what aspects of the learning environment specific to anesthesia fosters feedback, and how can the ACGME milestones provide a better framework for feedback.

All focus groups were audiotaped and subsequently transcribed in full with all identifiers removed from the transcripts. The transcripts were then thematically analyzed through an iterative process, which included independent coding, a reconciliation process and identifying emergent themes. The thematic analysis focused on elucidating current barriers to effective feedback, determining possible solutions to enhance feedback and identifying how anesthesia milestones can be used support the development of a feedback tool.

Results and Major Findings: We performed five focus groups with 37 participants across the three categorical resident years. Overall, residents felt that they value feedback and expressed a strong desire to incorporate feedback during discussions of their developmental progress across ACGME milestones. In addition, they expressed that feedback is a shared responsibility, and that a cultural shift will be necessary to value giving and receiving feedback. Residents want feedback that is concrete, behavior-specific, based on first-hand observations, in the moment or after an observed session, tailored to residents' developmental levels, and based on resident learning goals with clear follow up plans by attendings.

Based on these results, we developed a short online tool and are currently undergoing a pilot study to determine the impact on residents. The feedback tool is simple and easy to use, hence, there are only two questions: "What is one thing I did well today?" and "What is one thing I can improve upon?" The feedback tool collects written qualitative responses and we are tracking the types of behaviors residents do well and need improvement on, which are mapped on to ACGME developmental milestones for future curricular interventions. Currently, four specialty rotations in anesthesia have begun using the feedback tool, which has been met with enthusiasm from both residents and faculty, anecdotally. We will report preliminary findings on evaluation data using metrics as well as qualitative responses.

Conclusions: We developed a data-driven feedback tool in an effort to enhance how feedback is discussed between anesthesia residents and attendings. Qualitative findings suggest that residents desire feedback that is specific and intentional, the feedback tool tailors feedback to residents needs. Further work is needed, but this pilot study shows how a simple tool can be used to map ACGME milestones and determine gaps across resident behavior and skill levels.

OP 75 (58)

Anesthetic Postconditioning at the Initiation of CPR Improves Myocardial and Mitochondrial Function in a Porcine Model of Prolonged Untreated Ventricular Fibrillation

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Introduction: Anesthetic postconditioning (APoC) has been shown to attenuate myocardial injury following coronary ischemia/reperfusion (IR) in isolated hearts[1] as well as in vivo[2]. We tested the hypotheses that it is similarly effective in attenuating IR injury as ischemic postconditioning[3] in a porcine model of cardiopulmonary resuscitation (CPR) after untreated ventricular fibrillation (VF), and if this is based on improved mitochondrial function.

Methods: In 16 Yorkshire farm pigs isoflurane anesthesia was discontinued prior to induction of cardiac arrest by 15 min VF. Animals were randomized to CPR with automated compression/decompression and an impedance threshold device alone (CON), or APoC with 3 Vol% sevoflurane for 3 min at the initiation of CPR (SEVO). Pigs were first defibrillated after 4 min of CPR. After return of spontaneous circulation (ROSC), isoflurane was restarted at 0.8-1.5 Vol% in both groups. Epinephrine (EPI) was given as a 0.5 mg IV bolus at 3 min and repeated as per protocol. Systolic (SBP) and diastolic (DBP) blood pressure were measured continuously. Left ventricular ejection fraction (LVEF%) was assessed by echocardiography. Animals were euthanized 15 min after ROSC, and mitochondria were immediately isolated from the left ventricle for bioenergetic studies. Statistics: unpaired t-tests, significance assumed at $p<0.05$ (two-tailed).

Results: ROSC was achieved in 5 of 7 CON and 9 of 9 SEVO animals. APoC improved hemodynamics during CPR and post-CPR LVEF%. Mitochondrial ATP synthesis, coupling of oxidative phosphorylation and calcium retention capacity were improved in cardiac mitochondria isolated after APoC.

Discussion: We report preserved cardiac mitochondrial function associated with dramatically improved post-CPR hemodynamics and myocardial function in a porcine model of 15 min cardiac arrest and global ischemia when inhaled SEVO is given for 3 min at the initiation of CPR. These findings may have profound clinical implications on how to best perform advanced cardiac life support in humans in the future.

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CPR method	Parameter	Baseline	2 min CPR	4 min CPR (after epinephrine)	15 min ROSC	Number of shocks to initial ROSC	Total epinephrine dose (mg)	ROSC
CON	SBP	110.3±4.6	43.4±6.2	55.5±4.6	76.3±8.3	7.0±1.5	1.4±0.2	5/7
	DBP	75.9±3.5	16.6±3.0	23.6±1.8	41.0±4.2			
	RAP	1.6±1.2	3.1±0.8	4.1±0.6	11.0±2.6			
	CPP	75.0±3.8	13.5±3.2	19.5±1.9	30.3±7.2			
	LVEF%	61±7			37±4			
SEVO	SBP	128.1±10.0	64.7±5.2*	99.7±7.7*	94.3±10.0	5.1±0.9	0.7±0.1*	9/9
	DBP	90.5±6.8	27.0±3.0*	44.4±3.4*	56.2±6.3			
	RAP	3.6±0.7	2.7±0.6	3.7±1.0	10.0±1.7			
	CPP	86.9±6.9	24.3±2.8*	40.7±3.5*	45.4±8.1			
	LVEF%	63±6			53±5*			

Values are shown as mean ± SEM. CPR was performed with either with ACD and ITD alone (CON, n = 7) or with APoC in addition (SEVO, n = 9). Pressures are given in mmHg, flows in ml min^{-1}. SBP = systolic blood pressure, DBP = diastolic blood pressure, RAP = right atrial pressure, CPP = coronary perfusion pressure, LVEF%: percent of left ventricular ejection fraction (measured after ROSC had been achieved for 10 min). * Mean statistically significantly different between groups with $P < 0.05$ (two-tailed).

OP 76 (32)

Anesthesia-induced Neurotoxicity in the Developing Murine Retina: A Window of Opportunity?

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Introduction: Anesthetic agents cause widespread apoptosis in the developing brain. Vulnerability coincides with the peak in synaptogenesis and anesthesia-induced neurodegeneration has been shown to result in loss of neurons, cognitive impairment, and behavioral abnormalities in a variety of newborn animal models. However, it is unknown if anesthesia-induced neurotoxicity occurs in humans because there is currently no modality to assess for neuronal apoptosis in vivo. The retina is unique in that it is the only portion of the central nervous system that can be directly visualized by non-invasive means. As in the brain, programmed cell death occurs naturally in the developing retina and is critical for synaptogenesis and elimination of aberrant connections. Thus, we hypothesized that anesthetics can cause neurotoxicity in the developing retina. We aimed to demonstrate that isoflurane induces apoptosis in the retina following exposure. Because high resolution non-invasive methods have been developed to image single cell apoptosis within the retina in vivo, we also tested the hypothesis that a systemically injected fluorescent probe could cross the blood-retinal barrier and bind to cells undergoing programmed cell death.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. 7 day old CD-1 male mouse pups underwent 1 hour exposure to isoflurane (2%) or air. Following exposure, retina was harvested and immunohistochemistry for activated caspase-3, -9, and -8 was performed. Cytochrome c release from retinal mitochondria was assessed and steady-state levels of pro- and anti-apoptotic mediators were determined with immunoblot analysis. Significance was assessed with ANOVA and post hoc Tukey's test and significance set at $P<.05$. The types of cells undergoing apoptosis were identified with double labeling immunofluorescence. Retinal uptake and the ability of fluorescent-labeled annexin V to bind to cells undergoing natural cell death and anesthesia-induced apoptosis in the retina were determined following intraperitoneal injection.

Results: Isoflurane activated the intrinsic apoptosis pathway in the inner nuclear layer (INL) and activated both the intrinsic and extrinsic pathways in the ganglion cell layer of the retina. Immunofluorescence demonstrated that bipolar and amacrine neurons within the INL underwent physiologic cell death in air-exposed controls and were the likely targets of isoflurane-induced neurotoxicity. Following injection, fluorescent-labeled annexin V was readily detected in the INL of both air- and isoflurane-exposed mice and co-localized with activated caspase-3 positive cells.

Conclusions: These findings indicate that isoflurane-induced neurotoxicity occurs in the developing retina and lays the groundwork for development of a non-invasive imaging technique to detect anesthesia-induced neuronal apoptosis in infants and children. Thus, in future work, it may be possible to exploit neurodegeneration in the human retina as a surrogate for anesthesia-induced brain neurotoxicity.

OP 77 (68)

Microvesicles Derived from Human Bone Marrow Mesenchymal Stem Cells Improve Survival in E.coli Pneumonia-Induced Acute Lung Injury in Mice and Enhance Monocyte Phagocytosis of Bacteria

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Introduction: Microvesicles (MVs) are plasma membrane bound fragments constitutively released from intracellular compartments or shed from the surface membrane, which retain the phenotype of the parent cell due to the presence of mRNAs, microRNAs and proteins. Recently, investigators have demonstrated a possible therapeutic role of MVs in cell based therapy with mesenchymal stem cells (MSCs) in various inflammatory injuries[1-3]. We demonstrated that MVs derived from human MSCs (MSC-MVs) alone reduced the severity of lipopolysaccharide (LPS)-induced acute lung injury (ALI) in mice through the transfer of keratinocyte growth factor mRNA[1]. However, little is known about the therapeutic effect of MSC-MVs in an infectious model of ALI. In the current study, we hypothesized that MSC-MVs would reduce the severity of ALI and improve survival in E.coli pneumonia by enhancing bacterial clearance.

Methods: MSC-MVs were isolated from the conditioned medium of human MSCs after 48 h of serum starvation using ultra-centrifugation. ALI was induced in C57BL/6 male mice by intra-tracheal instillation of 3 x 106 colony forming units (CFU) of E.coli K1 strain. After 4 h, 90 µl of MSC-MVs (i.e. MVs released by 9 million MSCs over 48 h) or normal human lung fibroblast (NHLF) MVs or 750,000 MSCs were intravenously administered. Total white blood cell (WBC) and neutrophil influx in the BAL fluid was measured at 24 h and mortality at 72 h. In separate experiments, human monocytes and alveolar epithelial type II (ATII) cells were isolated from whole blood collected from healthy volunteers and from human lungs released from brain-dead donors by the California Transplantation Donor Network respectively. Primary cultures of human monocytes were primed with LPS and then treated with either MSCs, MSC-MVs, NHLF-MVs, or PBS before exposure to E.coli bacteria for 90 min. Supernatants were collected to measure CFU bacterial counts and TNF-α and IL-10 levels. Monocytes were collected and stained with Wright-Giemsa to measure phagocytosis % and phagocytic index of bacteria[4]. For uptake experiments, monocytes or ATII cells were cultured with or without an inflammatory injury and exposed to either plasma membrane stain or green fluorescent protein labeled MSC-MVs with or without blocking CD44 Abs. After 24 h, MV uptake was quantified using fluorescence microscopy. Additional experiments were performed using MVs released by MSCs pretreated with a TLR3 agonist, Poly I:C.

Results: Treatment with MSC-MVs improved survival in mice at 72 h (Figure) and decreased total WBC and neutrophil influx into the injured alveolus. MSC-MVs enhanced monocyte clearance of E.coli bacteria by 25% as measured by CFU counts by increasing the phagocytosis % of bacteria by 50%. MSC-MVs treatment also significantly decreased monocyte secretion of TNFα by 32%. Pretreatment of MSCs with Poly I:C further increased the phagocytic index by 50%, decreased TNF-α secretion by 14% and increased IL-10 secretion by 15% compared to monocytes treated with control MVs. In both human monocytes and ATII cells, MSC-MV uptake was dependent on the CD44 receptor during inflammation. Blocking CD44 with a neutralizing Ab significantly decreased MSC-MVs uptake.

Conclusions: MSC-MVs enhanced survival in E.coli-induced pneumonia injured mice and improved bacterial clearance by human blood monocytes. TLR3 agonist pretreatment of MSCs further increased the effects of MSC-MVs on monocytes on inflammation and bacterial clearance. In both injured human monocytes and ATII cells, MSC-MVs uptake was mediated by CD44 receptors. More importantly, MSC-MVs were as effective as MSCs as a therapeutic in ALI from several bacterial pneumonia.

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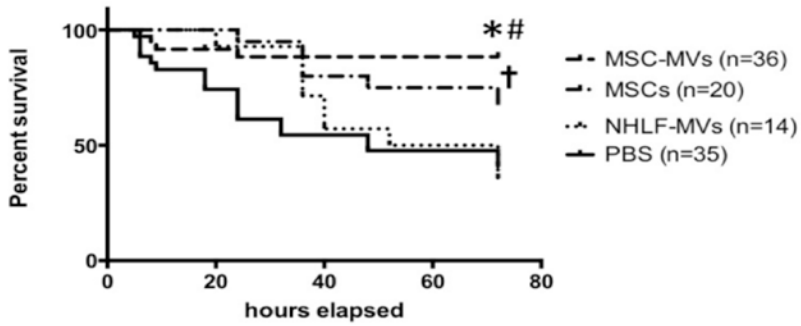

Figure. Microvesicles Derived From Human Mesenchymal Stem Cells Improved Survival in *E.coli* Pneumonia-Induced ALI in Mice. ALI was induced with 3 x 10^6 CFU of *E.coli* bacteria. After 4 h, either MSC-MVs, NHLF-MVs or MSCs was administered intravenously. Survival over 72 h was determined in each group, which was significantly higher in the MSC-MV group (* p<0.002 for MSC-MVs *vs.* PBS, # p=0.04 for MSC-MVs *vs.* NHLF-MVs, and † p=0.02 for MSCs *vs.* PBS using a log-rank test).

OP 78 (70)

Peptidylarginine Deiminase-4 Exacerbates Kidney Ischemia and Reperfusion Injury

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Introduction: Acute kidney injury (AKI) due to ischemia and reperfusion (IR) is a devastating clinical problem and results in renal tubular inflammation and neutrophil infiltration. Peptidylarginine deiminase-4 (PAD4) is a nuclear enzyme that catalyzes the post-translational conversion of arginine residues to citrulline. Interestingly, post-translational protein citrullination is implicated in several inflammatory autoimmune diseases including rheumatoid arthritis and multiple sclerosis[3]. However, the role for PAD4-mediated protein citrullination in renal IR injury has never been examined. Here, we tested the hypothesis that PAD4 contributes to ischemic AKI by exacerbating the inflammatory response after renal IR.

Methods: After IACUC approval, male C57BL/6 mice were subjected to 20 or 30 min renal IR injury. Mice were pretreated with vehicle (1% DMSO) or with 100 mg/kg 2-chloroamidine (a selective PAD4 inhibitor) before 30 min renal ischemia. Some mice were treated with vehicle or with 10 µg/kg recombinant PAD4 (rPAD4) before 20 min renal ischemia. In addition, cultured mouse kidney proximal tubule cells were treated with 5 µg/kg human rPAD4 for 6 hr to test whether rPAD4 directly induces neutrophil chemotactic pro-inflammatory mRNA (MIP-2 and KC) expression. Finally, we performed PAD4 immunohistochemistry in archived surgical kidney specimens from patients subjected to nephrectomy for tumor and from patients subjected to liver-related kidney transplantation (Columbia University IRB determined this as "non-human subject research" under 45CFR46).

Results: Renal IR increased PAD4 mRNA (Fig 1A), protein (Fig 1B) expression and activity (Fig 1C) in mouse kidney. In human kidneys, we found that PAD4 protein expression is localized to the nucleus in non-ischemic kidneys whereas kidneys subjected to ischemia showed cytosolic translocation of PAD4 (Figure 1D). After 30 min renal IR, vehicle-treated mice developed severe AKI with large increases in plasma Cr (Fig. 2). In contrast, mice pretreated with a PAD4 inhibitor had significantly reduced renal IR injury. Further supporting a critical role for PAD4 in generating ischemic AKI, mice pretreated with rPAD4 protein and subjected to mild (20 min) renal IR developed exacerbated ischemic AKI (Figure 2). Consistent with the hypothesis that PAD4 potentiates renal tubular inflammation after renal IR, mice treated with a PAD4 inhibitor had significantly reduced kidney proinflammatory cytokine mRNA (MIP-2, KC, MCP-1 and TNF-α) expression and neutrophil infiltration. Furthermore, mice treated with rPAD4 had significantly increased renal tubular inflammation well as secondary necrosis. Finally, cultured mouse kidney proximal tubules treated with rPAD4 had significantly increased neutrophil chemotactic MIP-2 (16±3 fold) and IL-8 (12±2 fold) mRNA expression compared to vehicle-treated cells (N=4).

Conclusions: Taken together, our studies suggest that PAD4 plays a critical role in renal IR injury most likely via increasing renal tubular cytokine synthesis and inflammatory response after renal IR. Selective inhibition of renal tubular PAD4 activity may reduce the morbidity and mortality arising from ischemic AKI.

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Figure 1

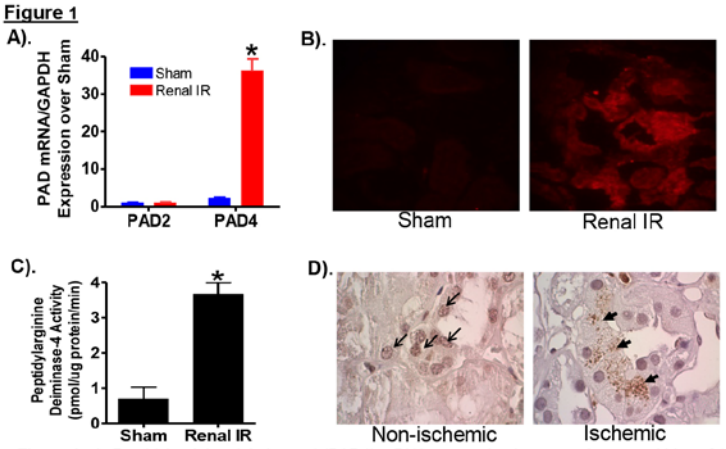

Figure 1. A. Peptidylarginine deiminase 4 (PAD4) mRNA expression increases in mouse kidney 24 hr after renal ischemia and reperfusion (IR) injury (N=4). Note the lack of increase in PAD2 mRNA after renal IR. B. Representative of 4 immunohistochemistry experiments showing increased renal tubule PAD4 protein expression (red florescence, 400X) in mouse kidney 24 hr after renal IR injury. C. Increased mouse kidney PAD4 activity 24 hr after renal IR injury (N=4). D. Representative human kidney PAD4 immunohistochemistry experiments. In kidneys not subjected to ischemia (normal kidney near a tumor), PAD4 is localized in the nucleus (thin arrows). In contrast, kidneys subjected to ~40 min of cold and warm ischemia during transplant surgery show cytosolic translocation of PAD4 (thick arrows). Biopsies taken <5 min after reperfusion (400X). Representative of 3 experiments. *P<0.05 vs. Sham group. Mean±Standard Error shown.

Figure 2

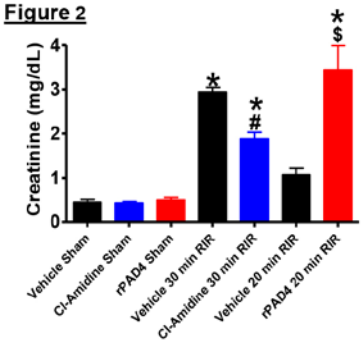

Figure 2. Peptidylarginine deiminase-4 (PAD4) plays a critical role in generating renal ischemia and reperfusion (RIR) injury. C57/BL-6 mice were subjected to sham-operation or to 20 min or 30 min RIR after pretreatment with vehicle (1% DMSO), 100mg/kg Cl-amidine (a PAD4 inhibitor) or with 10 µg recombinant PAD4 (rPAD4). Inhibition of PAD4 with Cl-amidine treatment protected against RIR. In contrast, rPAD4 exacerbated renal injury after IR. *P<0.001 vs. Vehicle Sham. #P<0.05 vs. Vehicle 30 min RIR, $P<0.001 vs. Vehicle 20 min RIR. N=5-6 per group. Data represented as mean±SEM.

OP 79 (76)

Single-Cell Deep Immune Profiling Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates

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More than 100 million surgeries are performed annually in Europe and the United States[1]. This number is expected to grow as the population ages. Convalescence after surgery is highly variable, and delays in recovery result in personal suffering and societal and economic costs[2]. Perioperative care now includes enhanced-recovery protocols and evidence-based practice guidelines largely anchored in observational data[3]. The physiologic and mechanistic underpinnings of surgical recovery remain a "black box" phenomenon, however[4]. Understanding the mechanisms that drive recovery after surgery will advance therapeutic strategies and allow patient-specific tailoring of recovery protocols.

Here mass cytometry, a highly parameterized single-cell based platform that can determine functional responses in precisely phenotyped immune cell subsets[5-9], was employed to identify immune cell subsets and corresponding signaling pathways that correlate with clinical recovery. The expression levels of 35 cell-surface proteins and intracellular phospho-specific epitopes were simultaneously measured at 1 h, 24 h, 72 h, and 6 weeks after surgery in whole blood samples from 32 patients undergoing primary hip arthroplasty (20 males, 12 females, ASA 1-2, age 59 [54; 68], BMI 26.5 [24.4; 28.1]). The simultaneous analysis of 14,000 phosphorylation events across 8 immune cell subsets revealed remarkably uniform signaling responses among patients, demarcating a "trauma-specific" immune signature. When regressed against clinical parameters of surgical recovery, including functional impairment and pain, strong positive correlates were found within signaling responses of specific cell subsets rather than in frequency changes of immune cell subsets (R=0.7-0.8, False Discovery Rate < 0.01). Notably, all signaling responses correlating with clinical recovery occurred in subsets of CD14+ monocytes, underscoring a central role of these cells in processes enabling or disabling recovery from surgery.

These data provide the first set of mechanistically derived immune correlates to guide post-operative care in surgical patients. While the technology used to assess the global immune state (mass cytometry) is relatively new, the diagnostic descriptors of the outcomes can be distilled into a total of six markers that are readily adaptable to a fluorescence-based flow cytometry test. We expect the approach outlined here might eventually be used to distinguish aspects of the immune response that are misdirected or impaired after trauma and that might be targeted for the benefit of patients with predicted poor recovery.

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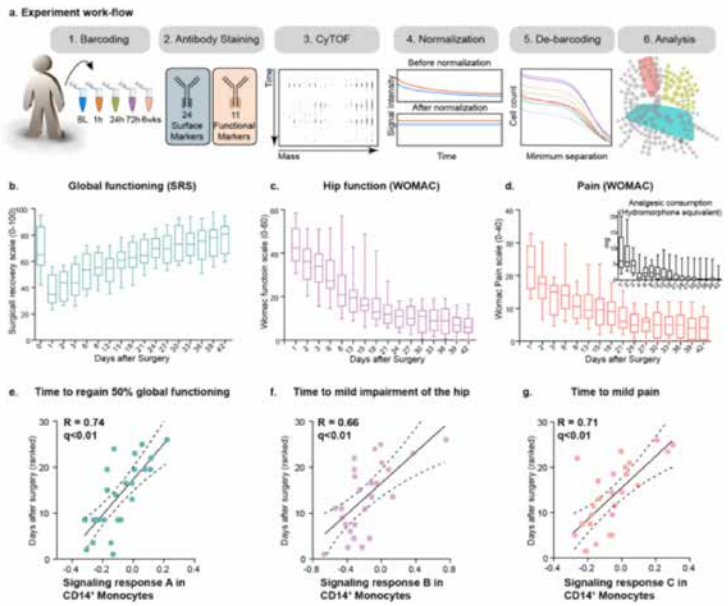

Single-Cell Deep Immune Profiling by Mass Cytometry Reveals Trauma-Specific Immune Signatures that Contain Surgical Recovery Correlates.

a. Experimental workflow. Whole blood samples from six patients undergoing primary hip arthroplasty were collected 1 h before surgery (baseline, BL), and 1 h, 24 h, 72 h, and 6 weeks after surgery. Following red blood cell lysis, leukocyte samples from each patient were barcoded using a unique combination of palladium isotopes (*panel 1*). Barcoded samples were pooled, stained with a panel of 35 antibodies (*panel 2*), and analyzed by mass cytometry (*panel 3*). Raw mass cytometry data were normalized for signal variation over time (*panel 4*), de-barcoded (*panel 5*) and analyzed using a method for unsupervised identification of cellular responses associated with a clinical outcome (*panel 6*).

b-d. Box plots depict medians and interquartile ranges of recovery parameters (*b*) global functioning, (*c*) hip function, and (d) pain for individual patients over the 6-week observation period (bars indicate 10th and 90th percentiles). Global functioning was assessed with the Surgical Recovery Scale (SRS; 0-100 = worst-best function). Pain and impairment of hip function were assessed with adapted versions of the Western Ontario and McMaster Universities Arthritis Index (WOMAC, pain 0-40 = no pain-worst imaginable pain; function 0-60 = no impairment-severe functional impairment). The heat maps reflect significant variability for extent and rate of recovery across all three outcome domains. An inset graph in panel d depicts the median daily analgesic consumption expressed as the dose equivalent of intravenous hydromorphone. Graphical information regarding pain and analgesic consumption are jointly presented, as these variables are inter-dependent.

e-g. CD45^{+}CD66^{-} mononuclear immune cells obtained at BL and at 1 h, 24 h, and 72 h after surgery were clustered using an unsupervised approach. Immune features, which include frequencies and signaling responses of 11 phospho-proteins, were derived for every cluster. SAM Quantitative was used to detect significant correlations between immune features and parameters of clinical recovery (False Discovery Rate, q<0.01). Cell cluster phenotypes were identified using cell surface marker expression. Significant correlations were obtained for signaling responses A, B and C with *(e)* recovery of global functioning, *(f)* function of the hip, and *(g)* resolution of pain. All signaling responses were phosphorylation events present in CD14^{+} monocytes. Signaling responses are denoted A, B and C for technical licensing purposes. STAN-1069PRV, S13-373 Patent under review.

OP 80 (79)

Endogenous Cardioprotection in Normothermic Isolated Hearts from Summer-Active Arctic Ground Squirrels is Enhanced by Intralipid

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Introduction: The degree of injury in response to myocardial ischemia/reperfusion (IR) is species-dependent (1). In this context, hibernating mammals such as the Arctic Ground Squirrel (AGS) have shown a profound resistance to myocardial IR injury compared to Brown Norway rats (BN)(2,3) which could be related to differences in substrate metabolism. We used a normothermic isolated heart model to compare AGS and BN under different metabolic conditions.

Methods: Langendorff-prepared AGS (n = 11) and BN hearts (n = 15) were perfused (80 mmHg perfusion pressure, 37°C) with Krebs solution containing either 7.5 mM glucose alone or 1% intralipid in addition to glucose. After 20 min stabilization and 5 min cardioplegic arrest hearts underwent 45 min global normothermic ischemia and 60 min reperfusion. Left ventricular pressure (LVP) was measured isovolumetrically via a saline-filled latex balloon. Infarct size was determined using TTC staining and cumulative planimetry. Statistics: two-way-ANOVA followed by SNK; alpha = 0.05 (two-tailed). RESULTS: Compared to BN, hearts from AGS displayed significantly improved diastolic and systolic LVP, dLVP/dt as indices of contractility/relaxation, and coronary flow on reperfusion when glucose only was used. When intralipid was added, AGS hearts had a significantly better return of all functional indices compared to glucose only and compared to BN hearts. Intralipid attenuated infarct size more in AGS than in BN.

Discussion: These experiments in summer active AGS feature several novel findings. Even under non-hibernating and normothermic conditions hearts from this hibernating mammal are better protected against IR injury than the best IR-protected non-hibernator, the BN rat. The cardioprotective phenotype, however, seems to strongly depend on substrate utilization: Intralipid leads to a remarkable improvement in return of function and attenuates infarction in AGS, more so than in BN rats. This suggests that not just a decreased metabolic rate during hypothermia and hibernation, but also year-round endogenous mechanisms of cellular protection contribute to prevention of organ injury by IR in AGS. While hibernation is a powerful behavior that reduces energy costs in some mammals, the concept of metabolic fuel switching in the AGS heart with an possible increase in fatty acid (FA) oxidation challenges the current paradigm that increased glucose utilization and inhibition of FA metabolism are favorable during myocardial IR. Further research in this novel cross-species model is warranted to investigate the role of FA metabolism in cardioprotection.

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OP 81 (110)

Ischemic Glomerular Endothelium May Protect Tubular Epithelial Cells from Ischemia

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Introduction: Despite significant advances in perioperative and critical care, acute kidney injury (AKI) still remains an untreatable cause of major perioperative morbidity.[1] Greater understanding of cell-cell interactions may allow better understanding of injury/protective mechanisms leading to therapy. We previously found that glomerular endothelial barrier function fails during ischemia and is protected by estrogen,[2] and hypothesized that barrier failure and endothelial function change might directly affect ischemic tubular epithelial cells.

Methods: 1) Ischemic barrier failure model : Ischemia was modeled by exposing human tubular epithelial (HK2) cells to oxygen-glucose deprivation (OGD) for 16h with 8h reoxygenation-glucose repletion (RGR). Barrier failure was modelled by addition of 25 mg/mL low-endotoxin albumin (representing roughly half the normal serum albumin level) to media at the beginning of OGD. 2)Effects of glomerular endothelial cell (gENC) media on ischemic tubular epithelial cells: gENC were exposed to OGD (or control conditions) for 24h with 8h reoxygenation. Media was filtered through a 0.22μM filter and stored at -80°C. HK2 cells were then exposed to 16h OGD/8h reoxygenation in either normoxic-gENC or OGD-gENC conditioned media. 3)Apoptosis assay: Cells were stained with H33342, propidium iodide, and FITC-Annexin V. Cells were imaged, processed in parallel in NIH ImageJ and counted. %Apoptosis was expressed as(#cells stained with FITC-Annexin V)/(total cells)(per image, 1 image/well). 3 replicates were imaged per experiment, and each experiment repeated 3 times. Multigroup comparison was performed using ANOVA with Holm-Sidak posttesting for multiple comparison. Two group comparisons are Student's two-tailed t-test.

Results: Normoxic exposure albumin for 24h did not significantly increase apoptosis in HK2 cells. Ischemic barrier failure as modeled by OGD/albumin exposure caused significantly greater tubular epithelial apoptosis than OGD alone (34.6±3.35 vs 25.3±3.03%, p=0.043), figure 1. Ischemia-conditioned gENC media was protective of HK2 cells exposed to the ischemic barrier failure model compared with normoxic gENC media (3.4±0.68 vs 11.5±1.11%, p=0.005, figure 2).

Conclusions: A cell-culture ischemic glomerular filtration barrier failure model reliably induces significant apoptosis in tubular epithelial cells. This model may provide further insight into mechanisms of tubular functional alteration and death in AKI. Transferred media from ischemia-challenged gENCs is protective of tubular epithelial cells exposed to modelled ischemic hyperalbuminuria. This suggests that cell-cell crosstalk may influence the outcome of AKI, and in particular, that gENCs may secrete a factor which protects tubular cells from injury. We are currently performing proteomic analysis to identify potential protective factors in ischemic gENC media.

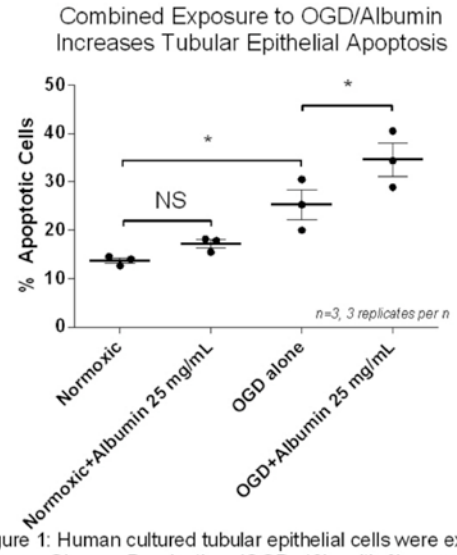

Figure 1: Human cultured tubular epithelial cells were exposed to Oxygen-Glucose Deprivation (OGD, 16h, with 8h reoxygenation) with or without albumin-supplemented media. Albumin supplementation during OGD significantly increased tubular apoptosis over OGD alone, but did not significantly increase apoptosis in normoxic cells. n= 3 experiments with 3 replicates per experiment. Mean±SEM, *p<0.05

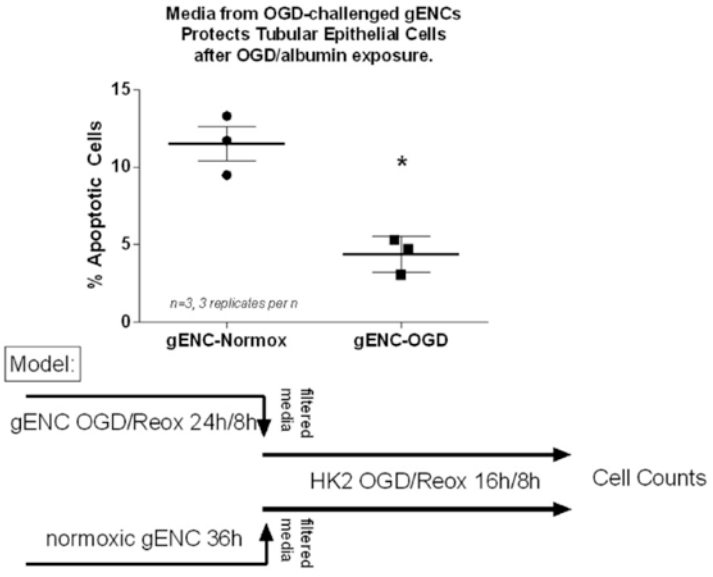

Figure 2: Human cultured tubular epithelial cells (HK2) were exposed to Oxygen-Glucose Deprivation with albumin supplementation (25 mg/mL, OGD, 16h, with 8h reoxygenation) in the presence of media from human glomerular endothelial cells (gENC) preconditioned with OGD (24 h OGD with 6h reoxygenation) or normoxic conditions. gENC media was filtered with a 0.22 μM filter prior to application to HK2 cells. Filtered gENC-OGD media protected HK2 cells from the apoptotic effect of OGD, suggesting a possible soluble mediator of cell-cell crosstalk is released by gENCs in response to ischemia. n= 3 experiments with 3 replicates per experiment. Mean±SEM, *p<0.05

References:

1. Anesthesiology. 107:6. 892-902
2. Am.J.Physiol.Renal Physiol. 303:3. F377-85

O 82 (111)

Exaggerated Acute Lung Injury in Response to Infection in the Metabolic Syndrome

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Introduction and General Purpose of the Study: Recently, we reported severe and persistent postoperative cognitive decline in rats with Metabolic Syndrome (MetaS) due to a dysregulated innate immune response to the aseptic trauma of surgery[1,2]. Whether this increased risk for a postoperative complication extends to infection is not known.

Methods: Adult low capacity runner (LCR; a model of MetaS) and high capacity runner (HCR) rats received intravenous (IV) injection with live Staph aureus (methicillin sensitive Staph aureus, Newman Strain) at the dose of 5×107 CFU/kg. After establishing Staph aureus bacteremia, blood and lungs were collected and analyzed for bacterial load, and markers of inflammation, evidence of lung injury through histological analysis, and measurement of protein levels in bronchoalveolar lavage fluid (BALF).

Results and major findings: Compared with sham rats, rats subjected to Staph aureus infection had increased IL-6 and IL-10 in blood and the lungs, bacterial load in blood, the lungs, and the BALF, and protein level in the BALF; these findings were paralleled by histological evidence of lung neutrophil recruitment and edema. Moreover, IL-6 (blood and the lungs), bacterial load (blood, the lungs, and the BALF) as well as protein level in the BALF were remarkably greater in LCRs than HCRs after infection, while IL-10 (blood and the lungs) were significantly less in LCRs than HCRs.

Conclusions: After staph aureus infection, LCR (MetaS) rats respond qualitatively differently compared to HCR (control) rats with respect to inflammatory markers, bacterial load in blood, BALF, and the lungs, as well as lung permeability. The evidence of less anti-inflammatory and more pro-inflammatory markers in LCR rats suggested that metabolic syndrome state may exacerbate lung response to injury because of an attenuate inflammation-resolving response.

References:

1. Feng X, Degos V, Koch LG, Britton SL, Zhu Y, Vacas S, Terrando N, Nelson J, Su X, Maze M. Surgery results in exaggerated and persistent cognitive decline in a rat model of the Metabolic Syndrome. Anesthesiology. 2013 May;118(5):1098-105.
2. Su X, Feng X, Terrando N, Yan Y, Chawla A, Koch LG, Britton SL, Matthay MA, Maze M. Dysfunction of inflammation-resolving pathways is associated with exaggerated postoperative cognitive decline in a rat model of the metabolic syndrome. Mol Med. 2013 Feb 8;18:1481-90.

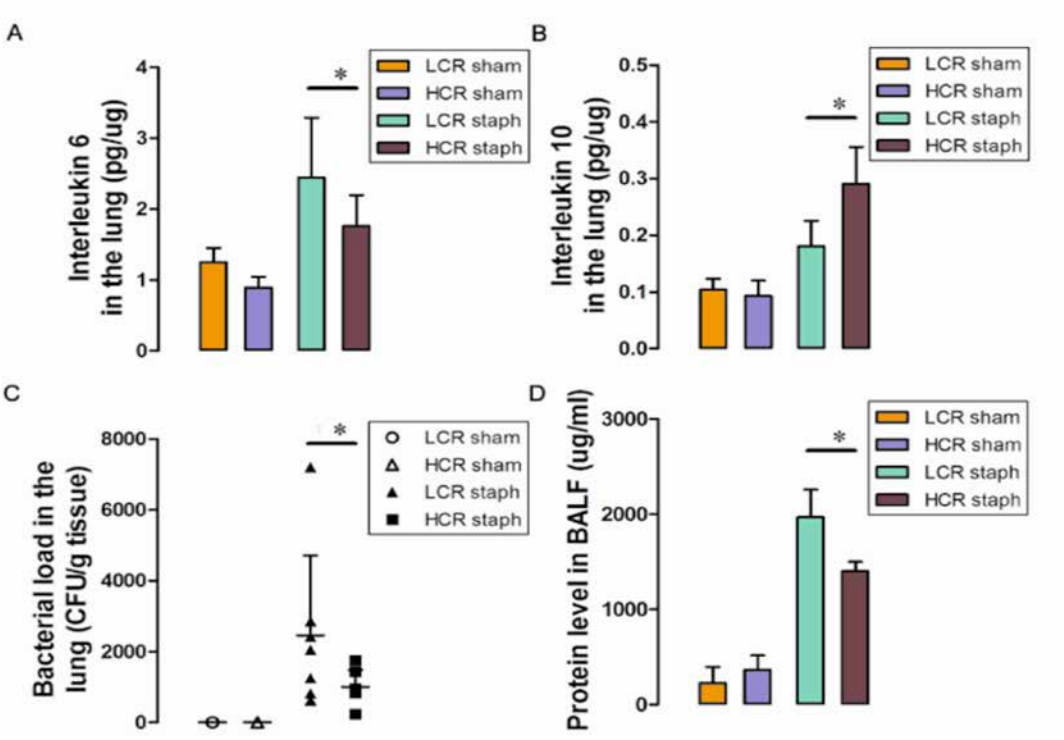

Figure: Changes of Interleukin 6 (A), Interleukin 10 (B), and bacterial load (C) in the lung, protein level in the BALF (D) at 2 days after Staph aureus infection in low (LCR) and high capacity runner (HCR) rats. Data represented as fold change normalized to HCR sham. N=7 for Staph aureus infection groups, and n=3 for sham groups. *P<0.05 for LCR staph group as compared to HCR staph group.

O 28 (41)

The Usefulness of a Cognitive Screening Test in Predicting Postoperative Delirium

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Introduction: Older surgical patients with preexisting cognitive impairment are at risk for developing postoperative delirium[1]. However, screening surgical patients for cognitive impairment has yet to become routine, in part because many cognitive screens are time-intensive.

We investigated the feasibility and prognostic significance of administering a 60-second cognitive screen to older patients before surgery.

Methods: Inclusion criteria were patients >65 years of age who underwent hip, knee, or spine surgery at a university hospital over a 6-month period. Patients were screened with an animal fluency test, which has been shown to be sensitive and specific for dementia in the clinic setting[2] and takes 60 seconds to administer. It was administered before surgery and scores were recorded in the electronic medical record.

An investigator measured postoperative delirium using a chart-based tool[3] and the results were then validated by a second investigator. A third investigator determined which patients had received the cognitive screen preoperatively.

Bivariate analyses were conducted using chi-square and t-tests, and the final model was constructed using multiple logistic regression.

Results: 432 patients met the study inclusion criteria. 82 patients (19%) developed postoperative delirium and 199 patients (46%) received the screen preoperatively. The most common reason for not screening patients was clinician oversight.

Of the 199 patients who were screened, 38 (19%) became delirious postoperatively. Patients with postoperative delirium had worse clinical outcomes than non-delirious patients, including higher ICU admission rate (42% vs. 16%, p<.01), longer length of hospital stay (7.8 days vs. 5.6 days, p<.01), higher rate of institutionalization after discharge (92% vs. 43%, p<.01), and higher mortality rate (5% vs. 0.6%, p=.03).

57 patients (29%) scored low on the cognitive screen. These patients were more likely to develop postoperative delirium than other patients (54% vs. 5%, p<.01). A multiple logistic regression, with postoperative delirium as the dependent variable, identified low cognitive screening score (odds ratio 20.1, 95% CI: 7.9-51.4) and higher ASA classification (odds ratio 3.5, 95% CI: 1.3-9.2) to be the independent predictors.

Conclusions: Our study shows that older patients who scored low on a 60-second cognitive screen before surgery were more likely to become delirious afterward, and that patients who became delirious had worse clinical outcomes overall.

This study also examined the feasibility of adding a cognitive screen to the routine preoperative evaluation. Given that clinician oversight was the most common reason for not administering cognitive screen, education and reinforcement of this practice would likely improve its success.

In conclusion, a brief cognitive screen was able to identify older surgical patients at risk for developing postoperative delirium.

References:

1. Preoperative risk assessment for delirium after noncardiac surgery. JAGS 2006;54:1578-89.
2. Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. Neurology 2004;62:556-62.
3. A chart-based method for identification of delirium. JAGS 2005;53:312-18.

O 29 (101)

Predictors of Postoperative Opioid Use in Veterans Affairs Surgical Patients: A National Level Cross-sectional Analysis

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Introduction: In non- Veterans Affairs (VA) surgical patients, a study has demonstrated that preoperative factors, including legitimate prescribed opioid use, self-perceived risk of addiction, and depressive symptoms were better predictors of prolonged opioid use than postoperative pain duration or severity.[1] While studies have examined the relationship between opioid use and psychological distress in VA medical cohorts[2], little information exists at a population level identifying patterns of preoperative opioid use and predictors for postoperative opioid use in VA surgical patients.

Methods: We examined retrospective data from the electronic medical record for all VA patients who underwent surgery, were discharged alive, and with lengths of stay >1 day for fiscal year 2011. We excluded non-veterans and patients with metastatic cancer. After collecting relevant data (sociodemographic; pharmacy;comorbidities; pain,mental health and substance abuse diagnoses), we further restricted our sample to include patients who took opioids in the 180 days postoperatively. A total of 71,030 patients were available for analysis. Opioid prescriptions were classified as either long- or short-acting. Preoperative opioid use was assessed for the 180 days period prior to admission; patients were stratified as 1) opioid-naïve, 2) taking tramadol only, 3) taking short-acting opioids only on an acute basis (<=90 days in the 180 day period preoperatively) 4) taking short-acting opioids only on a chronic basis (>90 days in the 180 day period preoperatively), or 5) taking any long-acting opioid. Surgery was categorized into families (i.e. abdominal, thoracic, etc.) using ICD-9 surgical procedure codes. We aggregated comorbidities into Charlson scores.

Descriptive statistics were calculated. We then used mixed-model logistic regression to compare the association of long-acting opioid use in the 180 days after discharge and preoperative opioid status adjusting for our independent variables. SAS software, version 9.2 (SAS Institute Inc, Cary, NC) was used for our analyses with two-sided P-values. A $P \leq 0.05$ was considered significant.

Results: Our sample consisted primarily of older men (55-65 years[47.3%]), white (75.1%), urban (61.2%), married (50.4%), who underwent a diverse set of surgeries, and significant comorbidity burden (Charlson score2+=38.7%). Many of our patients had chronic pain (58.1%) and were on adjunctive pharmacotherapy (i.e. tricyclic antidepressants; 53.4%) prior to admission. Our sample included a wide variance for preoperative opioid use: opioid-naïve (46.6%);tramadol only (7.4%); short-acting acute(69.6%); short-acting chronic(20.8%); and any long-acting (6.3%).

Table 1 shows the results of our logistic regression. Independent of other factors, preoperative short-acting acute and chronic and long-acting opioid use were stronger predictors for postoperative long-acting opioid use.

Conclusions: Preoperative opioid use is a better predictor for prolonged postoperative opioid use than pain or affective disorders. More work remains to be done to quantify the risks of adverse postoperative health outcomes for specific pre- and post-operative opioid use patterns.

References:

1. Anesth Analg Sep;115(3):694-702.
2. JAMA. 2012;307(9):940-947

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O 29 (101), continued

Table 1. Logistic regression predicting taking a long-acting opioid in the 180 days after discharge

Variable	Odds Ratio	95% CI	P-value
Preoperative opioid use			
Tramadol only	1.24	(0.99 - 1.56)	0.065
Short-acting acute	1.85	(1.61 - 2.13)	<.001
Short-acting chronic	3.61	(3.15 - 4.13)	<.001
Long-acting	184.22	(159.97 - 212.15)	<.001
No opioids	Ref.		
Had chronic pain in the year before admission	1.03	(0.92 - 1.16)	0.570
Had chronic pain in the 180 days after discharge	1.64	(1.50 - 1.80)	<.001
Surgery type			
Digestive	1.17	(1.00 - 1.38)	0.055
Integumentary	1.99	(1.59 - 2.51)	<.001
Male genital	0.66	(0.50 - 0.88)	0.005
Musculoskeletal	1.49	(1.30 - 1.72)	<.001
Nervous	1.31	(1.05 - 1.64)	0.016
Other	1.03	(0.87 - 1.23)	0.733
Respiratory	1.67	(1.31 - 2.13)	<.001
Urinary	1.02	(0.81 - 1.29)	0.863
Cardiac	Ref.		
Charlson-Deyo-Quan comorbidity index			
Score 1	1.15	(1.02 - 1.30)	0.018
Score 2+	1.55	(1.39 - 1.73)	<.001
Number of outpatient visits in the year before admission	1.00	(1.00 - 1.00)	0.081
Had a prior inpatient surgery in the 180 days before admission	1.16	(0.93 - 1.45)	0.188
Taking adjunctive pain pharmacotherapy in the 180 days before admission	0.95	(0.86 - 1.06)	0.389
Taking adjunctive pain pharmacotherapy in the 180 days after discharge	1.52	(1.36 - 1.70)	<.001
Age at surgery			
54 years and younger	2.01	(1.76 - 2.30)	<.001
55-65 years	1.66	(1.48 - 1.85)	<.001
66 years and older	Ref.		
Urban-rural status			
Highly rural	0.95	(0.68 - 1.34)	0.780
Rural	0.92	(0.83 - 1.01)	0.081
Urban	Ref.		
Female	0.75	(0.62 - 0.91)	0.004
Homeless	1.11	(0.94 - 1.31)	0.229
Currently married	0.93	(0.85 - 1.01)	0.093
American Indian	1.18	(0.80 - 1.73)	0.399
Asian	0.85	(0.55 - 1.31)	0.467
Black	0.74	(0.65 - 0.83)	<.001
Hispanic	0.74	(0.61 - 0.91)	0.005
Substance use diagnosis in the year before admission	1.35	(1.19 - 1.54)	<.001
Nicotine use diagnosis in the year before admission	1.03	(0.92 - 1.14)	0.637
Bipolar diagnosis in the year before admission	1.09	(0.88 - 1.36)	0.439
Major depression diagnosis in the year before admission	1.24	(1.08 - 1.42)	0.003
Post traumatic stress disorder diagnosis in the year before admission	0.91	(0.81 - 1.03)	0.125
Generalized anxiety diagnosis in the year before admission	0.83	(0.60 - 1.14)	0.238

O 30 (102)

Statistical Modeling of Perioperative β-Blockade Risks Accounting for a Heterogeneous Treatment Effect: Possible Long Term Mortality Benefit with Agents other than Metoprolol

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Introduction: Randomized controlled trials (RCTs) have reported decreased risk of perioperative myocardial infarct (MI) with the initiation of perioperative β-blockade. However, the POISE trial also reported increased risk of stroke and 30 day mortality.1,2 Recently published observational studies suggest metoprolol is more strongly associated with perioperative stroke and increased short term mortality than other β-blockers.3-5 No previously published meta-analysis has accounted for this heterogeneity of treatment effect. The theory tested in this work is that β-blockers other than metoprolol have a different risk profile than metoprolol when used to initiate perioperative β-blockade.

Methods: A literature search identified applicable RCTs with placebo controls (See Table). Outcomes of interest included non-fatal MI, non-fatal stroke, short term (≤ 30 day) and long term (> 6 month) mortality. Due to the binary nature of these outcomes, it was possible to reconstruct patient level data for analysis, as compared to traditional meta-analyses which utilize published summary statistics. All analyses were completed with mixed-effects logistic regression models stratified by metoprolol versus other β-blocker. This stratification accounts for heterogeneity of treatment effect due to medication. If unaccounted for, this heterogeneity would result in artificially narrow confidence interval estimates. An additional advantage of this modelling strategy is that it allows control data to be partially shared across study groups. Random intercepts were incorporated into each model to account for differing baseline event rates among studies.

Results: Forest plots of our meta-analysis results are presented in Figures 1-4. When stratified by medication, a decreased risk of MI ($p = 0.001$) and an increased risk of non-fatal stroke ($p = 0.037$) were observed with metoprolol treatment. These results are very similar to POISE results, likely due to the large sample size of the POISE trial. A sensitivity analysis for POISE data revealed that the remaining metoprolol data show no significant evidence for decreased MI or increased stroke. No significant short term results were found with other β-blocker treatment.

A likelihood ratio test was performed comparing the relative risk of long term mortality with metoprolol versus other β-blocker treatment, resulting in $\chi2(1) = 3.875$ ($p = 0.049$). Per Cochrane review guidelines, this test should be interpreted at the $p = 0.1$ level, suggesting a difference in these treatments. Further analysis shows that β-blockers other than metoprolol are associated with a statistically significant decrease in long-term mortality (OR = 0.50, 95% CI 0.26 - 0.95, $p = 0.034$).

Conclusions: These results support the theory that initiation of perioperative β-blockade with β-blockers other than metoprolol is associated with a different risk profile than metoprolol. The failure in past analyses to account for heterogeneous treatment effects has obscured evidence of a possible protective effect on long term mortality of β-blockers other than metoprolol. These analyses highlight the importance of thoughtful statistical model selection by illustrating the possibility of obtaining misleading results if an inappropriate model is employed. Future studies should utilize a range of dose and administration parameters and include long term follow up to allow estimation of the risk/benefit profiles of these agents.

References:

1. N Engl J Med 335:1713, 1996
2. Lancet 371:1839, 2008
3. Anesthesiology 119:777, 2013
4. Anesthesiology 119:1340, 2013
5. Anesthesiology 114:824, 2011

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O 30 (102), continued

Study	Reference	Size	Endpoints	Protocol	Dosing based on vitals
Mangano et al.	N Engl J Med 335:1713 1996	200	Survival analysis of mortality with 2year postop follow up	5-10mg IV atenolol 30 mins prior to surgery, directly after surgery, and daily every 12h until hospital discharge or 7 days (may substitute 50-100mg oral once/day)	Yes
Bayliff et al.	Ann Thorac Surg 67:182, 1999	99	Mortality and MI before hospital discharge	10mg propranolol q 6h before surgery and 5 days postop	No
EUROCARE	Circulation 101:1512, 2000	324	Mortality and MI for 7 months	25mg carvedilol bid 24 h preop and continuing for 5 months postop	No
POBBLE	J Vasc Surg 41:602, 2005	103	Mortality, Stroke, and MI for 30 days postop	man	No
DIPOM	BMJ 332:1482, 2006	921	Survival analysis of mortality, stroke, and MI for 6-30months postop	100mg oral metoprolol (CR/XL) 2h preop until hospital discharge or 8 days	Yes
MaVS	Am Heart J 152:983, 2006	496	Mortality and MI at 30 days, Composite endpoint at 6 months	25-100mg oral metoprolol 2h preop, 25-100mg oral or 0.2 mg/kg until hostpital discharge or 5 days	No - Weight
Neary et al.	Surgeon 4:139, 2006	38	Mortality at hospital discharge and 1-year postop	1.25mg IV atenolol immediately prior to surgery, up to 4 additional 1.25mg IV doses administered intraop at 30 min intervals, 5mg IV bid or 50mg po 1/day for 7 days postop	Yes
BBSA	Anesthesiology 107:33, 2007	219	Mortality, stroke, MI at 30 days and mortality at 6 months	5-10mg oral bisoprolol 3 hours preop continued until discharge or 10 days postop	Yes
POISE	Lancet 371:1839, 2008	8351	Mortality, stroke, MI at 30 days postop	100mg oral metoprolol (CR/XL) 2-4 hours preop, 100mg postop if needed, 100mg 6 hours postop, 200mg starting 12 hours after postop dose continuing 1/day for 30 days	Postoperative only

Short term non-fatal myocardial infarct meta-analysis

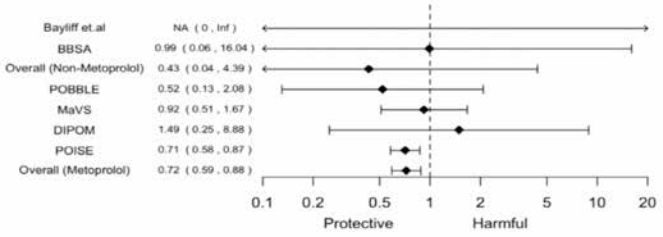

Figure 1: Forest plot displaying the odds ratios of each included study and also displays the pooled metoprolol and non-metoprolol odds ratios. 95% confidence intervals are included in parentheses. NA denoted inestimable values due to low event rate.

Short term non-fatal stroke meta-analysis

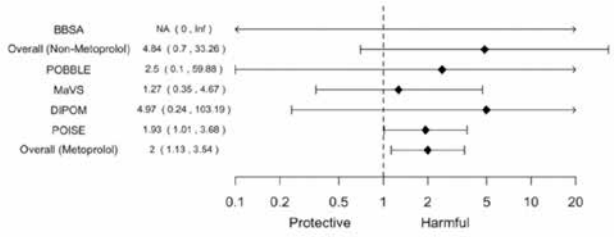

Figure 2: Forest plot displaying the odds ratios of each included study and also displays the pooled metoprolol and non-metoprolol odds ratios. 95% confidence intervals are included in parentheses. NA denoted inestimable values due to low event rate.

Short term mortality meta-analysis

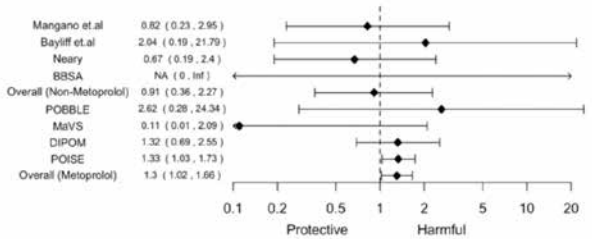

Figure 3: Forest plot displaying the odds ratios of each included study and also displays the pooled metoprolol and non-metoprolol odds ratios. 95% confidence intervals are included in parentheses.

Long term mortality meta-analysis

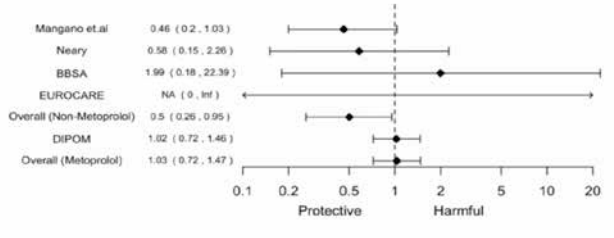

Figure 4: Forest plot of long term mortality meta-analysis. Odds ratios and associated 95% confidence intervals are visually presented for each study included in the long term mortality meta-analysis and for combined study groups stratified by metoprolol and non-metoprolol. Data were taken from the end of each included study's follow-up period, therefore the results of this analysis can be interpreted as mortality at some average follow-up time > 6 months. Notice that the metoprolol group includes only one study, the DIPOM study.

O 31 (103)

Variations in the Risk of Acute Kidney Injury Across Intra-Abdominal Surgery Procedures

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Background: Perioperative acute kidney injury (AKI) is a major complication after general surgery leading to increased morbidity and mortality. However, the literature on perioperative AKI focuses mainly on cardiac and major vascular surgery. Among non-cardiac general surgery procedures, intra-abdominal general surgery has been identified as high-risk for developing AKI[1], but intra-abdominal general surgery comprises a heterogeneous group of procedures and the variations in AKI within this group and its impact on 30-day mortality are not well characterized.

Methods: After IRB exemption, we conducted a retrospective, observational cohort study using American College of Surgeons National Surgical Quality Improvement Program data from 2005-2010. Patients in 16 intra-abdominal general surgery procedure categories were identified based on CPT codes (N=464,787) (Table 1). Those with preoperative renal insufficiency or dialysis were excluded. AKI was defined as an increase in the creatinine level of >2 mg/dl and/or dialysis within 30 days of the procedure. Relative risk regression modeling was used to assess the relative risks of AKI across the procedures. Preoperative comorbidities and demographic characteristics were identified and their associations with procedure type were determined with $\chi 2$ tests. The relationships between surgical procedure, AKI, and 30-day mortality stratified by procedure type were assessed using relative risk regression.

Results and Major Findings: The overall incidence of AKI among intra-abdominal surgery patients was 1.1%, which varied from 0.2% in appendectomy and 0.3% in gastric bypass patients to 2.6% in small bowel resection and 3.5% in exploratory laparotomy patients. Known risk factors were generally more prevalent in the procedures with the highest risks of AKI, including older age and higher rates of emergency procedures, congestive heart failure, and ascites. After accounting for procedure, comorbidities, and intraoperative factors, the lowest adjusted risk ratio (aRR) (compared to the reference group colorectal resection) for AKI ranged from 0.24 in appendectomy to 1.17 in small bowel resection, reflecting a nearly 5-fold difference in the adjusted risk of AKI in the highest risk category compared to the lowest risk category. The overall risk of 30-day mortality in our cohort was 2.2%, with a mortality rate of 1.8% in patients that did not develop AKI compared to 31% in those that developed AKI (Table 1). After adjusting for comorbidities and operative factors, overall, AKI was associated with a 3.5-fold increase in the risk of 30-day mortality [aRR 3.48, 95% confidence interval (CI) 3.26-3.71]. Among individual procedures, the estimated aRR of 30-day mortality associated with AKI ranged from 1.80 (95% CI 1.56, 2.08) in exploratory laparotomy to 35.5 (95% CI 20.5, 31.3) ingastric bypass.

Conclusions: Among patients undergoing intra-abdominal general surgery procedures, there is a differential risk of AKI and 30-day mortality based on the type of procedure and it is clear that the risk of adverse outcomes is not uniformly distributed among this group. This highlights the importance of preoperative risk stratification and identifies procedure type as a significant risk factor for AKI and 30-day mortality.

References:

1. Anesthesiology 110:505–15 (2009).

Table 1. Thirty-day mortality rates and adjusted risk of acute kidney injury on 30-day mortality among patients undergoing intra-abdominal general surgery, American College of Surgeons-National Surgical Quality Improvement Program, 2005-2010.

	30-day mortality rate (%)			Risk of AKI on 30-day mortality		
	No AKI	AKI	Total	aRR[a]		95% CI
Gastric bypass and volume reduction	0.1	15.1	0.2	35.5[b]	*	[20.5, 61.3]
Appendectomy	0.2	22.0	0.2	22.2	*	[12.6, 38.9]
Local excision of large intestine lesion (not endoscopic)	3.7	50.0	4.5	13.5[c]	*	[5.87, 31.2]
Other hernia repair	0.6	20.7	0.8	10.2	*	[7.28, 14.3]
Laparoscopy	1.5	42.6	1.7	7.11	*	[3.69, 13.7]
Other OR gastrointestinal therapeutic procedures	2.1	34.4	2.6	6.67	*	[5.34, 8.32]
Cholecystectomy and common duct exploration	0.7	24.8	0.9	5.71	*	[4.19, 7.78]
Ileostomy and other enterostomy	3.4	28.5	3.9	4.66	*	[3.61, 6.01]
Gastrectomy, partial and total	3.8	43.6	4.5	4.60	*	[3.15, 6.72]
Procedures on spleen	2.4	36.2	3.0	4.24	*	[2.51, 7.14]
Other OR lower GI therapeutic procedures	1.3	25.9	1.6	3.51	*	[2.44, 5.04]
Colostomy, temporary and permanent	5.4	33.3	5.8	3.30	*	[2.23, 4.88]
Small bowel resection	5.6	46.2	6.6	3.24	*	[2.77, 3.79]
Colorectal resection	2.9	28.9	3.4	2.94	*	[2.64, 3.28]
Excision, lysis peritoneal adhesions	3.8	37.4	4.2	2.57	*	[1.73, 3.84]
Exploratory laparotomy	11.1	46.7	12.4	1.80	*	[1.56, 2.08]
Total	**1.8**	**31.4**	**2.2**	**3.48**	*	**[3.26, 3.71]**

AKI, acute kidney injury; aRR, adjusted risk ratio; OR, operating room; GI, gastrointestinal.

[a]Adjusted risk ratio of 30-day mortality with AKI vs. 30-day mortality without AKI. Multivariable model includes the following covariates: age, female sex, body mass index, emergency, functional dependence, dyspnea, ventilator dependence, chronic obstructive pulmonary disease, pneumonia, current smoking, hypertension, congestive heart failure, coronary revascularization, peripheral vascular disease, stroke, bleeding disorders, ascites, estimated glomerular filtration rate, hematocrit, cancer, chronic steroid use, preoperative sepsis, and intra/postoperative transfusion.
[b]In gastric bypass patients, model includes: age, sex, body mass index, emergency, functional dependence, dyspnea, smoking, hypertension, coronary revascularization, bleeding disorders, chronic steroid use, preoperative sepsis, estimated glomerular filtration rate, hematocrit, and perioperative transfusion.
[c]In local excision of large intestine lesion patients, the risk ratio is not adjusted for covariates.
*P < 0.05

O 32 (104)

Decreasing Packed Red Blood Cell Utilization through Computerized Decision Support at a Large Academic Medical Center

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Introduction and General Purpose of the Study: Transfusion of packed red blood cells (PRBCs) has been associated with increased morbidity and mortality in a variety of clinical settings[1-6]. Evidence points to PRBC transfusion as an independent risk factor for the development of acute kidney injury, prolonged ventilatory support, and increased mortality[7].

Wide variation in blood product utilization between institutions and between providers within a single institution demonstrates failure to engage in an evidence-based approach to blood product transfusion[8-10]. In a large multicenter study conducted throughout Australia, decision support through computerized physician order entry (CPOE) systems was shown to be a more effective strategy for reducing inappropriate transfusion than educational modules or one-on-one provider coaching alone[11]. We hypothesized that the implementation of evidence-based CPOE decision support guiding PRBC transfusion with alerts triggered by clinical and laboratory parameters would achieve a significant hospital-wide decrease in inappropriate PRBC transfusions.

Methods: Based on evidence-based practice standards for the hospitalized population, a multidisciplinary focus group created two unique algorithms for PRBC transfusion in the setting of symptomatic anemia. These protocols were incorporated into the CPOE of the institution's preexisting ordering system. CPOE pop-up alerts were designed to analyze the patient record and hemodynamic status (patient's age, recent saturation, and the most recent serum Hb) and trigger one of two pop-up alerts to remind practitioners of the recent PRBC transfusion recommendations when an order is placed outside of evidence-based guidelines for symptomatic anemia.

The main outcome measure was the number of PRBC transfusions per patient-discharge. Secondary outcomes, including hospital mortality rates, ICU length of stay, hospital length of stay, and non-PRBC transfusions per patient-day were also collected. Utilization of non-PRBC blood products, including FFP, platelets, cryoprecipitate, was followed as a secondary outcome.

Severity of illness for the study population was determined during the control and study intervals. Case-mix index (CMI), based on the Centers for Medicare and Medicaid Services cost weights, was assessed monthly for the hospital and compared during the control and study intervals to further ensure that study findings were not attributed to differences in severity of illness between cohorts.

Results and Major Findings: After staged implementation of the CPOE protocol, PRBC transfusions decreased by 27% across the medical center. This resulted in a savings of ~$92,000/month. Transfusion of other blood products decreased by 20% despite no CPOEs for these.

Conclusions: In our large cohort study, we observed a significant decrease in PRBC and non-PRBC transfusions hospital-wide after implementation of a new, PRBC-specific, CPOE algorithm aimed at alerting providers of PRBC transfusion orders placed outside of evidence-based guidelines.

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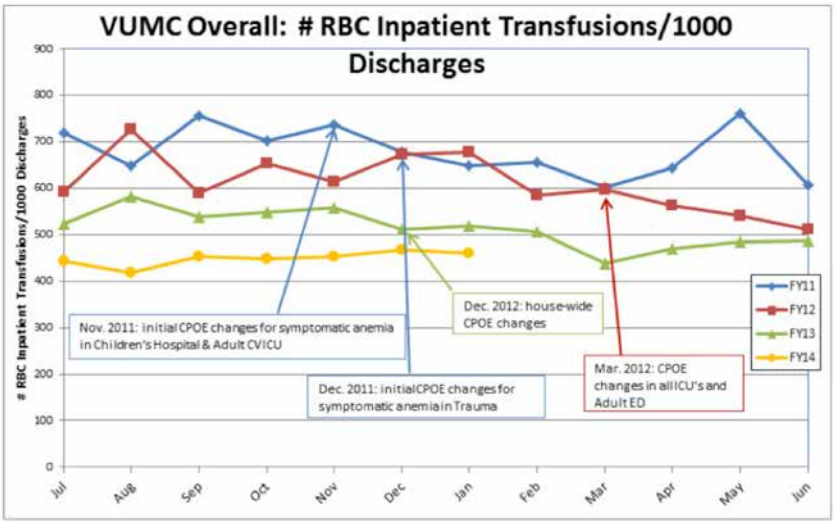

O 33 (106)

Are Hemoglobin Oximetry, Vital Signs and Laboratory Values Able to Predict Emergency Transfusion in Trauma Patients?

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A non-invasive decision support tool for emergency transfusion decisions would benefit acute trauma patient resuscitation. We tested whether 15 minutes of continuous pulse-oximetry-derived continuous hemoglobin measurements [SpHb] can predict emergency blood transfusion better than conventional oximetry, vital signs and invasive point-of –admission laboratory testing (POA). Hypothesis: Trends of non-invasive SpHb oximetric features predict emergency transfusion better than pre-hospital or admission shock index [SI =heart rate (HR) / systolic blood pressure (SBP)] or inclusion of POA laboratory measures. Methods: We enrolled direct trauma patient admissions ≥ 18 years with pre-hospital SI > 0.6. We continuously collected vital signs (conventional and SpHb oximetry, HR, BP) for 15 minutes and recorded any blood transfusion (pRBC) up to 3 hours after admission. Eighteen pRBC prediction models, including combinations of pre-hospital and admission vital signs, SpHb , conventional oximetry and POA, were selected by logistical regression. Models included features of vital signs, pulse oximetry (including slopes, 'dose' and direction of change in SpHb, maximum, median values etc.) and POA laboratory values (lactate, hematology, coagulation, glucose, creatinine). Predictions were compared via Area Under Receiver Operating Curve (AUROC) by De Longs method and validated by leave-one-out training and testing.

Results: Six hundred seventy-seven trauma patients were enrolled. Fifty-nine patients received blood within 3 hours. Conventional pulse oximetry, vital signs and POA laboratory testing predicted emergency blood need with AUROC of 0.96 which was significantly better ($p < 0.015$) than use of SpHb, vital signs and POA testing (AUROC 0.93). Predictions of pRBC based on monitoring trends of SpHb oximetric features and vital signs alone (AUROC 0.84) were not better than trends of conventional pulse oximetry features and vital signs (AUROC 0.83, $p = 0.43$)(see Figure below). Models including POA laboratory values were better than those without these values. No models including SI (and the need for blood pressure) were significantly better than those without SI. Training and testing of conventional pulse oximetry and POA laboratory model showed < 10 % differences with overall performance AUROC of 0.95 whereas models with SpHb had ~ 20% difference between training and testing, indicating less model robustness.

Conclusions: Pulse oximeter features together with routine laboratory POA samples had significantly better prediction of urgent pRBC transfusion within 3 hours of patient admission compared to predictions including trends and absolute values of SpHb and POA samples. Models containing only features of conventional pulse oximeter were robust and no different than models including SpHb. Both models containing oximetry features performed better at predicting pRBC use than pre-hospital SI, the current best non-invasive vital signs transfusion predictor.

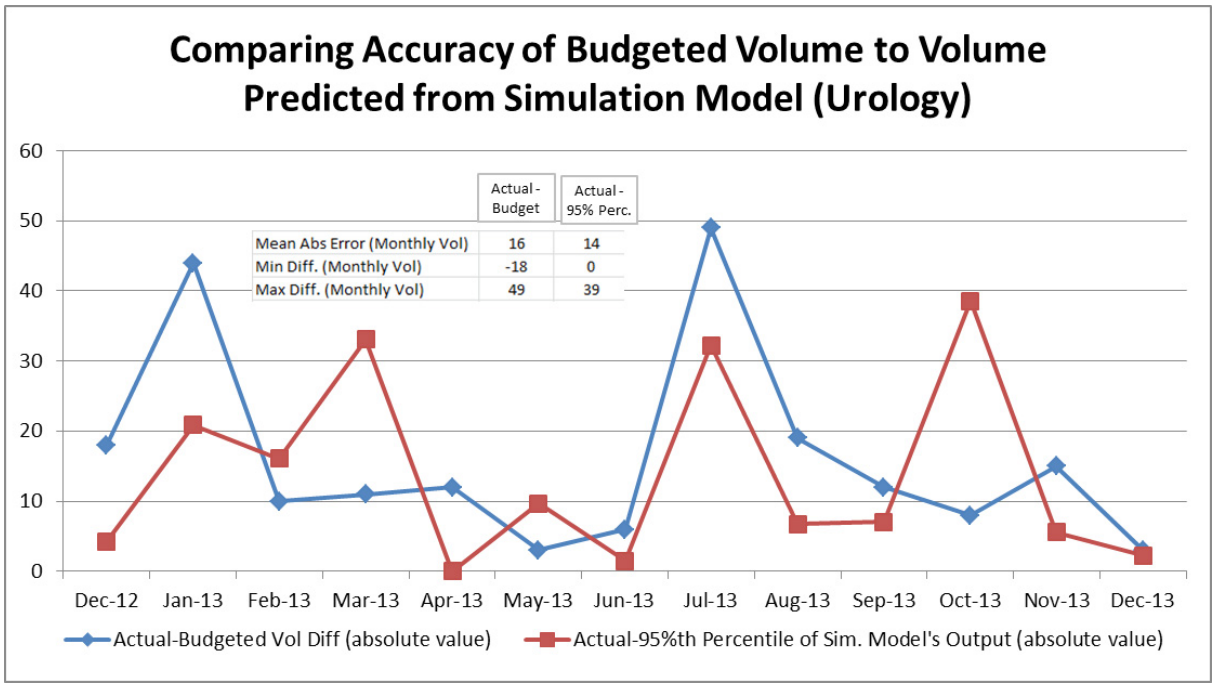

Figure: Shows Area Under the Receiver Operating Curve (AUROC) of emergency blood use predictions resulting from data analysis of trends slopes and direction of 18 different prediction models (on X axis). AUROC of each model is shown on Y axis, for prediction of transfusion within 3 hours after admission using 15 minute SpHb and conventional oximetry continuous data collection with pre-hospital and admission vital signs, +/- point of admission (POA) routine blood sampling. Model 6 using conventional pulse oximetry, vital signs (VS) and POA laboratory values was significantly better at predicting emergency transfusion ($p < 0.015$) than Model 8 using hemoglobin oximetry values (SpHb). Model 2 using conventional pulse oximetry + VS alone was no different ($p = 0.43$) to Model 5 including SpHb.

O 35 (118)

Improving Nutrition Practices at the Time of Tracheal Extubation in the ICU: The Extubation Safety Quality Improvement Project

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Background: Removal of the endotracheal tube in the intensive care unit (ICU) is commonly associated with undesired events including interruption of enteral nutrition and increases in serum glucose variability, as well as failed extubation leading to re-intubation. Re-intubation following planned extubation is independently associated with poor outcomes, including ventilator associated pneumonia, increased length of stay and death. In the context of a quality improvement (QI) initiative in a cohort of mechanically ventilated ICU patients (medical, surgical, and neuroscience) of a large academic medical center, we implemented an extubation safety algorithm to help reduce the occurrence of re-intubation, enteral nutrition interruptions and glycemic instability.

Methods: Eligible ICU patients were prospectively enrolled into pre and post-intervention cohorts over two consecutive six-month periods separated by a two-week rollout period. The QI intervention consisted of education of designated ICU team leaders who then disseminated the algorithm. Training materials illustrating the decision algorithm were distributed and a computerized extubation orderset created to streamline implementation. We compared frequencies of re-intubation, tracheostomy, enteral feed interruptions and glycemic events in the peri-extubation period between the pre and post-intervention cohorts.

Results: During the study period, 934 patients were included in the baseline period and 799 patients during the QI implementation period (Table 1). The baseline group was, on average, two years younger and had lower SAPS II scores than the QI implementation group. Out-of-operating room re-intubation was required for 20% of baseline patients compared to 18% in the post-intervention group (p = 0.24), with a reduction also seen in the occurrence of tracheostomy. Among patients receiving enteral nutrition, the interruption of continuous feeds in the 24 hours preceding and 24 hours following extubation was 1712 ± 199 min in the baseline period (n=428) and 1465 ± 129 min in the QI implementation period (n=369) (P=0.29). A significant decrease in the use of IV dextrose and a trend toward reduced insulin needs was observed in the QI implementation period. There were no significant changes in post-extubation aspiration events, mean glucose level or hypoglycemic events between the two study periods.

Conclusions: In the ICUs of one academic medical center, the use of an extubation safety algorithm led to similar occurrences of failed extubation and reduced tracheostomy procedures, with an overall increase in the proportion of patients successfully extubated. Although non-significant, nutrition interruption and insulin use tended to be reduced and use of IV dextrose decreased. These changes were not accompanied by an increase in aspiration events or changes in hypoglycemic events. It cannot be determined definitively if these observed changes are due to the QI-intervention or unrelated differences in study cohort characteristics or in clinical practice. Similarities in enteral feed interruptions between the groups may represent low uptake of the nutrition component of the algorithm.

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Table 1: Study Demographics and Results

Demographic Variables	Pre-intervention	Post-intervention	P value
Cohort size, n (%)	934 (53.9)	799 (46.1)	
Age, mean (SD)	49.4 (17.9)	51.4 (17.5)	0.02*
Male, no. (%)	375 (58.4)	267 (41.6)	0.29
BMI, mean (SD)	27.8 (7.0)	28.5 (8.8)	0.06
SAPS II, mean (SD)	41.9 (14.8)	34.9 (12.1)	<0.01*
Injury Severity Score, mean (SD)	21.2 (12.4)	21.0 (12.9)	0.84
Outcome Variables			
Patients requiring re-intubation, n (%)	179 (19.9)	146 (18.3)	0.24
Patients requiring tracheostomy, n (%)	43 (4.4%)	20 (2.0%)	0.03*
Aspiration events, n (%)	4 (0.9%)	1 (0.3%)	0.31
Minutes of pre-extub. feed interruption [a], mean (SD)	471 (170)	346 (93)	0.52
Minutes of post-extub. feed interruption [a], mean (SD)	1620 (190)	1490 (140)	0.60
Pre-extub. IV dextrose use (mL), mean (SD)	1130 (43)	980 (46)	0.02*
Post-extub. IV dextrose use (mL), mean (SD)	1230 (49)	1012 (46)	<0.01*
Pre-extub. mean glucose, mean (SD)	141 (36)	140 (43)	0.59
Post-extub. mean glucose, mean (SD)	134 (33)	133 (37)	0.59
Pre-extub. lowest glucose, mean (SD)	122 (31)	121 (34)	0.91
Post-extub. lowest glucose, mean (SD)	120 (27)	119 (30)	0.45
Pre-extub. hypoglycemia[b], n (%)	10 (1.1)	6 (0.8)	0.49
Post-extub. hypoglycemia[b], n (%)	3 (0.4)	4 (0.5)	0.57
Pre-extub. insulin use, n (%)	255 (27)	195 (24)	0.17
Total hospital charges, thousands of dollars, mean (SD)	176 (175)	175 (163)	0.85
ICU length of stay, days, mean (SD)	9.9 (13.9)	9.4 (11.0)	0.42
Hospital length of stay, days, mean (SD)	16.8 (20.1)	17.0 (18.2)	0.84
Hrs between first extub. and re-intub., mean (SD)	91 (191)	62 (94.5)	0.07
Total intubation duration, hrs, mean (SD)	77 (112)	81 (139)	0.50
First intubation duration, hrs, mean (SD)	53.3 (68.1)	56.3 (79.5)	0.4

[a]The pre-extubation period is 24 hours prior to extubation and the post-extubation period is 24 hours after extubation.
[b]Hypoglycemic events defined as glucose less than 70 mg/dL
*Significant p-value of <0.05

Abstract Author Index

Abstract Author Index

Abstract Author Index

Abstract Author Index

Abstract Author Index

CO 63 (59) **Patient-Reported Perioperative Non-Routine Events**
Matthew B. Weinger, MD, MS, Vanderbilt University Medical Center, Nashville, Tennessee

EDU 44 (61) **A Pilot Study to Measure the Impact of Blended Learning on Intern Wellness and Burnout**
Louise Wen, MD, Stanford University Hospital and Clinics, Palo Alto, California

CS 68 (71) **Resident Travel Award**
Genetic Deletion of the GABA-A α4 S ubunit Leads to Increased Airway Resistance and Inflammation
Gene T. Yocum, MD, Columbia University, New York, New York

EDU 45 (66) **Riding the Wave of the Future: Anesthesia Residents and Technology**
Lara N. Zador, MD, Yale University School of Medicine, New Haven, Connecticut

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