AUA 63RD ANNUAL MEETING

May 19-20, 2016

HOSTED BY

University of California, San Francisco

Hilton San Francisco Union Square
San Francisco, California

SYLLABUS

AUA
Association of University Anesthesiologists

UCSF
University of California
San Francisco

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Welcome to the Association of University Anesthesiologists 63rd Annual Meeting!

Welcome to the Association of University Anesthesiologists 63rd Annual Meeting, hosted by the University of California, San Francisco, in the vibrant city of San Francisco, California. The Annual Meeting Planning Committee, Drs. Charles W. Emala, Robert R. Gaiser, Michael A. Gropper, and Jeanine P. Wiener-Kronish, has developed robust content that will provide attendees with the valuable knowledge they need to advance their practice of academic anesthesia.

New this year, AUA attendees will benefit from an additional educational opportunity at the Aligned Meeting Day on Saturday, May 21 at the International Anesthesia Research Society 2016 Annual Meeting and International Science Symposium as part of their AUA registration fee. Our colleagues from the Anaesthetic Research Society in the United Kingdom will also join us this year at the AUA 63rd Annual Meeting.

Annual Meeting Highlights include:

Thursday, May 19

The **Scientific Advisory Board (SAB)** will highlight original research in the clinic and laboratory during two **Oral Sessions** and the first of two **Moderated Poster Discussion Sessions** during the meeting. The **Host Program Session** will showcase groundbreaking programs and developments that make the University of California, San Francisco unique. Take time to network and relax during the **AUA Social Event Reception**, from 6:30 pm to 9:30 pm, hosted by the University of California, San Francisco, at the California Academy of Sciences, one of the largest natural history museums in the world, and enjoy hearty refreshments, live music and access to the museum.

Friday, May 20

The **SAB** will continue the momentum with **two more engaging Oral Sessions** as well as the second **Moderated Poster Discussion Session**. The **Educational Advisory Board (EAB)** will focus on thought-provoking topics during two sessions on ***The Science of Communication*** and ***Publication of Education Research***. The **President's Panel: *How to Produce Successful Researchers*** will conclude the day with helpful tips on being an effective researcher from successful researchers currently in the field. Join us for a **Lively Reception** with the *British Journal of Anesthesia* and the Anaesthetic Research Society, from 6:00 pm to 7:30 pm, at the Hilton San Francisco Union Square.

Saturday, May 21

The Aligned Meeting Day will present a wide selection of invigorating education sessions, highlighting pioneering topics in anesthesia, celebrating advances in education, science, research and the art of anesthesiology.

Featured Sessions include:

- **T.H. Seldon Memorial Lecture: *Reproducible Research: Impact in Evidence-Based Decision Making*** with Dr. John P.A Ioannidis
- **Celebration of the Science of Anesthesiology Symposium: *Protective Lung Ventilation in the Operating Room***
- **IARS, AUA and SOCCA Science Symposium: *State of the Art Review: Endothelial Glycocalyx in Anesthesia Practice and Critical Care Medicine***
- **A Dedicated Scholars' Program**
- **Scholars' Program Reception – 5:00 pm to 6:00 pm**
- **IARS Alignment Reception – 6:00 pm to 7:30 pm**

We are confident you will find this time together meaningful and gratifying while discovering all that San Francisco has to offer. We look forward to sharing this time with you in San Francisco!

Sincerely,

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

Welcome from the University of California, San Francisco

We are delighted to host the Association of University Anesthesiologists 63rd Annual Meeting, and are excited to share our city, department and university with you. Although San Francisco needs little introduction, we look forward to showing you parts of the city that you may not have seen. We hope that you have the opportunity to explore the art, architecture, culture and culinary delights of our unique city.

San Francisco's unparalleled cultural diversity has underpinned the UCSF Department of Anesthesia and Perioperative Care's storied history of innovation in anesthesia, critical care, and pain medicine since the department's inception in 1958 by its first chair, Stuart Cullen. For ten of the last eleven years, the Department has been ranked #1 nationally in NIH-funded research. Important discoveries by the department include the first use of CPAP in premature infants, key contributions to the pharmacology of muscle relaxants and inhaled anesthetics, first demonstration of intraoperative transesophageal echocardiography, and many others. We have robust research programs, spanning the range from ion channel structure and function, to clinical and translational research.

Our trainees have become leaders across the country. We are particularly proud of our residency program, which provides unequalled diversity of experience in a major university medical center (Moffitt-Long Hospital), the San Francisco Veterans Hospital, Mount Zion Hospital, the UCSF Orthopedic Institute, and the brand new Benioff Children's, Betty Irene Moore Women's and Bakar Cancer (NIH-designated Cancer Center) Hospitals in the Mission Bay neighborhood. This month, the new Zuckerberg San Francisco General Hospital and Trauma Center will open. We offer ACGME fellowships in Critical Care Medicine, Pain Management, Cardiac Anesthesia, Obstetric Anesthesia, Pediatric Anesthesia, and many additional non-ACGME fellowships. The faculty is dedicated to teaching, nurturing, and mentoring the next generation of leaders.

The host program has adopted the theme of the UCSF campus, which is Precision Medicine. Although it's tempting to think of precision medicine as a laboratory endeavor, we take a much broader view. At UCSF, we are driven by the idea that when the best research, the best teaching, and the best patient care converge, we can deliver breakthroughs that help heal the world.

The host program features four outstanding leaders of our university. Talmadge E. King, Jr., MD, is Dean of the UCSF School of Medicine, and Professor of Medicine. Aside from being one of the world's leading authorities on interstitial lung disease, he is a visionary leader of the school, and a champion of diversity in academic medicine. Joe L. DeRisi, PhD, is Professor and Chair of the UCSF Department of Biochemistry and Biophysics. He is a Howard Hughes Investigator and recipient of a MacArthur Genius Award. DeRisi has pioneered innovative technologies using DNA micro-arrays for rapid pathogen detection. Diane Havlir, MD, is Professor of Medicine and Chief of the HIV/AIDS Division, at Zuckerberg San Francisco General Hospital. She leads the UCSF HIV programs, which have served as a model for both the United Nations and U.S. AIDS efforts. Stephen L. Hauser, MD, is Professor and Chair of the Department of Neurology at UCSF. He is internationally renowned for his work on immune mechanisms of multiple sclerosis.

We look forward to welcoming you to San Francisco, and are committed to ensuring you have an engaging and rewarding meeting.

Michael A. Gropper, MD, PhD
Professor and Chair, Department of Anesthesia and Perioperative Care, UCSF

Office of the Mayor
City & County of San Francisco

Edwin M. Lee

GREETINGS FROM THE MAYOR

As Mayor of the City and County of San Francisco, it is my pleasure to join in welcoming everyone attending the Association of University Anesthesiologists (AUA) 63rd Annual Meeting, the International Anesthesia Research Society (IARS) 2016 Annual Meeting and International Science Symposium, and the Society of Critical Care Anesthesiologists (SOCCA) 29th Annual Meeting and Critical Care Update. For the first time ever, these three organizations are aligning and bringing together over 1,500 of the world's leading anesthesia educators and investigators to San Francisco. Our City is proud to host you all.

The work that all of you have committed to – in your everyday lives and in the next few days as you share ideas – is a significant contribution to the vitality of our communities. Your many efforts have positively impacted the landscape of anesthesiology, whether your role is academic or working in clinics and laboratories. Thank you for your outstanding dedication to striving for greater knowledge and better practices for anesthesiology professionals towards the health, well-being and overall vitality of all.

San Francisco is proud to be a leader in access to world-class health care and a trailblazer in innovative breakthroughs. I commend AUA, IARS, SOCCA and all the individuals who helped to ensure these events will be a great success. Congratulations and best wishes for productive meetings and success in your future endeavors.

With warmest regards,

Edwin M. Lee
Mayor

1 Dr. Carlton B. Goodlett Place, Room 200, San Francisco, California 94102-4641
(415) 554-6141

Planning Committee & Program Faculty

Planning Committee

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and Perioperative Care, Professor, Physiology,
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Henry Isaiah Dorr Professor of Research
and Teaching in Anaesthetics and Anaesthesia,
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Anesthetist-in-Chief, Massachusetts
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Planning Committee & Program Faculty, *continued from page 6*

Program Faculty *Continued*

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Diane Havlir, MD
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Talmadge E. King, Jr., MD
Dean, School of Medicine, Vice-Chancellor for Medical Affairs, Professor of Medicine, University of California, San Francisco, San Francisco, California

Meghan Lane-Fall, MD, MSHP
Assistant Professor of Anesthesiology and Critical Care; Co-Director, Penn Center for Perioperative Outcomes Research and Transformation; Core Faculty, Center for Healthcare Improvement and Patient Safety; Perelman School of Medicine; Senior Fellow, Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania

Alex Macario, MD, MBA
Professor of Anesthesiology, Perioperative and Pain Medicine and, by courtesy, of Health Research and Policy, Stanford University, Stanford, California

Rebecca D. Minehart, MD, MSHPEd
Assistant Professor of Anaesthesia, Harvard Medical School; Assistant Program Director, Anesthesia Residency Program; Program Director, Obstetric Anesthesia Fellowship Program; Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Mark D. Neuman, MD, MSc
Assistant Professor of Anesthesiology and Critical Care, Senior Fellow, Leonard Davis Institute for Health Economics, University of Pennsylvania; Attending Anesthesiologist, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

Maxine Papadakis, MD
Professor, Medicine, Associate Dean for Students, Chair, Journal Oversight Committee for *Academic Medicine,* University of California, San Francisco, San Francisco, California

Davinder Ramasingh, MD
Associate Professor, Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, California

Edward Sherwood, MD, PhD
Professor and Vice-Chair for Research, Department of Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tennessee

Jeanine P. Wiener-Kronish, MD
President Elect, Association of University Anesthesiologists,
Henry Isaiah Dorr Professor of Research and Teaching in Anaesthetics and Anaesthesia, Department of Anesthesia, Critical Care and Pain Medicine, Harvard Medical School, Anesthetist-in-Chief, Massachusetts General Hospital, Boston, Massachusetts

**As of press time and subject to change.*

Continuing Medical Education (CME) Information

Activity Overview

Findings from new research and the evolution of anesthesiology practice based on emerging evidence create an inherent gap between existing practice and new practice models. The purpose of the Association of University Anesthesiologists (AUA) 63rd Annual Meeting is to provide an evidence-based and clinically-oriented educational activity that will improve competence and performance in the anesthesiology specialty, resulting in improved patient care and outcomes.

Target Audience

The AUA 63rd Annual Meeting is designed to address the continuing medical education needs of anesthesiologists, anesthesiologists-in-training, and anesthesia investigators in academic, clinical and laboratory settings.

Educational Objectives

As a result of participating in this live CME activity, learners will be able to:

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

Accreditation Statement

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

CME Credit

The International Anesthesia Research Society (IARS) designates this live activity for a maximum of *14.5 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure

The International Anesthesia Research Society (IARS) makes every effort to develop CME activities that are independent, objective, scientifically balanced presentations of information. The IARS has implemented mechanisms requiring everyone in a position to control content to disclose all financial relationships with commercial interests. Disclosure of any or no relationships is made available in advance of all educational activities. The IARS evaluates, and if necessary, resolves any conflicts of interest prior to the start of the activity. Individuals who refuse or fail to provide the required disclosures are disqualified from being a planning committee member, teacher, or author of CME, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.

Disclaimer

The information provided in this CME activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.

Commercial Support

This CME activity is supported entirely by the Association of University Anesthesiologists. There is no commercial support for this activity.

General Information

Welcome to the Association of University Anesthesiologists 63rd Annual Meeting at the Hilton San Francisco Union Square in San Francisco, California!

Over the next two days, we hope you will take advantage of the wide variety of learning opportunities during the Educational Advisory Committee, Scientific Advisory Committee and Host Institution programs while networking with your peers and colleagues. Plus, be sure to stay on Saturday, May 21 for a special Aligned Meeting Day at the IARS 2016 Annual Meeting and International Science Symposium! AUA registrants attend as part of their AUA registration fee.

HEADQUARTERS HOTEL

Hilton San Francisco Union Square, 333 O'Farrell Street, San Francisco, CA 94102

Phone: 415-771-1400

All education sessions will take place on the Lobby Level and Ballroom Level at the Hilton San Francisco Union Square.

The **Program Schedule**, included in your registration packet, will list the locations for all education sessions, lunches and special events. Aligned Meeting Day materials will be included as well and require advanced registration.

REGISTRATION

AUA Onsite Registration Hours

Thursday, May 19, 7:00 am – 5:30 pm

Friday, May 20, 6:00 am – 6:00 pm

Your registration materials will be available for pickup at the Registration Desk in the East Lounge on the Ballroom Level of the hotel.

Name Badges

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

Dress Code

The dress code for the AUA 63rd Annual Meeting is business / business casual.

CME Information

The International Anesthesia Research Society (IARS) designates this live activity for a maximum of *14.5 AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Participants will receive an email at the conclusion of the course with a link to an online evaluation survey. **Please complete the survey within 2 weeks from receipt of that 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.

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).

Aligned Meeting Day at the IARS 2016 Annual Meeting

Aligned Meeting Day education sessions and special events include the T.H. Seldon Memorial Lecture, Celebration of the Science of Anesthesiology Symposium, IARS, AUA, & SOCCA Science Symposium, Scholars' Program – Day 1 Education Sessions, Scholars' Program Reception and Alignment Reception. The Aligned Meeting Day sessions at the IARS 2016 Annual Meeting are included in the registration fees for the AUA and SOCCA Annual Meetings and required advanced

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registration. CME for the Aligned Meeting Day sessions may only be claimed by full, two-day, or one-day registrants of the IARS 2016 Annual Meeting. Tickets will be provided for entrance to all Aligned Meeting Day sessions.

Annual Meeting App

IARS 2016 is the official interactive app for the AUA 2016 Annual Meeting.

With the IARS 2016 app, you can view the complete event schedule, discover sessions, and get detailed speaker information. Stay informed with the highlights of the day through the app's Activity Feed, providing useful comments, photos, ratings and more. Expand your professional network and make the most of your Annual Meeting experience!

Visit the Apple Store or Google Play Store to download the IARS 2016 app today, using the free WiFi provided in the meeting spaces during the Annual Meeting.

Your username for the app is the email with which you registered for the Annual Meeting, and the password for all users is IARS2016.

Internet Availability

Complimentary wireless internet is available in all the AUA scheduled meeting rooms. Open your internet browser and click on the network labeled "Hilton Events." When prompted for an access code, enter "AM2016." Please no streaming or video downloading. Please note that the password is case sensitive.

Photography Release

The AUA plans to take photographs at the Annual Meeting and reproduce them in the AUA news or promotional materials, whether in print, electronic or other media, including the AUA website. By participating in the AUA 2016 Annual Meeting, you grant the AUA the right to use your name, photograph, and biography for such purposes.

Smoke-Free Policy

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

Social Event

If you pre-registered for the AUA Social Event, please bring your ID as it is occurring during a 21 and over event at the California Academy of Sciences.

Special Services

If you have a special need, please contact the AUA staff at AUA@iars.org or stop by the Registration Desk onsite.

San Francisco Travel Tips

Time Zone

San Francisco follows Pacific Time (PT).

Transportation

San Francisco is full of walkable neighborhoods if you don't mind climbing hills! Bay Area Rapid Transit (BART) and regular Muni buses also offer easy access to all neighborhoods. Muni is the local transit system which consists of buses, lightrail, and street cars. Taxis, Lyft and Uber cars are also readily available throughout the city. Click here for more information.

Weather

Temperatures seldom rise above 70° F (21°C) or fall below 40°F (5° C). San Francisco has a temperate climate with mild weather year-round. Morning and evening fog rolls in during the summer months. August through October is the warmest time of the year. Dressing in layers is recommended. The weather can change by the hour (and also within just a few blocks), so keep a light jacket handy. Comfortable shoes are a must as well.

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Moderated Poster Discussion Sessions

Poster viewing is scheduled for each break. The following Scientific Advisory Board (SAB) and Educational Advisory Board (EAB) members will moderate the Moderated Poster Discussion Sessions:

Nabil J. Alkayed, MD, PhD, Oregon Health & Science University, Portland, Oregon

Brenda Bucklin, MD, University of Colorado, School of Medicine, Aurora, Colorado

Wei Chao, MD, PhD, The University of Maryland School of Medicine, Baltimore, Maryland

Holger K. Eltzschig, MD, PhD, University of Colorado School of Medicine, Aurora, Colorado

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

Thomas F. Floyd, MD, Stony Brook University, Stony Brook, New York

George Gallos, MD, Columbia University, New York, New York

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

Tomoki Hashimoto, MD, University of California, San Francisco, San Francisco, California

Stephanie B. Jones, MD, Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, Massachusetts

Jae-Woo Lee, MD, University of California, San Francisco, San Francisco, California

Roy C. Levitt, MD, University Of Miami, Miami, Florida

Manuel Pardo, MD, University of California, San Francisco, San Francisco, California

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

Matthias L. Riess, MD, PhD, Vanderbilt University, Nashville, Tennessee

Randall Schell, MD, MACM, University of Kentucky Department of Anesthesiology, Lexington, Kentucky

Edward R. Sherwood, MD, PhD, Vanderbilt University Medical Center, Nashville, Tennessee

Zhongcong Xie, MD, PhD, Harvard Medical School; Massachusetts General Hospital, Boston, Massachusetts

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Restaurants at the Hilton San Francisco Union Square

Illy Coffee
Coffee
Main Lobby
Hours: 6:00 am – 12:00 am

Herb n' Kitchen
Contemporary All-Day Restaurant
Main Lobby
Breakfast, Lunch, & Dinner:
6:00 am – 12:00 am
Delivery to Guest Rooms:
6:00 am – 10:00 am; 6:00 pm – 10:00 pm

Urban Tavern
Breakfast Only
Main Lobby
6:00 am - 11:00 am

Restaurants near the Hilton San Francisco Union Square

398 Brasserie
Breakfast & Brunch, Brasseries
398 Geary St. / 415-212-8196
398restaurantsf.com

Colibri Mexican Bistro
Mexican
438 Geary St. / 415-440-2737
Distance from Hotel: 2 minutes
colibrimexicanbistro.net

Farmerbrown
Southern, Soul Food, Breakfast & Brunch
25 Mason St. / 415-409-3276
Distance from Hotel: 2 minutes
farmerbrownsf.com

Kare-Ken
Japanese
552 Jones St. / 15-292-5273
Distance from Hotel: 2 minutes
kare-ken.com

Kusina Ni Tess
Filipino
237 Ellis St. / 415-351-1169
Distance from Hotel: 2 minutes

Shalimar Restaurant
Indian
532 Jones St. / 415-928-0333
Distance from Hotel: 2 minutes
shalimarsf.com

Bluestem Brasserie
Brasseries
One Yerba Buena Ln. / 415-547-1111
bluestembrasserie.com

Daily Grill
American
347 Geary St. / 415-616-5000
Distance from Hotel: 2 minutes
dailygrill.com

Fish & Farm
American
339 Taylor St. / 415-474-3474
Distance from Hotel: 2 minutes
fishandfarmsf.com

Katana-Ya
Japanese
430 Geary St. / 415-771-1280
Distance from Hotel: 2 minutes
katanayausa.com

Liholiho Yacht Club
Japanese
871 Sutter St. / 415-440-5446
Distance from Hotel: 2 minutes
liholihoyachtclub.com

Pho Tan Hoa
Vietnamese
431 Jones St. / 415-673-3163
Distance from Hotel: 2 minutes

Taylor Street Coffee Shop
Breakfast & Brunch, Burgers, Sandwiches
375 Taylor St. / 415-567-4031
Distance from Hotel: 2 minutes

Chabaa Thai Cuisine
Thai
420 Geary St. / 415-346-3121
Distance from Hotel: 2 minutes
chabaathaicuisinesf.com

Daniel's Café
Coffee & Tea, Bagels, Delis
154 Ellis St. / 415-956-1760
Distance from Hotel: 2 minutes

Hops & Hominy
Southern, American
1 Tillman Pl. / 415 373-6341
hopsandhominy.com

Kin Khao
Thai
55 Cyril Magnin St. / 415-362-7456
Distance from Hotel: 2 minutes
kinkhao.com

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Other Restaurants of Note

Acquerello
Italian
1722 Sacramento St. / 415-567-5432
acquerello.com

Gary Danko
American
800 N Point St. / 415-749-2060
garydanko.com

Jardinière
French
300 Grove St. / 415-861-5555
jardiniere.com

Boulevard
French
1 Mission St. / 415-543-6084
boulevardrestaurant.com

The House
Asian Fusion
1230 Grant Ave. / 415-986-8612
thehse.com

Nopa
American, Modern European
560 Divisadero St. / 415-864-8643
nopasf.com

Foreign Cinema
Mediterranean
2534 Mission St. / 415-648-7600
foreigncinema.com

House of Prime Rib
Steakhouse
1906 Van Ness Ave. / 415-885-4605
houseofprimerib.net

State Bird Provisions
American, Brasseries
500 Brannan St. / 415-777-1413
statebirdsf.com

Coffee near the Hilton San Francisco Union Square

Angel Café & Deli
700 Geary St. / 415-931-3467
Distance from Hotel: 2 minutes

Coffee Bean & Tea Leaf
773 Market St. / 415-896-5029
Distance from Hotel: 5 minutes
coffeebean.com

Paris Café
704 Post St. / 415-292-6856
Distance from Hotel: 2 minutes

Beanstalk Café
724 Bush St. / 415-567-1966
Distance from Hotel: 3 minutes

Farm Table
754 Post St. / 415-567-1966
Distance from Hotel: 2 minutes
farmtablesf.com

Philz Coffee
399 Golden Gate Ave. / 415-621-7000
Distance from Hotel: 7 minutes
philzcoffee.com

Blue Bottle Coffee Co.
611 Post St. / 510-653-3394
Distance from Hotel: 3 minutes
bluebottlecoffee.com/cafes/mint-plaza

Fresh Brew Coffee
882 Bush St.
415-567-0915
Distance from Hotel: 3 minutes

Starbucks
201 Powell St. / 415-835-2470
Distance from Hotel: 2 minutes
starbucks.com

For more information on restaurants in San Francisco, click here.

Special Events

Thursday, May 19

Resident, Fellow, and Junior Faculty Lunch

12:00 pm to 1:15 pm, Golden Gate 1-5, Lobby Level, Hilton San Francisco Union Square

Tables will be reserved for residents, fellows, junior faculty members, and their sponsoring chair. Members of the AUA Council will be present to meet with these future leaders in academic anesthesiology.

AUA Social Event Reception

6:30 pm to 9:30 pm, California Academy of Sciences (55 Music Concourse Drive)

The AUA Social Event Reception, sponsored by Host Institution, University of California, San Francisco, will take place on Thursday, May 19, from 6:30 pm to 9:30 pm, at the California Academy of Sciences, one of the largest natural history museums in the world, located in Golden Gate Park. The event includes hearty appetizers and drinks, live music and access to the museum. Bus transportation will be provided from the Taylor Street entrance off the Main Lobby of the hotel to the California Academy of Sciences for all registered attendees to the AUA Social Event Reception.

Note: The AUA Social Event Reception requires advanced registration to attend. This event also takes place during the California Academy of Sciences NightLife event and is a 21 and over event. Please be sure to bring your ID for entrance to the event.

Friday, May 20

***British Journal of Anesthesia* & Anaesthetic Research Society Reception**

6:00 pm to 7:30 pm, CityScape, 46th Floor, Hilton San Francisco Union Square

Join the *British Journal of Anesthesia* & Anaesthetic Research Society for a lively reception. This event requires advanced registration and tickets will be included with registration materials.

Saturday, May 21

Two Receptions during the Aligned Meeting Day at the IARS 2016 Annual Meeting

The following receptions will take place as part of the IARS 2016 Annual Meeting and International Science Symposium. AUA registered attendees are invited to attend these IARS receptions as part of their AUA registration fee.

Scholars' Program Reception

5:00 pm to 6:00 pm, Golden Gate 1-5, Lobby Level, Hilton San Francisco Union Square

Network and socialize with scholars at the Scholars' Program Reception on Saturday, May 21, from 5:00 pm to 6:00 pm, and celebrate the new knowledge gained during the Scholars' Program. This mentorship opportunity is supported by FAER's Academy of Research Mentors in Anesthesiology. The Scholars' Program Reception requires advanced registration and tickets will be provided with registration materials.

IARS Alignment Reception

6:00 pm to 7:30 pm, East Lounge, Ballroom Level, Hilton San Francisco Union Square

Celebrate the Alignment of the IARS, AUA & SOCCA Annual Meetings at this special event and toast the educational magnetism that results when leading minds in all subspecialties of anesthesiology join forces in one location. Plus, taste a little bit of the unique flavor that San Francisco has to offer.

Travel Information

Airports: The Bay Area has two airports serving the region: San Francisco International Airport (SFO) and Oakland International Airport (OAK).

The San Francisco International Airport is 14 miles away or a 25-minute drive from the Hilton San Francisco Union Square. The Oakland International Airport is 20 miles away or a 35-minute drive from the Headquarters Hotel. Both airports are connected to the region's subway system, Bay Area Rapid Transit (BART), for easy access to the city and offer multiple flights a day from a wide selection of airlines.

To learn more about available transportation options and rates to the Hilton San Francisco Union Square, click here.

What to Do in San Francisco

The sights and scenery. The one-of-a-kind events and world-class culinary scene. The welcoming people, the diversity and rich history. Known for its many hills, San Francisco is one of the most interesting 7-square-miles on the planet.

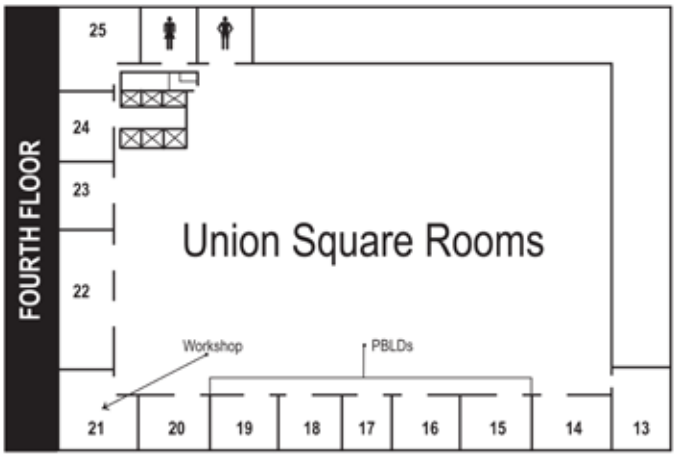
Walk or ride a Cable Car up the hills that make San Francisco famous. Experience the many micro-climates in the city. Taste the wide range of culinary selections provided by the city with more restaurants per capita than any other U.S. city. Explore distinctive neighborhoods such as Chinatown, Haight-Ashbury, Mission District, and dozens of other cities within the city, an array of art and cultural institutions, theater, dance, and musical performances and absorb the magnetic, vibrant energy that makes San Francisco unique.

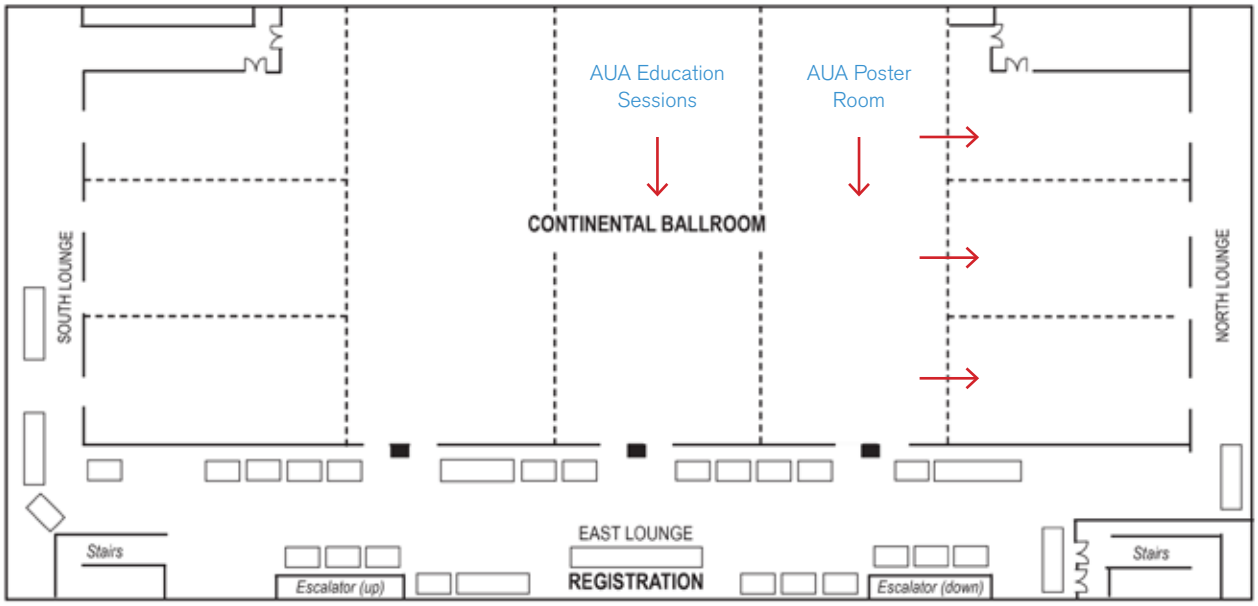
For more information on what to do in San Francisco, click here.

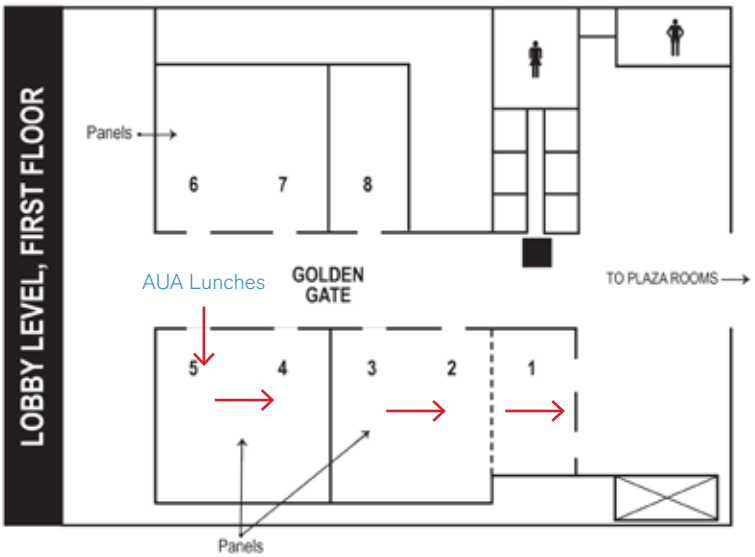
Hilton San Francisco Union Square Floor Plan

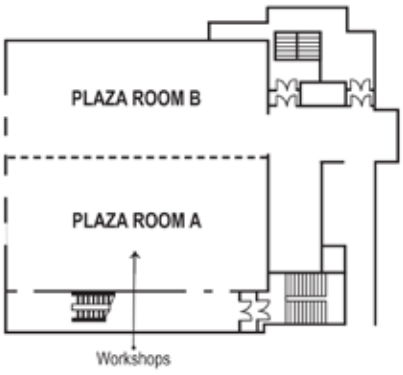
Hilton San Francisco Union Square

The Hilton San Francisco Union Square is the Headquarters Hotel for the AUA 63rd Annual Meeting. All Annual Meeting education sessions will be conveniently located at the Hilton. One of the largest and tallest hotels on the West Coast, the Hilton San Francisco Union Square puts you in easy proximity to the famous cable cars and makes it easy to visit attractions such as the Golden Gate Bridge, Fisherman's Wharf, Pier 39, the Marina, and Nob Hill.









Program Schedule

Join the leading academic anesthesia educators and researchers at the AUA 63rd Annual Meeting, May 19-20, 2016, at the Hilton San Francisco Union Square in San Francisco, California for a robust program, featuring education sessions from the Educational Advisory Board (EAB), Scientific Advisory Board (SAB), and the Host Institution, University of California, San Francisco, focused on cutting-edge topics, and two days of Moderated Poster Discussion Sessions.

Plus, new this year, AUA attendees will benefit from a special Aligned Meeting Day at the IARS 2016 Annual Meeting and International Science Symposium on Saturday, May 21 with education sessions on thought-provoking topics in anesthesiology. AUA registrants may attend all Aligned Meeting Day sessions at the IARS 2016 Annual Meeting as part of their AUA registration fee.

Thursday, May 19

7:00 am – 5:30 pm **Registration**

8:00 am – 8:15 am **Welcome from AUA President and Host Institution Chair**
Thomas J.J. Blanck, MD, PhD
Michael A. Gropper, MD, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe transformational changes that have recently occurred in the AUA and the AUA meeting including alignment with the IARS, establishment of a Scholars Program, and expansion of our International membership; (2) Identify developments in science and education that the Anaesthesia Research Society of the UK attendees bring to the meeting; and (3) Discuss key programs and breakthroughs in health care that the Host Institution, University of California, San Francisco, will describe during the meeting.

8:15 am – 9:15 am **Scientific Advisory Board (SAB) Oral Session I**

Moderators: Nabil Alkayed, MD, PhD, Oregon Health & Science University, Portland, Oregon, and Peter Goldstein, MD, Weill Cornell Medical College, New York, New York

- ***Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO***
  H.T. Lee, MD, PhD, Columbia University, New York, New York
- ***Role of the Gut-Lung Axis and IL-1b Signaling in Sterile Inflammation Following Lung Ischemia Reperfusion Injury***
  Arun Prakash, MD, PhD, University of California, San Francisco, San Francisco, California
- ***Inhibition of Free Fatty Acid Receptor GPR40 Abolishes Cardioprotection Conferred by Intralipid in Two Rodent Models of Bupivacaine Cardiotoxicity and Ischemia Reperfusion Injury***
  Soban Umar, MD, PhD, University of California, Los Angeles, Los Angeles, California

Resident Travel Award

- ***Low Molecular Weight Hyaluronan Mediated Inflammation And Airway Hyperresponsiveness in Acid Aspiration Induced Acute Lung Injury in Mice***

  Weifeng Song, MD, PhD, University of Alabama at Birmingham, Birmingham, Alabama

Session Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe the latest developments in anesthesiology research, in basic, clinical and population science; (2) Examine recent research findings relative to anesthesiology and evaluate their application to the learner's own research and clinical practice; and (3) Construct strategies for integrating new knowledge into their anesthesiology research program.

9:15 am – 9:30 am **Break**

9:30 am – 10:30 am **SAB Oral Session II**

Moderators: Nabil Alkayed, MD, PhD, Oregon Health & Science University, Portland, Oregon, and Peter Goldstein, MD, Weill Cornell Medical College, New York, New York

- ***Therapeutic Effects of Microvesicles Derived From A Mouse Macrophage Cell Line (RAW264.7) in Severe Pneumonia in Mice***

  Jae-Woo Lee, MD, University of California, San Francisco, San Francisco, California

Junior Faculty Research Award

- ***Gating of the TREK1 Tandem Pore Potassium Channel, A Molecular Signal Integrator and Anesthetic Target***

  Paul M. Riegelhaupt, MD, PhD, Weill Cornell Medicine, New York, New York

- ***Microglia Exacerbate Neuronal Death After Cardiac Arrest***

  Ines P. Koerner, MD, PhD, Oregon Health & Science University, Portland, Oregon

- ***Systemic HMGB1 Impairs Synaptic Plasticity after Surgery in Aged Rats***

  Niccolo Terrando, BSc (Hons), DIC, PhD, Duke University, Durham, North Carolina

Session Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe the latest developments in anesthesiology research, in basic, clinical and population science; (2) Examine recent research findings relative to anesthesiology and evaluate their application to the learner's own research and clinical practice; and (3) Construct strategies for integrating new knowledge into their anesthesiology research program.

10:30 am – 12:00 pm **Moderated Poster Discussion Session I**

Session Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify a broad range of current basic science and clinical research in anesthesiology and critical care medicine; (2) Describe the latest developments in academic anesthesiology, critical care medicine, perioperative medicine, and other anesthesiology subspecialty areas.

12:00 pm – 1:15 pm **All Attendee Lunch**

12:00 pm – 1:15 pm **Resident, Fellow and Junior Faculty Lunch**

Tables will be reserved for residents, fellows, junior faculty members and their sponsoring chair. AUA Council Members will also be present.

1:15 pm – 2:30 pm **Host Panel Session: Part I:**

Precision Medicine: From Molecules to Social Justice

Moderator: Michael A. Gropper, MD, PhD

Panelists:

- ***Genomics and Infectious Disease: Clinical Case Studies***

  Joseph L. DeRisi, PhD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Articulate how life-threatening conditions could benefit from a genomic approach to diagnosis; (2) Describe the steps taken from receipt of patient sample, to amplification of genomic material, to next-generation sequencing, to analysis of results; (3) Describe several clinical cases in which NGS was an advantageous approach from a practical, economic, and medical standpoint.

- ***The Multiple Sclerosis BioScreen: A Model for Chronic Disease Management***

  Stephen L. Hauser, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Appreciate basic principles of management of multiple sclerosis in 2016; (2) Understand a point-of-care tool to track disease course; contextualize how an individual is doing compared with others with similar disease characteristics; and predict future outcomes of decisions taken today; (3) Identify the value of digital medical devices for care of patients with diverse complex disease states.

2:30 pm – 2:45 pm **Break**

2:45 pm – 4:15 pm **Host Panel Session: Part II:**

Precision Medicine: From Molecules to Social Justice

Moderator: Michael A. Gropper, MD, PhD

Panelists:

- ***Precision Medicine at UCSF: Turning the Hype into Reality***

  Talmadge E. King, Jr., MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe how the University of California, San Francisco School of Medicine's customization of healthcare with medical decisions and practices leads to improved patient care; (2) Discuss how his research on inflammatory and immunologic lung injury and pioneering work in the management of the interstitial pneumonias distinguish his decisions as Dean of the UCSF School of Medicine; and (3) Describe key factors that help UCSF to deliver the highest level of biomedical research and patient care, and why its faculty and alumni have a seat at the table in guiding health policy throughout the world.

- ***Frontiers in HIV Medicine***

  Diane Havlir, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify updates on the latest advances in HIV medicine; (2) Discuss implications of these advances for practicing physicians; (3) Distinguish between pre exposure prophylaxis (PReP) and post exposure prophylaxis (PEP).

4:15 pm – 4:30 pm **Break**

4:30 pm – 5:30 pm **AUA Annual Business Meeting**

6:30 pm – 9:30 pm **AUA Social Event Reception**

Hosted by University of California, San Francisco
California Academy of Sciences (55 Music Concourse Drive)

Friday, May 20

6:00 am – 6:00 pm **Registration**

8:00 am – 9:00 am **SAB Oral Session III**

Moderators: Y.S. Prakash, MD, PhD, Mayo Clinic, Rochester, Minnesota, and Zhongchong Xie, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

- ***Using Social Network Analysis Tools to Assess the Effect of Isoflurane Anesthesia on Gene Networks in Rat Brain***

  Helen F. Galley, PhD, University of Aberdeen, Aberdeen, Abderdeenshire, United Kingdom

Junior Faculty Research Award

- ***The Analgesic Effects of Dopamine***
  Norman E. Taylor, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts
- ***Pharmacodynamics and Pharmacokinetics of Novel GABA-A Receptor Alpha 4 Subunit Selective Ligands that Treat Bronchoconstriction***
  Gene T. Yocum, MD, Columbia University, New York, New York
- ***The 'Meyer-Overton Quantum Underground' – Where Anesthetics Act to Prevent Consciousness***
  Stuart R. Hameroff, MD, The University of Arizona, Tucson, Arizona

Session Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe the latest developments in anesthesiology research, in basic, clinical and population science; (2) Examine recent research findings relative to anesthesiology and evaluate their application to the learner's own research and clinical practice; and (3) Construct strategies for integrating new knowledge into their anesthesiology research program.

9:00 am – 9:15 am **Break**

9:15 am – 10:15 am **SAB Oral Session IV**

Moderators: Y.S. Prakash, MD, PhD, Mayo Clinic, Rochester, Minnesota, and Zhongchong Xie, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

Resident Travel Award

- ***Mitochondrial TRPV1 Regulates Endothelial Dysfunction in Diabetes***
  Nana-Maria Wagner, MD, Stanford University, Stanford, California

Margaret Wood Resident Research Award

- ***A Novel Association Between High Density Lipoprotein Levels and the Risk of Acute Kidney Injury After Cardiac Surgery***
  Loren E. Smith, MD, PhD, Vanderbilt University, Nashville, Tennessee
- ***Impaired Relaxation of Airway Smooth Muscle in Mice Lacking the Cytoskeletal Regulatory Protein Gelsolin: A Potential Novel Target for Airway Relaxation***
  Maya Mikami, MD, PhD, MPH, Columbia University, New York, New York
- ***Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness***
  Christopher G. Hughes, MD, Vanderbilt University, Nashville, Tennessee

Session Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe the latest developments in anesthesiology research, in basic, clinical and population science; (2) Examine recent research findings relative to anesthesiology and evaluate their application to the learner's own research and clinical practice; and (3) Construct strategies for integrating new knowledge into their anesthesiology research program.

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

Session Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify a broad range of current basic science and clinical research in anesthesiology and critical care medicine; (2) Describe the latest developments in academic anesthesiology, critical care medicine, perioperative medicine, and other anesthesiology subspecialty areas.

11:45 am – 1:00 pm **All Attendee Lunch**

11:45 am – 1:00 pm **Educational Advisory Board (EAB) Lunch**

11:45 am – 1:00 pm **President's Lunch**

11:45 am – 1:00 pm **Scientific Advisory Board (SAB) Lunch**

1:00 pm – 2:30 pm **Educational Advisory Board (EAB) Program Session I:**
The Science of Communication

Moderator: Robert R. Gaiser, MD

- ***The Science of Hand-off Communication***

  Meghan Lane-Fall, MD, MSHP

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Distinguish three types of handoffs or care transitions in perioperative care; (2) Evaluate evidence associating anesthesia handoffs with harm; (3) Identify elements common to handoff standardization strategies for OR to ICU handoffs.

- ***The Science of Communication Among Professionals***

  Rebecca D. Minehart, MD, MSHPEd

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe why effective communication is critical for high-reliability organizations; (2) Demonstrate a conversational rubric for uncovering other team members' thoughts; and (3) Explain why curiosity can lead to improved learning and teamwork.

- ***Skills in the ART of Delivering Effective Feedback***

  Calvin Chou, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe representative literature on feedback in medical education; (2) Define "feedback" and discuss past experiences to develop a formalized structure for giving feedback; (3) Name skills for giving feedback and identifying barriers to effective feedback.

2:30 pm – 4:00 pm **EAB Program Session II:**

Publication of Education Research

Moderator: Robert R. Gaiser, MD

- ***Education Research: How to Get Started***

  Davinder Ramasingh, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Evaluate the roadblocks to starting educational research; (2) Discuss development of an educational research study; (3) Name a strategy to receive funding; (4) Discuss the implementation and completion of a funded educational research study.

- ***Closing the Loop in Education Research***

  Alex Macario, MD, MBA

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Evaluate the effectiveness of the curriculum and the instruction by measuring learning outcomes of the trainee; (2) Describe qualitative and quantitative assessment of the learning outcomes for informing the faculty to make changes to improve teaching and the curriculum in an iterative cycle; (3) Discuss how published research can help optimize curriculum, assessment, and instruction by identifying best practices; (4) Discuss why barriers to closing the loop and implementing best practice education techniques in graduate medical education exist and include not being familiar with or not agreeing with the published research, not thinking it is doable in one's setting or not thinking it will work, and external barriers such that proposed changes are blocked by system factors.

- ***How to Publish Education Research***

  Maxine Papadakis, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Evaluate the effectiveness of the curriculum and the instruction by measuring learning outcomes of the trainee; (2) Describe qualitative and quantitative assessment of the learning outcomes inform the faculty to make changes to improve teaching and the curriculum in an iterative cycle; (3) Discuss how published research can help optimize curriculum, assessment, and instruction by identifying best practices; (4) Discuss why barriers to closing the loop and implementing best practice education techniques in graduate medical education exist and include not being familiar with or not agreeing with the published research, not thinking it is doable in one's setting or not thinking it will work, and external barriers such that proposed changes are blocked by system factors.

4:00 pm – 4:15 pm **Break**

4:15 pm – 5:45 pm **President's Panel:**

How to Produce Successful Researchers

- ***Basic Science Research: Columbia University***

  Charles W. Emala, MD

  George Gallos, MD

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe important components to the career development of anesthesiology physician scientists in the basic sciences; (2) Examine departmental challenges in the support of anesthesiology physician scientists; and (3) Construct strategies for integrating new approaches to supporting the development of anesthesiology physician scientists.

- ***Mentoring in Health Services and Translational Research: University of Pennsylvania***

  Lee A. Fleisher, MD

  Mark D. Neuman, MD, MSc

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Discuss available resources for career development in health policy research within and outside of anesthesiology; (2) Identify promoters and barriers to successful career development in health policy research; (3) Discuss the value of interdisciplinary collaboration and mentorship in developing a health policy research career.

- ***Clinical Research: Vanderbilt University Medical Center***

  Edward R. Sherwood, MD, PhD

  Frederic T. (Josh) Billings, MD, MSCI

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Describe a trainee/junior faculty anesthesiology physician-scientist development program; (2) Appraise the value of building a clinical research support service team; (3) Identify the importance of establishing a culture of scientific inquiry and research within a medical center; (4) Describe a faculty development program that incentivizes academic productivity.

- ***Educational Research: Massachusetts General Hospital***

  Jeanine P. Wiener-Kronish, MD

  Rebecca D. Minehart, MD, MSHPEd

  Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify opportunities, as leaders, to support your educational researchrs; (2) Describe a framework for faculty development for educational researchers; and (3) Consider why cross-professional mentorship may be especially important for novice educational researchers.

6:00 pm – 7:30 pm ***British Journal of Anesthesia*** **& Anaesthetic Research Society Reception**

CityScape, 46th Floor, Hilton San Francisco Union Square

Saturday, May 21—Aligned Meeting Day at the IARS 2016 Annual Meeting

The following sessions are part of the IARS 2016 Annual Meeting and International Science Symposium. AUA registered attendees are invited to attend these IARS sessions as part of their AUA registration fee.

7:30 am – 8:00 am **Welcome to the Aligned Meeting Day at the IARS 2016 Annual Meeting**

8:00 am – 9:00 am **T.H. Seldon Memorial Lecture:**
Reproducible Research: Impact in Evidence-Based Decision Making
John P.A. Ioannidis, DSc, MD, Stanford University, Stanford, California

9:00 am – 9:30 am **Break**

9:30 am – 12:00 pm **Celebration of the Science of Anesthesiology Symposium:**
Protective Lung Ventilation in the Operating Room

Co-Moderators: Brian Kavanagh, MB, BSc, MRCP(I), FRCP, University of Toronto, and Toronto Hospital for Sick Children, Toronto, Ontario, Canada, and Marcos F. Vidal Melo, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

Panelists:

Holger Eltzschig, MD, PhD, University of Colorado School of Medicine, Aurora, Colorado

Marcelo Gama de Abreu, MD, MSc, PhD, DESA, University Hospital Carl Gustav Carus, and Dresden University of Technology, Dresden, Germany

Brian Kavanagh, MB, BSc, MRCP(I), FRCP, University of Toronto, and Hospital for Sick Children, Toronto, Ontario, Canada

Marcos F. Vidal Melo, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

12:00 pm – 1:00 pm **Lunch-On-Your-Own**

1:00 pm – 2:30 pm **Scholars' Program Panel:**
Research in the 21st Century

Panelists:

- ***Choosing A Scientific Research Question That Inspires Passion and Creates Impact***
  Judith Hellman, MD, University of California, San Francisco, San Francisco, California
- ***Opportunities on the Horizon: Current Trends in Academic Anesthesiology***
  Alex Evers, MD, Washington University in St. Louis, St. Louis, Missouri
- ***Collaborative Research: Tapping into the CTSA Network***
  Jennifer Grandis, MD, University of California, San Francisco, San Francisco, California

1:00 pm – 4:00 pm **IARS, AUA, and SOCCA Science Symposium:**

State of the Art Review: Endothelial Glycocalyx Practice and Critical Care Medicine

Moderator: Randal Dull, MD, PhD

Panelists:

- ***Endothelial and Glycocalyx Damage in Trauma – Drivers of Coagulopathy***
  Sisse R. Ostrowski, MD, PhD, DMSc, Copenhagen University Hospital, Copenhagen, Denmark
- ***The Glycocalyx, Barrier Regulation and Resuscitation***
  Randal Dull, MD, PhD, University of Illinois at Chicago, Chicago, Illinois
- ***Hyaluronan and Circulating Tumor Cell Metastatic Potential***
  Hans Vink, PhD, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands
- ***Glomerular Glycocalyx Degradation in Septic Kidney Injury***
  Eric Schmidt, MD, University of Colorado School of Medicine, Aurora, Colorado
- ***The Glycocalyx in Acute Lung Injury***
  Jean-Francois Pittet, MD, University of Alabama at Birmingham, Birmingham, Alabama

2:45 pm – 4:15 pm **Scholars' Program:**

Dynamic and Interactive Small Group Sessions

The Scholars' Education Program will break into small group sessions.

Registrants may select the two group sessions they want to attend.

Presenters:

- ***Mock Study Section***
  Max Kelz, MD, PhD, University of Pennsylvania, Philadelphia, Pennsylvania
- ***Interactive Workshop on Designing A Clinical Trial***
  Anke Winter, MD, MSc, Washington University in St. Louis, St. Louis, Missouri
- ***Independent Discussion for Scientific Manuscripts***
  Ben Julian A. Palanca, MD, PhD, MSc, Washington University in St. Louis, St. Louis, Missouri
- ***Grant Writing Session***
  Laure Aurelian, MSc, PhD, University of Maryland Medical School, Baltimore, Maryland

Program Schedule

4:15 pm – 5:00 pm **Scholars' Program Panel:**

Showcasing Career Trajectory of Young Anesthesiology Leaders

Panelists:

- ***Building A Career in Perioperative Comparative Effectiveness Research***

  Mark D. Neuman, MD, MSc, University of Pennsylvania, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

- ***How Alcohol and Hot Sauce Jump-started My Career as an Academic Anesthesiologist***

  Eric R. Gross, MD, Stanford University, Stanford, California

- ***Building A Program of Research Using Secondary Data***

  May Hua, MD, Columbia University, New York, New York

5:00 pm – 6:00 pm **Scholars' Program Reception**
AUA Attendees Invited
Hilton San Francisco Union Square (333 O'Farrell Street)

6:00 pm – 7:30 pm **IARS Alignment Reception**
AUA Attendees Invited
Hilton San Francisco Union Square (333 O'Farrell Street)

**As of press time and subject to change.*

Thursday, May 19

Scientific Advisory Board Oral Session I
8:15 am – 9:15 am

Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO
H.T. Lee, MD, PhD

Friday, May 20

Scientific Advisory Board Oral Session IV
9:15 am – 10:15 am

Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness
Christopher G. Hughes, MD

Educational Advisory Board Program Session I: The Science of Communication
1:00 pm – 2:30 pm

Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD

Educational Advisory Board Program Session II: Publication of Educational Research
2:30 pm – 4:00 pm

Closing the Loop in Education Research
Alex Macario, MD, MBA

How to Publish Education Research
Maxine Papadakis, MD

President's Panel: *How to Produce Successful Researchers*
4:15 pm – 5:45 pm

Mentoring in Health Services and Translational Research: University of Pennsylvania
Lee A. Fleisher, MD
Mark D. Neuman, MD

Educational Research: Massachusetts General Hospital
Jeanine P. Wiener-Kronish, MD

Notes:

Thursday, May 19

Scientific Advisory Board (SAB) Oral Session I

Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

H.T. Lee, MD, PhD

Peptidyl arginine deiminase-4 exacerbates ischemic acute kidney injury by finding NEMO

Mihwa Kim, May Rabadi, Kevin Brown and H.T. Lee

Department of Anesthesiology, Columbia University, New York, NY

Disclosures

- No conflict of interest
- Research funded by Columbia University Department of Anesthesiology and by NIH RO1 DK-58547, GM-067081

Unmet Need

- Inflammation is a major contributor of Acute Kidney Injury
- Limiting the inflammatory response after ischemia or hypoxia will attenuate the severity of kidney injury
- No effective therapy available to limit inflammation

Peptidylarginine Deiminase (PAD)

- Calcium dependent enzyme that converts peptidyl-arginine to peptidyl-citrulline

- Citrullination changes protein charge, structure and function

Peptydylarginine Deiminase (PAD)

- Activated by diverse stimuli
  - Calcium influx
  - TLR4 agonists (e.g., LPS)
  - Cytokines (TNF-α, IL-8)
  - Free radicals
  - all of these increase during and after kidney IR

Peptidylarginine Deiminase 4 (PAD4)

- Of 5 subtypes, only PAD4 protein expressed in the kidney
- Implicated in several auto-immune and inflammatory diseases including rheumatoid arthritis, colitis, lupus and multiple sclerosis

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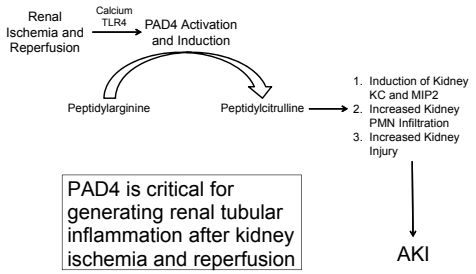
Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

H.T. Lee, MD, PhD

We found previously…



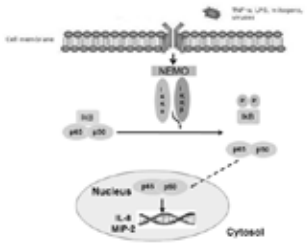
PAD4 is critical for generating renal tubular inflammation after kidney ischemia and reperfusion

We next asked……

- What are the mechanisms of PAD4-mediated exacerbation of renal injury and inflammation??

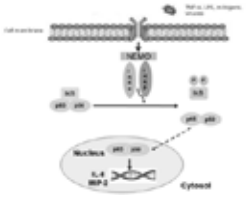
NFkB

- A prolific transcription factor involved in many aspects of renal inflammation
- Induces several pro-inflammatory cytokines



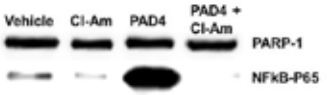
Hypothesis

- Does PAD4 cause NFkB nuclear translocation in human proximal tubule cells?



PAD4 causes nuclear translocation of NFkB in human proximal tubule cells

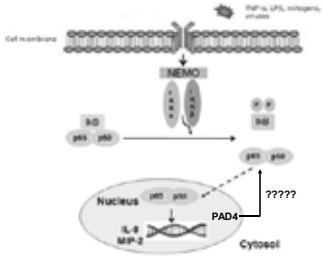
- Isolated nuclear fraction after vehicle or PAD4 treatment



Cl-Am = 2-chroloamidine, a selective PAD4 inhibitor

But!!!!

- NFkB lives in cytosol and PAD4 lives in the nucleus



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Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

H.T. Lee, MD, PhD

Immunological Reviews

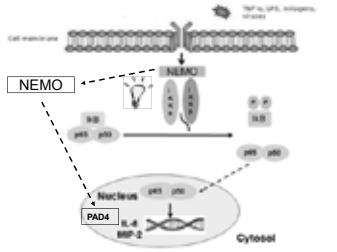
DNA damage-dependent NF-κB activation: NEMO turns nuclear signaling inside out

(NEMO = NFkB Essential Modulator)

Immunological Reviews

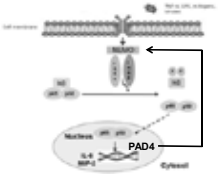
DNA damage-dependent NF-κB activation: NEMO turns nuclear signaling inside out

(NEMO = NFkB Essential Modulator)



Hypotheses for next sets of studies

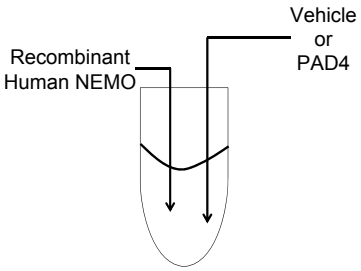
- Does PAD4 regulate NEMO (IKKγ) via citrullination?
- Does NEMO modulation affect PAD4-mediated renal tubular inflammation and injury??



Experimental plans

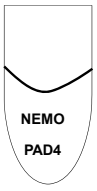
1. PAD4 citrullination of NEMO
2. PAD4 promotes nuclear NFkB translocation and inflammation via NEMO citrullination
3. NEMO blockade attenuates PAD4-mediated exacerbation of ischemic AKI and renal inflammation

Test whether PAD4 Citrullinates NEMO

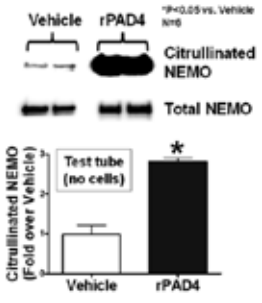


Cell free system

PAD4 citrullinates NEMO!!!



Cell free system



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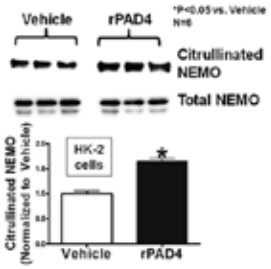
Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO
H.T. Lee, MD, PhD

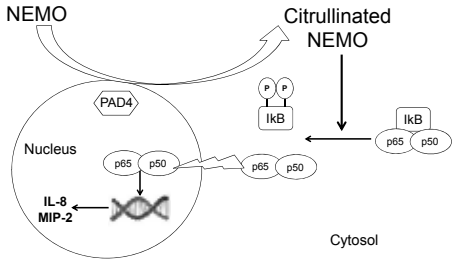
PAD4 also citrullinates NEMO in human kidney proximal tubule cells



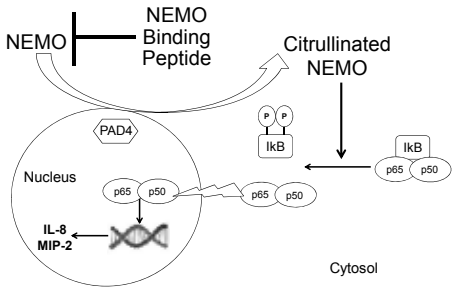
Experimental plans

1. PAD4 citrullination of NEMO
2. PAD4 promotes nuclear NFkB translocation and inflammation via NEMO citrullination
3. NEMO blockade attenuates PAD4-mediated exacerbation of ischemic AKI and renal inflammation

Role of NEMO in NFkB activation

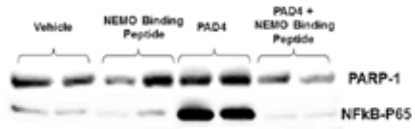


Neutralize NEMO with a binding peptide



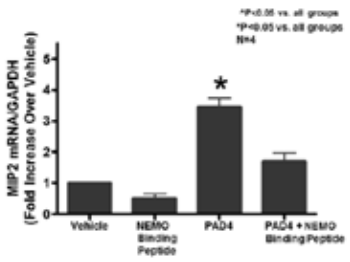
Neutralizing NEMO prevents PAD4-mediated NFkB activation

- Isolated nuclear fraction after vehicle or PAD4 treatment



Human kidney proximal tubule cells

Blocking NEMO attenuates PAD4-mediated inflammation



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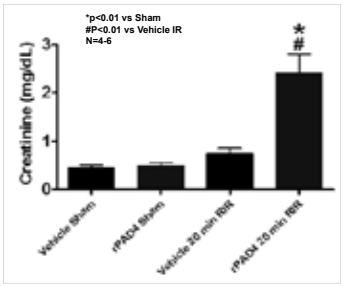
Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO
H.T. Lee, MD, PhD

Experimental plans

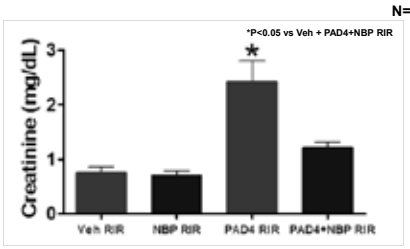
1. PAD4 citrullination of NEMO
2. PAD4 promotes nuclear NFkB translocation and inflammation via NEMO citrullination
3. NEMO blockade attenuates PAD4-mediated exacerbation of ischemic AKI and renal inflammation

Previously, we found that PAD4 exacerbates kidney IR injury



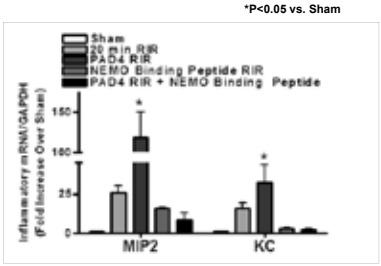
AJP Renal (2014)

Blocking NEMO attenuates PAD4-mediated exacerbation of renal injury

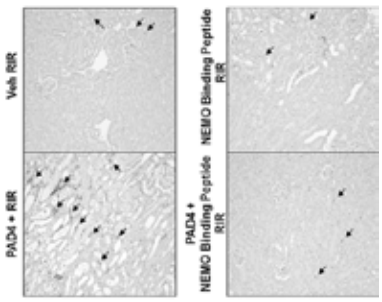


NBP = NEMO Binding Peptide

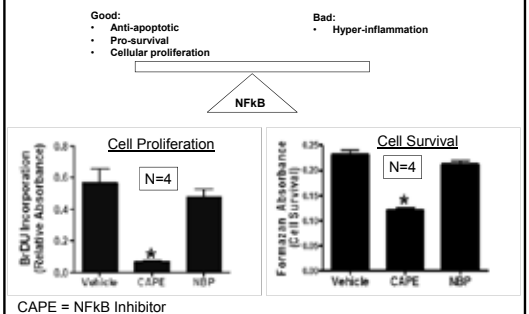
Blocking NEMO attenuates PAD4-mediated chemokine induction



Blocking NEMO attenuates PAD4-mediated neutrophil infiltration



Why not block NFkB itself rather than NEMO??



CAPE = NFkB Inhibitor
NBP = NEMO Inhibitor

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Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

H.T. Lee, MD, PhD

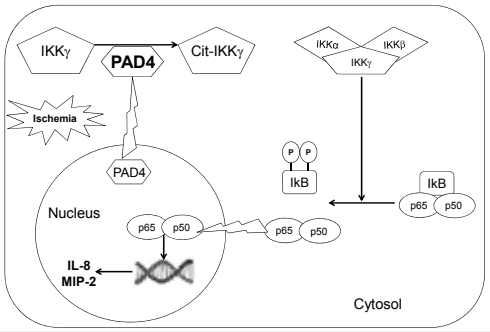
Advantage of NEMO Binding Peptide vs. NFκB inhibition

- Will not affect basal NFkB activity
- Specific for classical NFkB activation pathway, will not affect NFkB alternative pathway
- Does not affect cell proliferation
- Does not affect cell survival

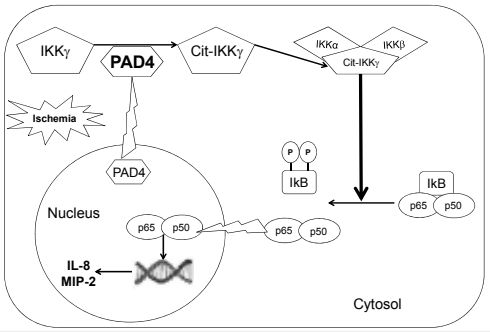
Summary

1. PAD4 directly citrullinates NEMO to cause nuclear NFkB translocation
2. NEMO inhibition attenuates kidney injury and reduces the inflammatory response after renal IR injury
3. NEMO inhibition reduces PAD4-mediated renal neutrophil infiltration after ischemic AKI
4. NEMO neutralization may serve as a potential therapy for this devastating clinical problem

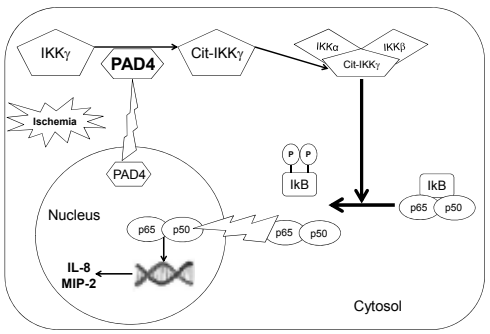
PAD4 modulation of NFkB??



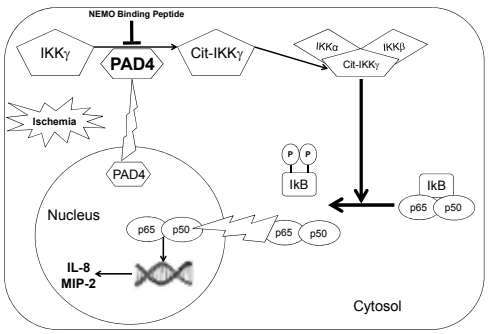
PAD4 modulation of NFkB??



PAD4 modulation of NFkB??



PAD4 modulation of NFkB??



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Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO
H.T. Lee, MD, PhD

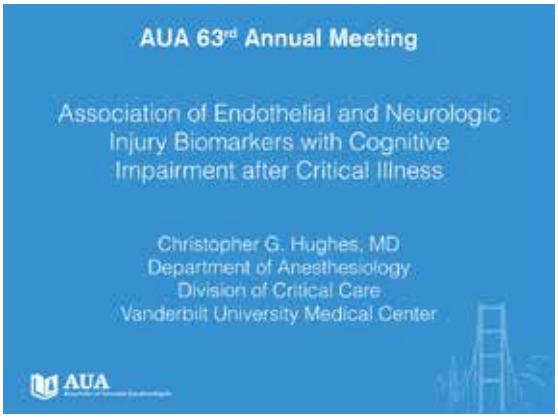
Acknowledgement

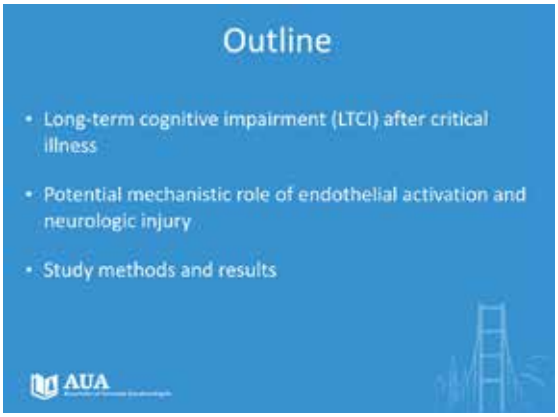
- Mentor: Dr. HT Lee
- Columbia University Department of Anesthesiology
- NIH RO1 DK-58547, GM-067081
- Mihwa Kim
- Kevin M. Brown

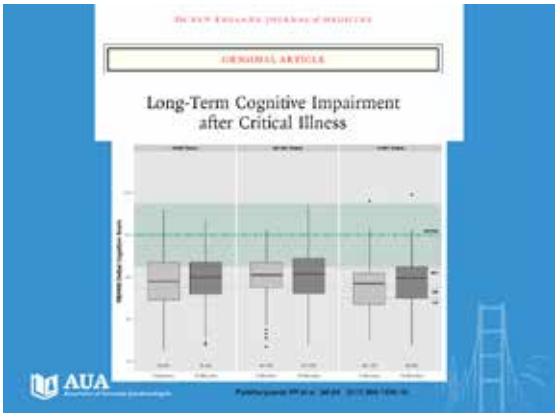
Friday, May 20

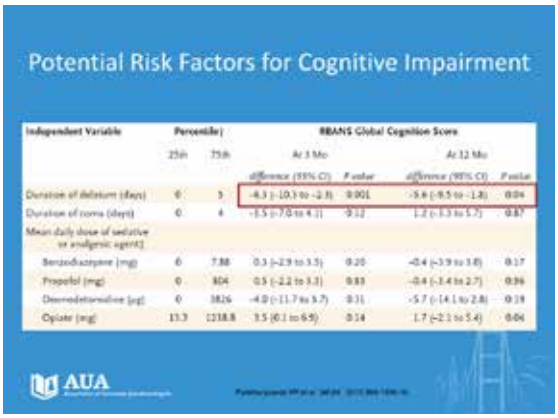
Scientific Advisory Board (SAB) Oral Session IV

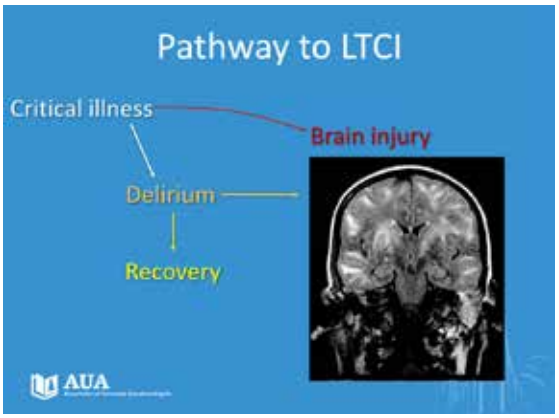
Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness
Christopher G. Hughes, MD











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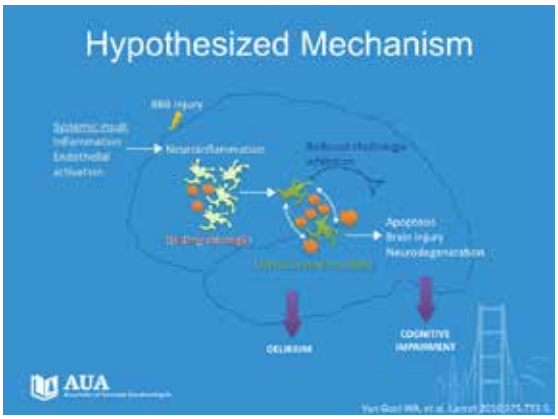
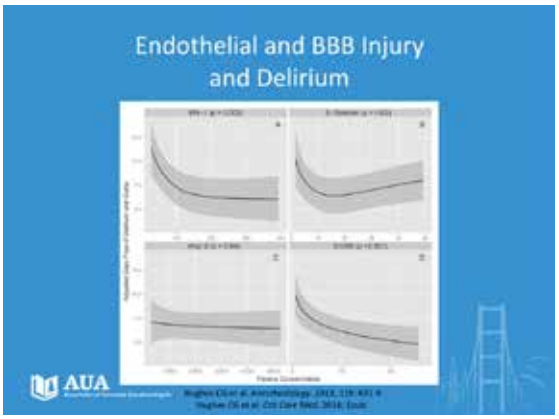
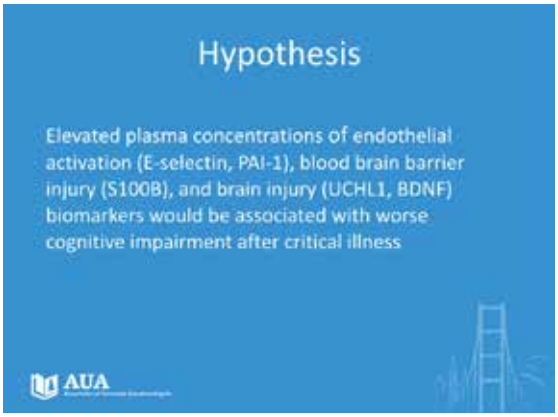
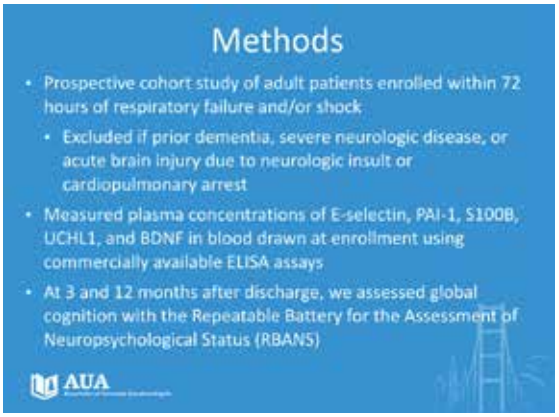
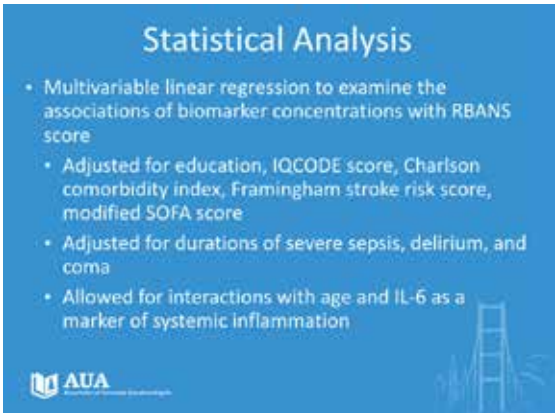
Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness
Christopher G. Hughes, MD

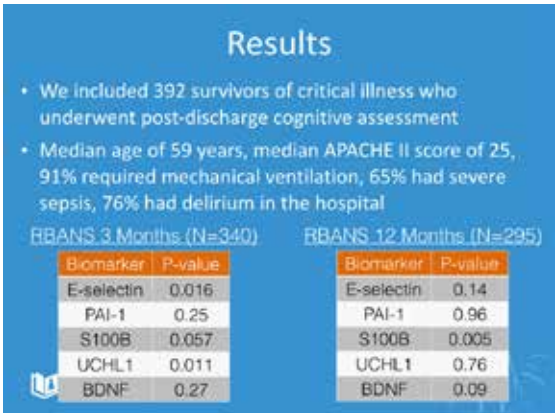












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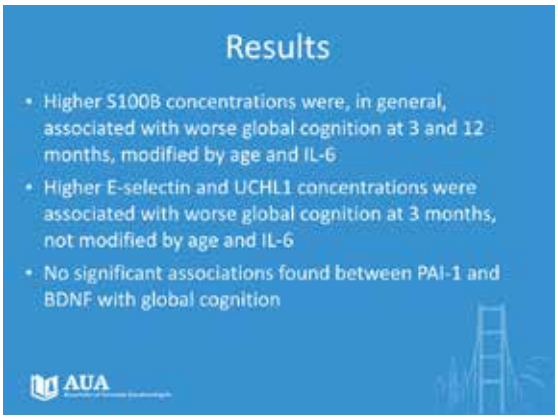
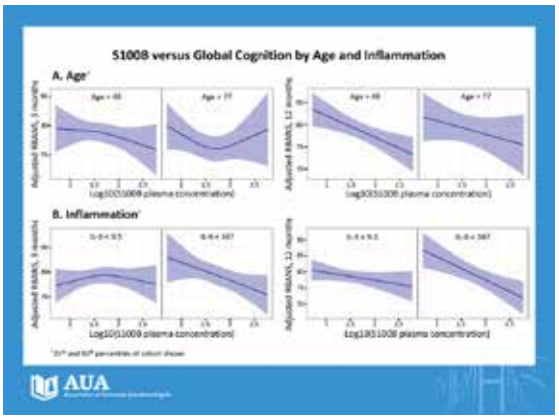
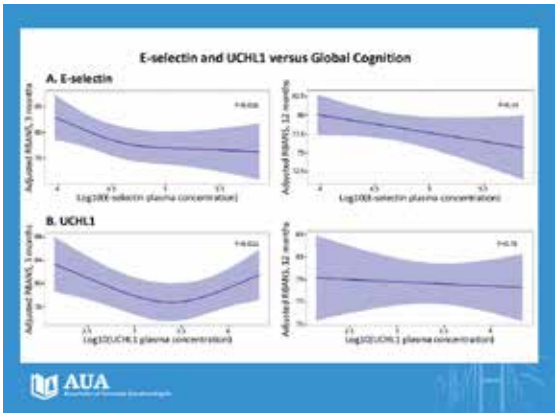
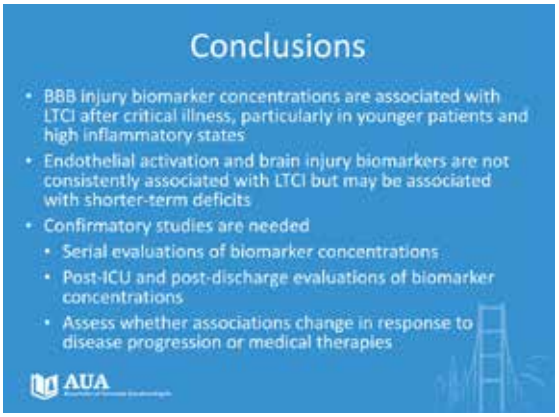
Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness
Christopher G. Hughes, MD





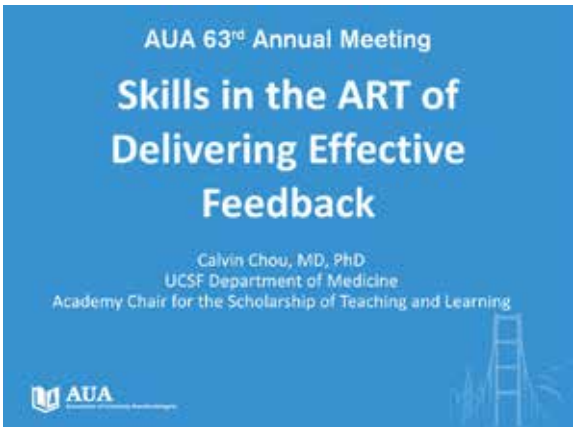


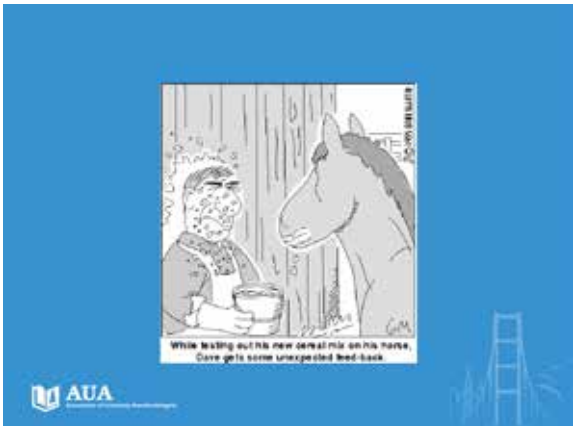


Friday, May 20

Educational Advisory Board Session I: The Science of Communication

Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD





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Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD

Scenario 1

- You say only positive things to Michael.
- In your evaluation, you write: "resident was terrific."

AUA

Scenario 2

- You say only positive things to Michael.
- In your evaluation, you write: "resident did fine but could have been more detail-oriented during a-line placements."

AUA

Scenario 3

After you watch Michael fumble a bit with the a-line, he finally succeeds. You say to him, "You could have positioned the patient's arm better."

AUA

Scenario 4

- You stand behind Michael during the next a-line procedure and at every moment you see him being a bit sloppy, you correct him.
  - "no, be more careful about arm positioning"
  - "really feel the line of the artery with both fingers"
  - "that's too steep an angle"

AUA

Scenario 5

At the end of Michael's shift one day, you say:

"I like how detail-oriented you are about setting up the room and preparing yourself for the day. When placing an a-line, you could use that same detail orientation by positioning the patient's arm more carefully. But overall you're doing great."

AUA

The sandwich

AUA

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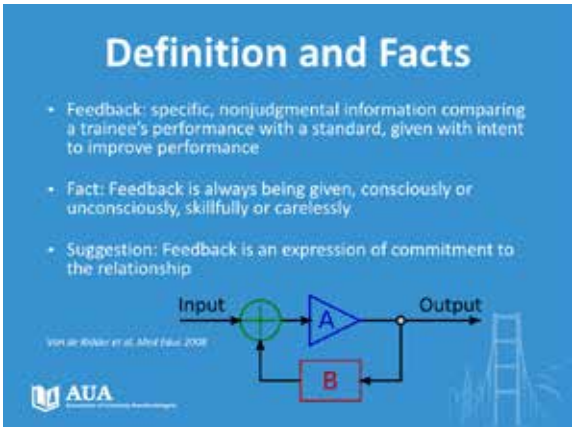
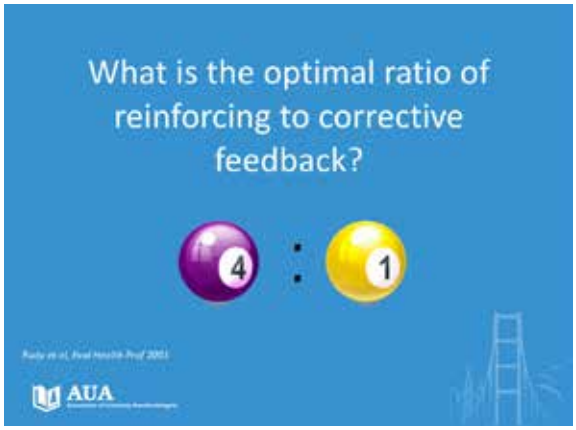
Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD





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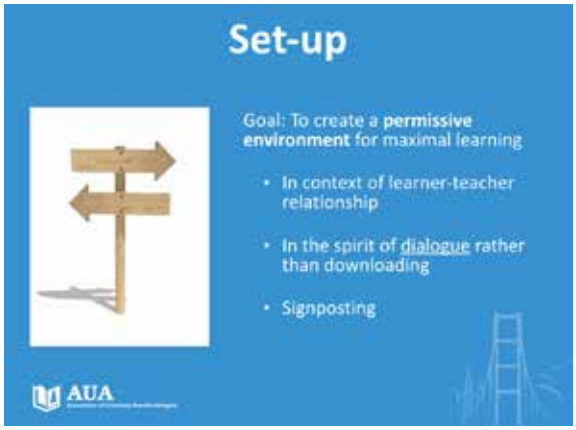
Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD



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Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD

Set-up Features

- Temporally as close as possible to event
- In accordance with learner's goals: *what are you hoping to achieve after this experience?*
- In accordance with learner's readiness
- Anticipating common issues (for procedures, may involve intervening), and promising to debrief them afterwards

AUA

Gather information

AUA

Feedback Steps

- Set up
- Gather Information / Observe
- ARTful Feedback
  - Reinforcing
  - Constructive
  - Take Homes

AUA

ARTful Skills

- **Ask:** Learner's self-assessment; recall goals
- **Respond:** Requires active listening, and sometimes empathy
- **Teach:** Your own assessment and thoughts, framed behaviorally and specifically

AUA

ARTful Reinforcing Feedback

- Ask: What do you think you'd like to **do effectively**?
- Respond, Teach
- The ART cycle continues: ask for reactions to your feedback

AUA

ARTful Constructive Feedback

- Ask: What do you think you'd like to **do differently**?
- Respond, Teach (remain nonjudgmental)
- Continue the ART cycle: ask for reactions to your feedback

AUA

continued on page 44

Skills in the ART of Delivering Effective Feedback
Calvin Chou, MD

Friday, May 20

Educational Advisory Board (EAB) Session II: Publication of Education Research

Closing the Loop in Education Research

Alex Macario, MD, MBA

Closing the Loop in Education Research

Alex Macario MD, MBA
Professor
Department of Anesthesiology, Perioperative and Pain Medicine
Stanford University

Disclosure

Nothing to disclose.

Learning objectives

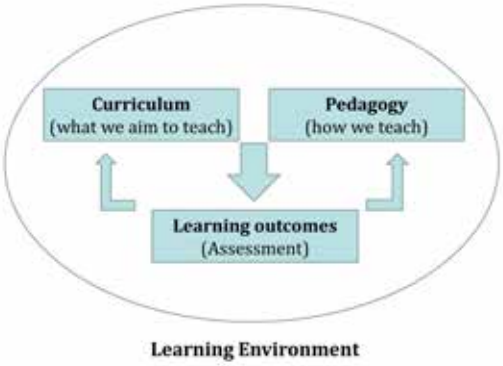
- Educators evaluate the effectiveness of the curriculum and instruction by measuring learning outcomes of the trainee
- Assessment of learning outcomes inform the faculty to make changes to improve teaching & curriculum in an iterative cycle
- Published research can help optimize curriculum, assessment, and instruction by identifying best practices
- Barriers to implementing best practice education techniques exist
  - not being familiar with or not agreeing with the published research
  - not thinking it is doable in one's setting or not thinking it will work
  - system factors

Outline

- Learning objectives
- Show relationship between curriculum, teaching, & assessment
- Give example of education intervention to illustrate needs assessment
- Show data illustrating that many best practice teaching techniques are not followed by faculty giving lectures
- Emphasize that faculty development programs can overcome some of the barriers to implementing best practices in education
- Tips on submitting papers, and on applying for research grants

Five areas in Education

- Administration
- Curriculum
- Teaching
- Advising/mentoring
- Assessment
  - how do we know what residents learn



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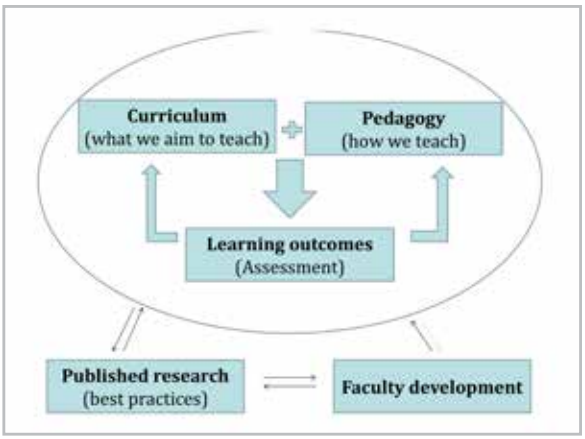
Closing the Loop in Education Research
Alex Macario, MD, MBA



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Closing the Loop in Education Research

Alex Macario, MD, MBA

Needs assessment: focus groups with residents

- Housestaff (adult learners) want explicit instruction of ABA keyword medical knowledge
- Recommend delivery method: short 15-minute lecture
- Lecture repeated three times every weekday by same attending at 10AM, noon, and 2PM
- Increases access for residents to attend, given schedule constraints of each resident
  - A predetermined computer slide template developed to provide uniformity for how content is delivered
- This resulting educational intervention continues daily more than two years after initial implementation

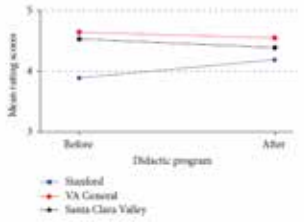
Research Article

Impact of an Innovative Classroom-Based Lecture Series on Residents' Evaluations of an Anesthesiology Rotation

Pedro Tanaka,[1] David Yanez,[2] Hendrikus Lemmens,[3] Adam Djurdjulov,[4] Lena Scotto,[3] Lindsay Borg,[3] Kim Walker,[3] Sylvia Bereknyei Merrell,[3] and Alex Macario[1]

[1]Department of Anesthesiology, Perioperative and Pain Medicine, 300 Pasteur Drive H3580, Stanford University School of Medicine, Stanford, CA 94305-5640, USA

This new formal teaching session significantly improved score on "overall teaching quality of this rotation," from 3.9 (SD 0.8) to 4.2 (SD 0.7) as judged by residents, compared to controls at two comparison hospital rotations



Ten recommended lecture elements based on learner input & published research on best practices

#1. Define learning objectives
#2. Use of an outline
#3. Clinical case vignette to introduce keyword
#4. Reinforcement of learning points/repetition
#5. Specific recommendations for patient care
#6. Graphics /visuals as attention grabbers
#7. Test/quiz/multiple choice question
#8. Active involvement of residents
#9. Provide take home messages
#10. References/directions for further reading

Mapping of Primary Instructional Methods and Teaching Techniques for Regularly Scheduled, Formal Teaching Sessions in an Anesthesia Residency Program

Matias Vested Madsen, MD, Alex Macario, MD, Satoshi Yamamoto, MD, and Pedro Tanaka, MD

BACKGROUND: In this study, we examined the regularly scheduled, formal teaching sessions in a single anesthesiology residency program to (1) map the most common primary instructional methods, (2) map the use of 10 known teaching techniques, and (3) assess if residents scored sessions that incorporated active learning as higher quality than sessions with little or no verbal interaction between teacher and learner.

METHODS: A modified Delphi process was used to identify useful teaching techniques. A representative sample of each of the formal teaching session types was mapped, and residents anonymously completed a 5-question written survey rating the session.

RESULTS: The most common primary instructional methods were computer slides-based classroom lectures (66%), workshops (15%), simulations (9%), and journal club (5%). The number of teaching techniques used per formal teaching session averaged 5.31 (SD, 1.92; median, 5; range, 0–9). Clinical applicability (85%) and attention grabbers (80%) were the 2 most common teaching techniques. Thirty-eight percent of the sessions defined learning objectives, and one-third of sessions engaged in active learning. The overall survey response rate equaled 42%, and passive sessions had a mean score of 8.44 (range, 5–10; median, 9; SD, 1.2) compared with a mean score of 8.63 (range, 5–10; median, 9; SD, 1.1) for active sessions ($P = 0.63$).

CONCLUSIONS: Slides-based classroom lectures were the most common instructional method, and faculty used an average of 5 known teaching techniques per formal teaching session. The overall education scores of the sessions as rated by the residents were high. (A&A Case Reports 2016;000:00–00)

To help increase learner comprehension, a faculty clinical teacher aims to use proper structure to deliver information, across the learner's prior knowledge, explicitly communicate the learning goals, and summarize [illegible] for all house staff, whereas other sessions are designed for one specific postgraduate year class of residents. Residents are expected to attend all formal teaching sessions unless post-call or otherwise unavailable. Because the depth and [illegible]

% of sessions that had best practice elements

Define learning objectives	21%
Use of an outline	13%
Clinical case vignette for keyword	31%
Reinforcement of learning points	65%
Specific recommendations- pt. care	75%
Graphics/visuals-attention grabbers	78%
Test/quiz/multiple choice question	56%
Active involvement of residents	65%
Provide take home messages	44%
References for further reading	49%

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Closing the Loop in Education Research
Alex Macario, MD, MBA

Why don't more faculty follow established best practice techniques for formal classroom based presentations?

Barriers to faculty clinical educators implementing best practice education practices

- not familiar with best practices described in literature
  - could be lack of inquiry by teacher or lack of easy access
- not agreeing with the published research
- thinking implementing best practice is not doable
- thinking implementing best practices will not work for their learners
- system barriers
  - university and medical school incentive reward system
  - published studies focus on independent effect of one intervention, which may not work if other parts of system aren't aligned

Mechanisms for connecting evidence with on-the-ground decision making

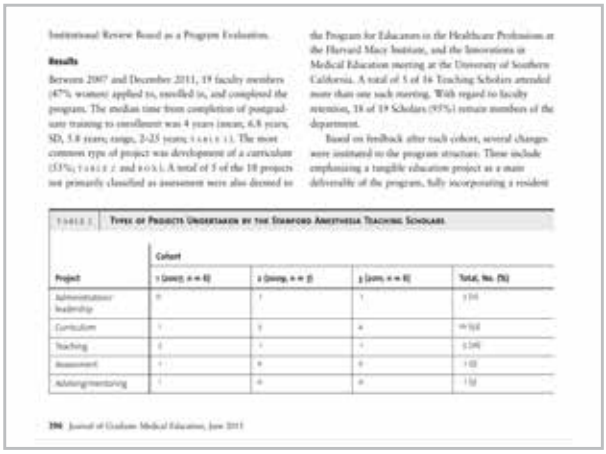
Need for faculty development in education


The Stanford Anesthesia Faculty Teaching Scholars Program: Summary of Faculty Development, Projects, and Outcomes

continued on page 49

Closing the Loop in Education Research

Alex Macario, MD, MBA



Institutional Review Board as a Program Evaluation.

Results

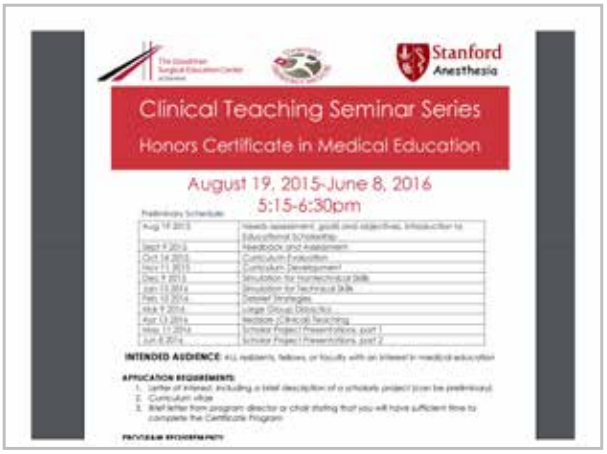
Between 2007 and December 2011, 19 faculty members (47% women) applied to, enrolled in, and completed the program. The median time from completion of postgraduate training to enrollment was 4 years (mean, 6.8 years; SD, 5.8 years; range, 2–25 years; TABLE 1). The most common type of project was development of a curriculum (33%; TABLE 2 and BOX). A total of 5 of the 18 projects not primarily classified as assessment were also deemed to the Program for Educators in the Healthcare Profession at the Harvard Macy Institute, and the Innovations in Medical Education meeting at the University of Southern California. A total of 5 of 16 Teaching Scholars attended more than one such meeting. With regard to faculty retention, 18 of 19 Scholars (95%) remain members of the department.

Based on feedback after each cohort, several changes were instituted to the program structure. These include emphasizing a tangible education project as a main deliverable of the program, fully incorporating a resident

TABLE 2 Types of Projects Undertaken by the Stanford Anesthesia Teaching Scholars

Project	Cohort 1 (2007; n = 6)	2 (2009; n = 7)	3 (2011; n = 6)	Total, No. (%)
Administration/ leadership	0	1	1	2 (11)
Curriculum	1	3	4	8 (42)
Teaching	2	1	1	4 (21)
Assessment	1	0	0	1 (5)
Advising/mentoring	1	0	0	1 (5)

396 Journal of Graduate Medical Education, June 2013



Tips given to me from an editor on getting published in medical education research

- IRB approval is necessary. Journals will not take manuscript if project has not been examined by IRB.
- The major reason for a paper not being accepted is failure to offer advance in understanding of a process in education.
- Second most common reason is unsupported conclusion, followed by methodological flaws.
- Aim to refine understanding of the problem we face rather than attempting to provide the solution.
- Don't mention the local context until the Methods section.
- Build a story that answers: So What? Who Cares?

Tips for getting education research grants funded

- Most common major flaws
  - overambitious
  - poor scientific design
  - no preliminary data to support project is doable
- Positive attributes
  - Likely to be achievable in a reasonable time frame
  - Need simple, interesting, testable hypothesis, solid design including controls, & validated measures of meaningful learning outcomes including proper psychometrics
  - Preliminary data showing feasibility and leading to proper sample size estimates
  - Addressing an important question in physician education
  - PI with training in research and education

Take Home Messages

- Educators evaluate the effectiveness of the curriculum and instruction by measuring learning outcomes of the trainee
- Assessment of learning outcomes inform the faculty to make changes to improve teaching & curriculum in an iterative cycle
- Published research can help optimize curriculum, assessment, and instruction by identifying best practices
- Barriers to implementing best practice education techniques exist
  - not being familiar with or not agreeing with the published research
  - not thinking it is doable in one's setting or not thinking it will work
  - system factors

Further reading

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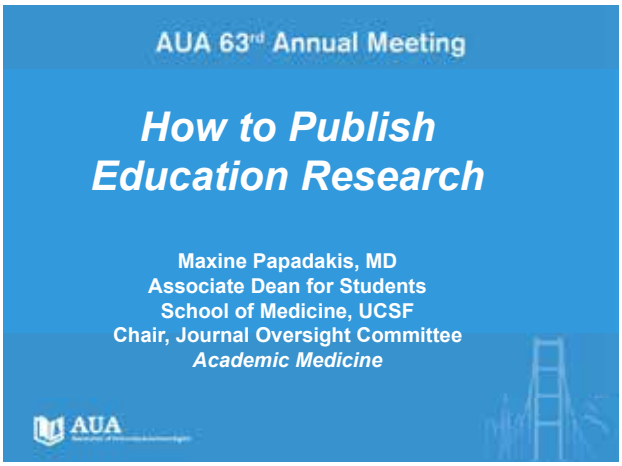
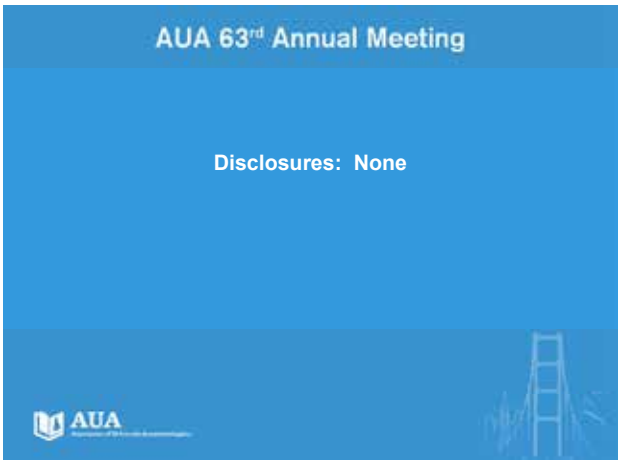
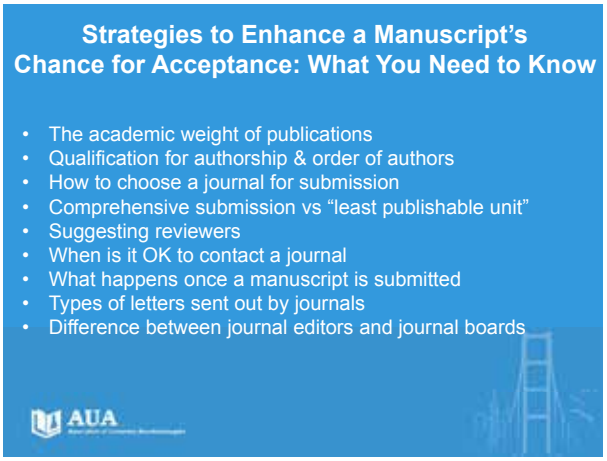
Friday, May 20

Educational Advisory Board Session II: Publication of Education Research

How to Publish Education Research
Maxine Papadakis, MD







Friday, May 20

President's Panel: How to Produce Successful Researchers
Lee A. Fleisher, MD
Mark D. Neuman, MD

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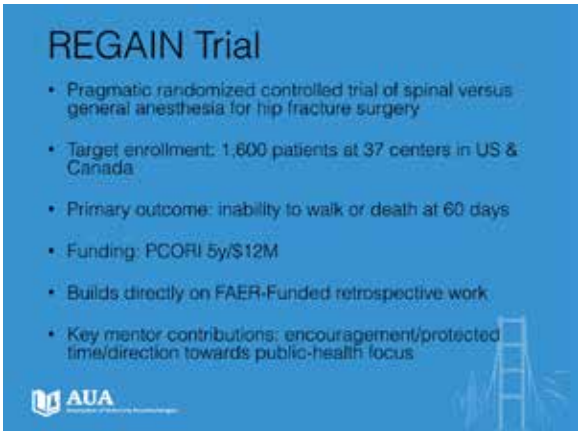
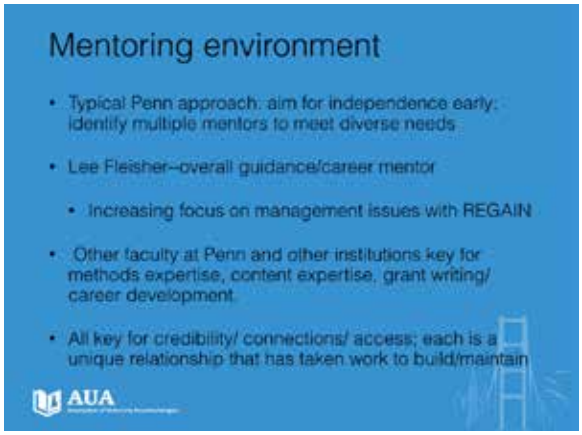
Mentoring in Health Services and Translational Research

Lee A. Fleisher, MD
Mark D. Neuman, MD

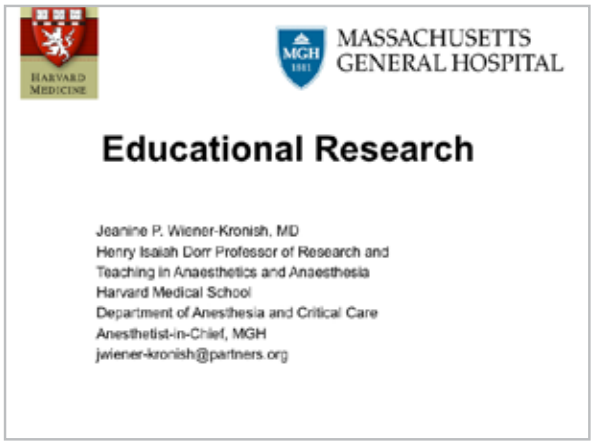


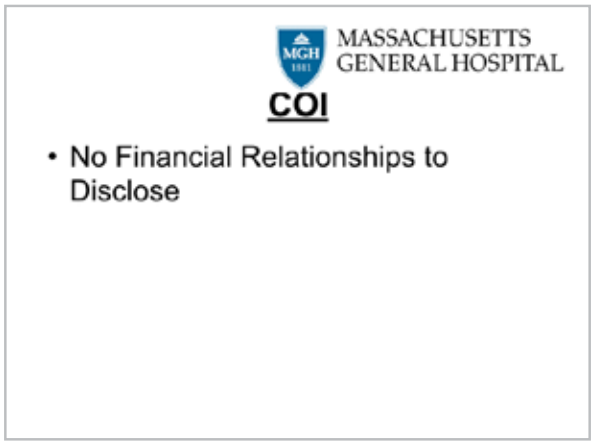


Friday, May 20

President's Panel: How to Produce Successful Researchers

Educational Research: Massachusetts General Hospital
Jeanine P. Wiener-Kronish, MD





2016 Abstract Award Winners

MARGARET WOOD RESIDENT RESEARCH AWARD	**CS/ Organ Inj 87 (151)** **A Novel Association Between High Density Lipoprotein Levels and the Risk of Acute Kidney Injury After Award Cardiac Surgery** **Loren E. Smith, MD, PhD**; Derek K. Smith, DDS; MacRae F. Linton, MD; Frederic T. Billings IV, MD, MSc *Vanderbilt University Medical Center, Nashville, Tennessee*	*Oral Presentation:* **SAB Oral Session (Part IV)** Friday, May 20, 2016 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
RESIDENT TRAVEL AWARD	**CS/Organ Inj 63 (132)** **Low Molecular Weight Hyaluronan Mediated Inflammation And Airway Hyperresponsiveness in Acid Aspiration Induced Acute Lung Injury in Mice** **Weifeng Song, MD, PhD**[1]; Zhihong Yu, MS[1]; Stavros Garantziotis, MD[2]; Sadis Matalon, PhD[1] *[1]University of Alabama at Birmingham, Birmingham, Alabama; [2]National Institute of Environmental Health Sciences, Research Triable Park, North Carolina of Environmental Health Sciences, Research Triable Park, North Carolina*	*Oral Presentation:* **SAB Oral Session (Part I)** Thursday, May 19, 2016 8:15 am – 9:15 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
RESIDENT TRAVEL AWARD	**CS 117 (140)** **Mitochondrial TRPV1 Regulates Endothelial Dysfunction in Diabetes** **Nana-Maria Wagner, MD**; Carl M. Hurt, MD, PhD; Honit Piplani, PhD; Stacy L. McAllister, PhD; Eric R. Gross, MD, PhD *Stanford University, Stanford, California*	*Oral Presentation:* **SAB Oral Session (Part IV)** Friday, May 20, 2016 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
JUNIOR FACULTY RESEARCH AWARD	**Pain 112 (101)** **The Analgesic Effects of Dopamine** **Norman E. Taylor, MD, PhD**[1]; JunZhu Pei, BS[2]; Ksenia Y. Vlasov, BA[2]; Jennifer A. Guidera, BA[1]; Ken Solt, MD[1]; Emery Brown, MD, PhD[1] *[1]Massachusetts General Hospital, Boston, Massachusetts, [2]Massachusetts Institute of Technology, Cambridge, Massachusetts*	*Oral Presentation:* **SAB Oral Session (Part III)** Friday, May 20, 2016 8:00 am – 9:00 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
JUNIOR FACULTY RESEARCH AWARD	**Anesth Cell Signaling/Genetics 11 (154)** **Gating of the Trek1 Tandem Pore Potassium Channel, a Molecular Signal Integrator and Anesthetic Target** **Paul M. Riegelhaupt, MD, PhD**[1], Marco Lolicato, PhD[2], Daniel Minor, PhD[2] *[1]Weill Cornell Medical College, New York, New York, [2]University of California, San Francisco, San Francisco, California*	*Oral Presentation:* **SAB Oral Session (Part II)** Thursday, May 19, 2016 9:30 am – 10:30 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm

Margaret Wood Resident Research Award

Clin Studies/OC 87 (151)

A Novel Association between High Density Lipoprotein Levels and the Risk of Acute Kidney Injury after Award Cardiac Surgery

Loren E. Smith, MD, PhD; Derek K. Smith, DDS; MacRae F. Linton, MD; Frederic T. Billings IV, MD, MSc

Vanderbilt University, Nashville, Tennessee

Introduction and General Purpose of the Study: Acute kidney injury (AKI) after cardiac surgery occurs in up to 30% of patients and is an independent predictor of death.[1] HDL has known anti-oxidant and anti-inflammatory properties and may attenuate mechanisms of AKI.[2] We hypothesized that a high preoperative HDL cholesterol concentration is protective against postoperative AKI.

Methods: After IRB approval, data were obtained from a prospective, 393-subject trial of perioperative atorvastatin to prevent post-cardiac surgery AKI. Statin-using patients were randomized to placebo or 80mg atorvastatin the morning of surgery and 40mg on postoperative day[1]. Stain-na¯ve patients were randomized to placebo or 80mg the day prior to surgery and 40mg daily thereafter during hospitalization. The association between HDL level and maximum serum creatinine change from baseline in the first 48 postoperative hours was assessed using a two-component latent variable mixture model and AKI risk factors. Regression analyses assessed interactions of chronic statin use, perioperative atorvastatin treatment, and HDL level on AKI risk.

Results and Major Findings: Postoperative AKI occurred in 99 patients (25.2%). Median (10th, 90th percentile) preoperative HDL was 37.6 (25.0, 54.0) mg/dl and postoperative creatinine change 0.09 (-0.11, 0.59) mg/dl. Lower HDL levels were independently associated with increased creatinine rise (p=0.02) (Figure 1A). Regression analysis showed this association was present in statin-using but not statin-na¯ve patients (p=0.008) (1B). The protective effect of high HDL in chronic statin users was enhanced with perioperative atorvastatin treatment (p=0.004) (1C) and with increasing chronic statin dose (p=0.003) (1D). Similar analyses using LDL found no association with postoperative AKI risk (p=0.51).

Conclusions: Higher preoperative HDL was associated with less risk of AKI. Statin exposure modified this association. Specifically, subjects with higher HDL levels on chronic statin therapy had less creatinine rise and appeared to further benefit from higher chronic statin dose and perioperative atorvastatin therapy. These findings support a possible pleotropic effect of statins on HDL in the context of AKI and a potential new role for HDL during the perioperative period. Future work involves identifying the biological mechanism underlying these associations.

References

1. Perioperative Medicine, vol 1, pg 6, 2012.
2. Journal of Clinical Lipidology, vol 6, pg 524, 2012.

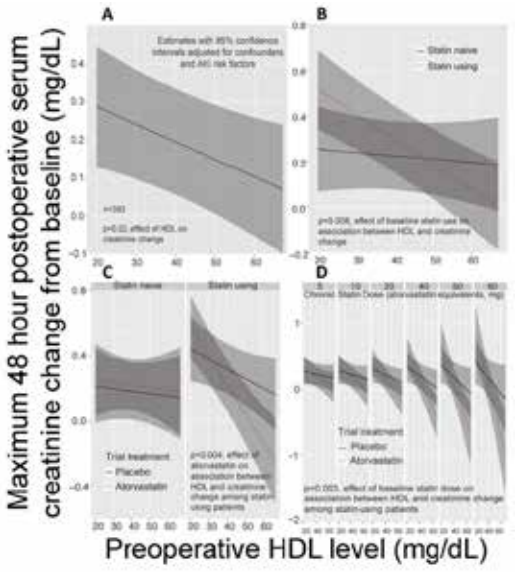
CS/Organ Inj 63 (132)

Low Molecular Weight Hyaluronan Mediated Inflammation and Airway Hyperresponsiveness in Acid Aspiration Induced Acute Lung Injury in Mice

Weifeng Song, MD, PhD[1]; Zhihong Yu, MS[1]; Stavros Garantziotis, MD[2]; Sadis Matalon, PhD[1]

[1]University of Alabama at Birmingham, Birmingham, Alabama; [2]National Institute of Environmental Health Sciences, Research Triable Park, North Carolina

Introduction: Pulmonary aspiration of acid and/or gastric contents is a severe complication of general anesthesia with even higher incidence in susceptible population (i.e. trauma or critical care patients etc), which is recognized as a major direct cause of acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Clinical symptoms are characterized by hypoxia, bronchospasm, pulmonary edema and respiratory failure arsing from inflammation and airway hyperresponsiveness (AHR). Despite the clinical importance, the underlying mechanisms responsible for progression to acute lung injury are not fully understood, therefore the treatment is limited to be mainly supportive. We aim to investigate the injury process after aspiration and identify the roles of low molecular weight hyaluronan (LMW-HA), the degradation product of lung matrix and one of the endogenous danger-associated molecular patterns (DAMPs) in aspiration induced acute lung injury.



Methods: A mouse pulmonary acid aspiration model was used. Mice were intratracheally given HCl (pH 1.25, 2ml/kg), lung inflammation and airway resistance and reactivity were assessed after aspiration. CD44 and TLR4 knockout mice, which are deficient of the two major receptors of hyaluronan, were used to investigate the roles of LMW-HA.

Results: We found mice developed significant pulmonary edema, inflammation and airway hyperresponsiveness to methacholine challenge at 1, 5 and 24 hours after acid aspiration as measured by flexiVent. BALF analysis showed increased protein and inflammatory cells exudation, as well as elevation of inflammatory cytokines and chemokines. In addition, a significant increase of hyaluronan (HA) and its binding facilitate protein, inter-Î±-trypsin inhibitor (Ial) also occurred in the BALF at 24 hours after aspiration. Agar gel electrophoresis analysis of BALF concentrate demonstrated the size of HA was that of LMW-HA. The time course of the elevation of LMW-HA was in consistent with that of the neutrophil infiltration, indicating a reactive oxygen species induced matrix degradation. However, both CD44 and TLR4 knockout mice exhibited decreased airway reactivity to methacholine challenge after acid aspiration compared with their wild type controls. Moreover, nasopharyngeally administered high molecular weight hyaluronan (HMW-HA, 3mg/ml, 50microliter), a competitive inhibitor of LMW-HA, at 1 and 23 hours after HCl aspiration significantly mitigated the airway hyperresponsiveness at 24 hours after aspiration.

Conclusion: Our data for the first time suggest a critical role of LMW-HA in mediating the inflammation and AHR in acid aspiration induced lung injury, and provide insight into the mechanisms of injury progression after pulmonary acid aspiration. We further propose that HMW-HA, which is currently used in clinical trials in Europe for the treatment of asthma, may serve as a novel therapeutic agent for aspiration induced lung injury.

References

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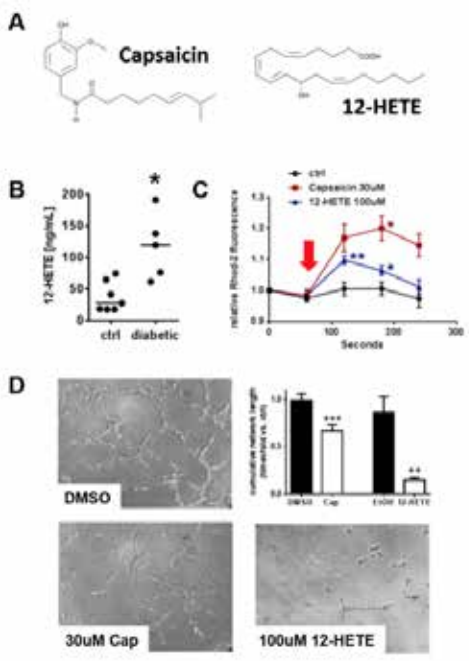
2. Am J Physiol Lung Cell Mol Physiol. 2015. 308(9):L891-903.

CS 117 (140)
Mitochondrial TRPV1 Regulates Endothelial Dysfunction in Diabetes

Nana-Maria Wagner, MD; Carl M. Hurt, MD, PhD; Honit Piplani, PhD; Stacy L. McAllister, PhD; Eric R. Gross, MD, PhD

Stanford University, Stanford, California

Introduction: Patients with diabetes mellitus are at risk for perioperative adverse cardiovascular complications[1]. A biomarker estimating existing vascular pathology for pre-operative risk stratification is currently unavailable. High glucose levels induce increased lipid peroxidation in endothelial cells and can cause endothelial dysfunction[2]. The lipid peroxidation product, 12-hydroxyeicosatetraenoic acid (12-HETE), shares structural similarity with capsaicin (Fig. A). Further, 12-HETE is considered the endogenous activator of the transient receptor potential vanilloid 1 (TRPV1)[3]. Therefore, we hypothesize 12-HETE is increased in diabetes and induces endothelial dysfunction by activating mitochondrial TRPV1.



Methods: Male Sprague-Dawley rats were given either streptozotosin (65mg/kg) to induce diabetes or vehicle. Rats were maintained without insulin for 2 weeks. Blood samples drawn via tail vein were used to measure 12-HETE plasma concentrations in diabetic and non-diabetic rats by mass spectrometry. Further, TRPV1 expression was investigated in human umbilical vein endothelial cells (HUVECs) employing immunohistochemistry. HUVECs were subjected to stimulation with the TRPV1 agonist capsaicin (30uM) or 12-HETE (100uM). Changes in mitochondrial calcium and transmembrane potential by flow cytometry of rhodamine-2 and JC-10 aggregate emission was performed. Mitochondrial function was also assessed using a Seahorse Extracellular Flux Analyzer, endothelial cell function by in vitro capillary tube formation, and cell viability via annexin V/propidium iodide binding. Statistical analysis was performed using ANOVA followed by Bonferroni correction.

Results and Major Findings: In diabetic rats, a higher plasma concentration of 12-HETE was detected compared to non-diabetic rats (117Â±23 vs. 37Â±9ng/mL, *P<0.05, n=5-7, Fig. B). TRPV1 was located primarily at endothelial cell mitochondria. Stimulation with capsaicin or 12-HETE induced mitochondrial calcium influx (*P<0.05 or **P<0.01 vs. DMSO or ethanol-vehicle control, respectively, n=4-6, Fig. C) and caused a decline in mitochondrial transmembrane potential (P<0.01 and P<0.05, n=4-5). Capsaicin also induced mitochondrial dysfunction (P<0.001; n=4) and reduced endothelial cell capillary formation, similar to 12-HETE (***P<0.001 and **P<0.01, n=3, Fig. D). These effects occurred independent of cell viability.

Conclusions: We identified a key endogenous lipid peroxidation product, 12-HETE, is elevated during diabetes and in human endothelial cells can induce changes in mitochondrial dynamics leading to endothelial cell dysfunction. Although further studies are needed, our results suggest 12-HETE plasma concentration mirrors in diabetics the severity of vascular dysfunction. 12-HETE could thus serve as a potent biomarker to assess perioperative risk in patients with known or previously undiagnosed diabetes mellitus.

References

1. J Am Coll Cardiol, 2014;64:e77-137
2. Int J Diabetes Mellit, 2010;2:189-195
3. Proc Natl Acad Sci, 2000;97:6155-6160

Pain 112 (101)
The Analgesic Effects of Dopamine

Norman E. Taylor, MD, PhD[1]; JunZhu Pei, BS[2]; Ksenia Y. Vlasov, BA[2]; Jennifer A. Guidera, BA[1]; Ken Solt, MD[1]; Emery Brown, MD, PhD[1]

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

Introduction: Despite years of study, current treatments do not adequately treat chronic pain. Drugs which modulate neural dopamine (DA) levels produce significant analgesic effects, while also preventing the opioid-induced side effects of nausea, respiratory depression and sedation. Despite their potential, DA modulating agents have never become a clinical tool for the relief of pain, possibly due to a lack of understanding about their mechanism of action. We hypothesized that DA neurons in the periaqueductal gray (PAG) exert a powerful modulating effect on pain and are important participants in descending pain inhibition. To test this hypothesis, we used DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to see if selective stimulation of DA neurons in the PAG could produce analgesia in an inflammatory pain model.

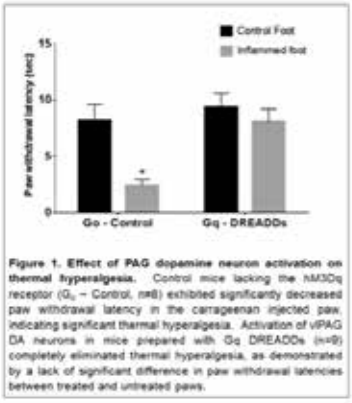


Figure 1. Effect of PAG dopamine neuron activation on thermal hyperalgesia. Control mice lacking the hM3Dq receptor (G_o – Control, n=8) exhibited significantly decreased paw withdrawal latency in the carrageenan injected paw, indicating significant thermal hyperalgesia. Activation of vlPAG DA neurons in mice prepared with Gq DREADDs (n=9) completely eliminated thermal hyperalgesia, as demonstrated by a lack of significant difference in paw withdrawal latencies between treated and untreated paws.

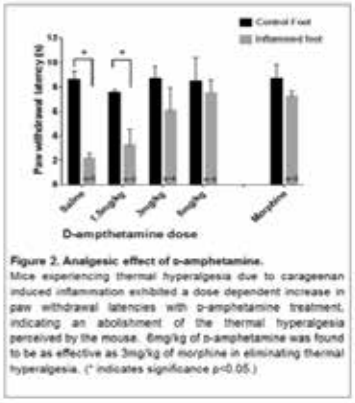


Figure 2. Analgesic effect of d-amphetamine. Mice experiencing thermal hyperalgesia due to carrageenan induced inflammation exhibited a dose dependent increase in paw withdrawal latencies with d-amphetamine treatment, indicating an abolishment of the thermal hyperalgesia perceived by the mouse. 6mg/kg of d-amphetamine was found to be as effective as 3mg/kg of morphine in eliminating thermal hyperalgesia. (* indicates significance $p<0.05$.)

Methods: DREADDs are G-protein coupled receptors engineered to be selectively activated by the ligand Clozapine N-Oxide (CNO). Male, adult, DAT-cre mice received bilateral injections of adeno-associated virus carrying an excitatory DREADDs construct (hM3Dq) into the ventral lateral PAG. Control mice were similarly prepared, but were injected with a construct lacking the hM3Dq receptor. After at least 4 weeks to allow stable viral transfection, thermal hyperalgesia was measured by injecting a carrageenan solution into a single hind paw and measuring the time latency for paw withdrawal upon thermal stimulation. Viral expression and localization were confirmed using immunohistochemistry upon completion of the study.

á´…-amphetamine is a clinically available drug which modulates neural DA levels, and provides a translational approach to examining the relevance of the modulatory effect of DA neurons in the PAG. We subsequently treated carrageen-induced hind limb pain in adult male C57BL/6 mice with intraperitoneal (ip) á´…-amphetamine, and compared the analgesic effect with morphine treated mice.

Results: We found that following ip CNO injection in control mice (n=8), paw withdrawal latency in the carrageenan injected paw was significantly decreased at 2.4Â±0.7s compared with 8.0Â±1.5s in the non-injected paw, indicating significant thermal hyperalgesia ($p<0.005$) (FIG 1). Animals with DREADD activation of vlPAG DA neurons by CNO (n=9) showed no significant difference in paw withdrawal latencies between treated (8.2Â±1.7s) and untreated paws (9.3Â±1.6s), indicating that DA neuron activation in the PAG prevented the inflammation-induced thermal hyperalgesia. Histologic examination of neural tissue following the experiments confirmed DREADD viral expression in PAG DA neurons.

As shown in FIG 2, a dose dependent increase in paw withdrawal latencies was observed with ip. á´…-amphetamine treatment, indicating an abolishment of the thermal pain perceived by the mouse. 6mg/kg of á´…-amphetamine was found to be as effective as 3mg/kg of morphine in eliminating hind paw pain in carrageenan induced inflammation, suggesting a powerful analgesic role for DA modulating drugs.

Conclusions: In summary, selective activation of DA neurons in the vlPAG as well as systemic administration of á´…-amphetamine produced profound analgesia in an inflammatory pain model. DA modulating agents may represent a novel new treatment for pain.

Anesth Cell Signaling/Genetics 11 (154)
Gating of the Trek1 Tandem Pore Potassium Channel, a Molecular Signal Integrator and Anesthetic Target

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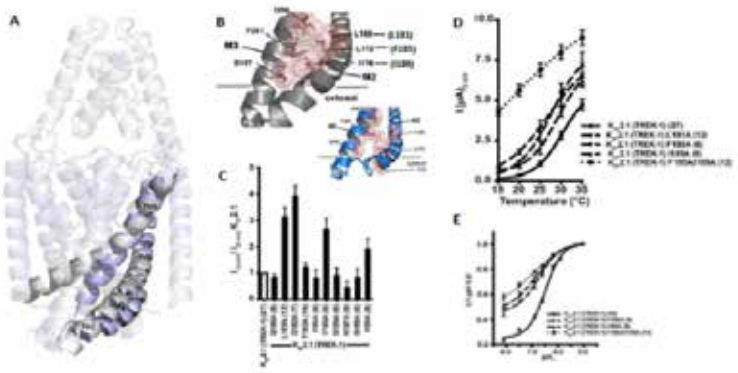
Introduction: Background (or "leak") potassium channels of the K2P family are essential to the function of neuronal cells. These channels are constitutively open potassium selective pores that set the cellular resting membrane potential, and modulation of their activity alters the action potential firing rate of electrogenic cells. K2P channels are expressed throughout the central nervous system, as well as in cardiac, renal, vascular, and other tissues[1]. Of the 13 members of this family, TREK1 (TWIK related potassium channel 1) is the most widely studied. It is modulated by both intracellular and extracellular acidosis, polyunsaturated fatty acids, temperature, membrane stretch, and volatile anesthetics[2, 3]. TREK1 knockout mice exhibit resistance to general anesthetics, and TREK1 channels are proposed to play a role in neuronal disease states including epilepsy, pain, and depression[4]. Given TREK1's importance to human physiology and its potential as a drug target, we sought to understand the basic mechanisms by which TREK1 senses and responds to such diverse and dissimilar gating stimuli.



Methods: To approach this problem, we paired functional studies with protein purification and crystallography of WT and constitutively activate K2P channel mutants. Functional studies involved alanine-scanning mutagenesis and subsequent characterization of mutants within the second transmembrane (TM2) domain of TREK1. Site directed mutagenesis was performed on a mouse TREK1 cDNA clone, and clones were in-vitro transcribed to generate mRNA. TREK1 mRNA was injected into X. Laevis oocytes for subsequent two-electrode voltage clamp studies. These findings were correlated with crystallographically defined structures of TRAAK WT and a constitutively active TRAAK G124I mutant.[5]

Results: Our structural and functional studies identify the conformational moves that underlie gating transitions in K2P channels. Channel activation causes the 4th transmembrane domain (TM4) of TRAAK to straighten, leading to buckling of the TM2 (A). Our alanine scanning approach identified four residues within involved in channel gating (L181, G182, F185 and I189), all of which line one face of the TM2 helix involved in the observed structural rearrangements (B,C). Further characterization of these mutant demonstrates that they have increased basal currents and attenuated responses to temperature or external pH gating cues (D,E). These functional findings validate our structural data and define a mechanism by which structural movements lead to channel activation.

Conclusions: K2P potassium channels are increasingly being recognized at important modulators of a wide range of physiologic processes. Our study elucidates key structural movements that underlie gating of a candidate member of this group. We provide a framework for understanding how a diverse set of gating signals combine to modulate K2P ion channels, and suggest a physical site at which anesthetics might modulate this class of channels.

References

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SAB Oral Session I
Thursday, May 19, 2016 ▪ 8:15 am – 9:15 am

Moderators: Nabil Alkayed, MD, PhD, Oregon Health & Science University, Portland, Oregon, and Peter Goldstein, MD, Weill Cornell Medical College, New York, New York

	CS/Organ Inj 59 (39) **Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO** **HT Lee, MD, PhD**; May Rabadi, PhD; Kevin Brown, BA; Mihwa Kim, PharmD *Columbia University, New York, New York*	*Oral Presentation:* **SAB Oral Session (Part I)** Thursday, May 19, 2016 8:15 am – 9:15 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
	CS/Organ Inj/Sep 72 (68) **Role of the gut-lung axis and IL-1b signaling in sterile inflammation following lung ischemia reperfusion injury** **Arun Prakash, MD, PhD**; Judith Hellman, MD *University of California, San Francisco, San Francisco, California*	*Oral Presentation:* **SAB Oral Session (Part I)** Thursday, May 19, 2016 8:15 am – 9:15 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
	CS/Organ Inj 60 (113) **Inhibition of Free Fatty Acid Receptor GPR40 abolishes Cardioprotection Conferred by Intralipid in Two Rodent Models of Bupivacaine Cardiotoxicity and Ischemia Reperfusion Injury** **Soban Umar, MD, PhD**; Jingyuan Li, MD, PhD; Parisa Partownavid, MD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD *University of California, Los Angeles, Los Angeles, California*	*Oral Presentation:* **SAB Oral Session (Part I)** Thursday, May 19, 2016 8:15 am – 9:15 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
RESIDENT TRAVEL AWARD	**CS/Organ Inj 63 (132)** **Low Molecular Weight Hyaluronan Mediated Inflammation And Airway Hyperresponsiveness in Acid Aspiration Induced Acute Lung Injury in Mice** **Weifeng Song, MD, PhD**[1]; Zhihong Yu, MS[1]; Stavros Garantziotis, MD[2]; Sadis Matalon, PhD[1] *[1]University of Alabama at Birmingham, Birmingham, Alabama; [2]National Institute of Environmental Health Sciences, Research Triable Park, North Carolina.* *See Page 56 for complete abstract*	*Oral Presentation:* **SAB Oral Session (Part I)** Thursday, May 19, 2016 8:15 am – 9:15 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm

SAB Oral Session II
Thursday, May 19, 2016 ▪ 9:30 am – 10:30 am

Moderators: Nabil Alkayed, MD, PhD, Oregon Health & Science University, Portland, Oregon, and Peter Goldstein, MD, Weill Cornell Medical College, New York, New York

	Organ Inj 70 (48) **Therapeutic Effects of Microvesicles Derived From A Mouse Macrophage Cell Line (RAW264.7) in Severe Pneumonia in Mice** **Jae-Woo Lee, MD** *University of California, San Francisco, San Francisco, California*	*Oral Presentation:* **SAB Oral Session (Part II)** Friday, May 20, 2016 9:30 am – 10:30 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
JUNIOR FACULTY RESEARCH AWARD	**Anesth Cell Signaling/Genetics 11 (154)** **Gating of the TREK1 Tandem Pore Potassium Channel, a Molecular Signal Integrator and Anesthetic Target** **Paul M. Riegelhaupt, MD, PhD**[1], Marco Lolicato, PhD[2], Daniel Minor, PhD[2] *[1]Weill Cornell Medical College; [2]University of California, San Francisco* *See Page 59 for complete abstract*	*Oral Presentation:* **SAB Oral Session (Part II)** Friday, May 20, 2016 9:30 am – 10:30 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
	Basic Neuro/Inj 45 (152) **Microglia Exacerbate Neuronal Death after Cardiac Arrest** **Ines P. Koerner, MD, PhD**; Mizuko Ikeda, MD, PhD *Oregon Health and Science University, Portland, Oregon*	*Oral Presentation:* **SAB Oral Session (Part II)** Friday, May 20, 2016 9:30 am – 10:30 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
	Basic Neuro/Inj 36 (162) **Systemic HMGB1 Impairs Synaptic Plasticity after Surgery in Aged Rats** **Niccolo Terrando, BSc (Hons), DIC, PhD**[1]; Wen Ouyang, MD[2]; Ting Yang, MD, PhD[1]; Jianbin Tong, MD, PhD[2] *[1]Duke University, Durham, North Carolina; [2]Third Xiangya Hospital, Hunan, China*	*Oral Presentation:* **SAB Oral Session (Part II)** Friday, May 20, 2016 9:30 am – 10:30 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm

CS/Organ Inj 59 (39)
Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

HT Lee, MD, PhD; May Rabadi, PhD; Kevin Brown, BA; Mihwa Kim, PharmD

Columbia University, New York, New York

Acute kidney injury (AKI) due to ischemia and reperfusion injury (IR) is a devastating clinical problem without effective clinical therapy. We previously showed that peptidylarginine deiminase-4 (PAD4 - an enzyme that converts peptidylarginine to peptidylcitrulline) plays a critical role in ischemic AKI injury by promoting renal tubular inflammation and neutrophil infiltration. However, the mechanisms of PAD4-mediated renal inflammation and injury remain unknown. Here, we tested the hypothesis that PAD4 induces renal inflammation and exacerbates renal IR injury by citrullinating NFkB Essential MOdulator (NEMO) thereby promoting renal tubular pro-inflammatory NFkB signaling. Furthermore, we tested whether targeted inhibition of NEMO attenuates renal inflammation and protects against ischemic AKI in vivo.

To test whether PAD4 directly citrullinates NEMO, human recombinant NEMO or human proximal tubule (HK-2) cells were treated with either vehicle (1% DMSO) or with recombinant human PAD4 (rPAD4, 1 µg/ml) for 3 hr and were then subjected to immunoblotting for citrullinated NEMO and total NEMO. HK-2 cell nuclear and cytosolic fractions were isolated to test whether rPAD4 treatment (10 µg/ml for 4 hr) promotes nuclear NFkB translocation via NEMO citrullination. In addition, HK-2 cells were treated with 10 g/ml human rPAD4 for 6 hr with or without NEMO binding peptide (NBP) to test whether NEMO neutralization attenuates rPAD4-mediated induction of pro-inflammatory mRNAs (MIP-2, MCP-1, TNF-± and IL-8). To determine whether NEMO blockade attenuates rPAD4-mediated exacerbation of ischemic AKI and renal inflammation, male C57BL/6 mice were pretreated with vehicle (saline) or with NBP (5mg/kg) before 10 µg rPAD4 treatment and 20 min renal IR injury (obtained IACUC approval). Kidney injury was assessed by analyzing plasma creatinine and tissue injury scores and renal inflammation was measured by measuring neutrophil infiltration and pro-inflammatory mRNA expression using qRT-PCR.

Human rPAD4 directly citrullinated recombinant human NEMO (Fig 1A, N=6) in a cell free system as well as in HK-2 cells (Fig. 1B, N=6). In addition, rPAD4 caused nuclear NFkB-p65 subunit translocation which was attenuated by NEMO neutralization with NBP (Fig. 2). Furthermore, NEMO neutralization attenuated rPAD4-mediated induction of pro-inflammatory genes (MCP-1 by 59±11%, MIP-2 by 43±10%, TNF-± by 59±12% and IL-8 by 83±3%) in HK-2 cells ($P<0.05$, N=5-8). Consistent with our in vitro findings, mice pretreated with rPAD4 protein and subjected to 20 min renal IR developed exacerbated ischemic AKI and renal inflammation measured by plasma creatinine, neutrophil infiltration (Fig. 3, N=4-6) and pro-inflammatory mRNA expression (data not shown). NEMO neutralization significantly attenuated rPAD4-mediated exacerbation of ischemic AKI as well as renal inflammation in mice (Fig. 3).

Taken together, our studies show that PAD4 exacerbates ischemic AKI and inflammation by promoting renal tubular NFkB activity via NEMO citrullination. Furthermore, we show that NEMO inhibition attenuates kidney injury and reduces the inflammatory response after renal IR injury. NEMO neutralization with NBP may serve as a potential therapy for this devastating clinical problem.

CS/Organ Inj/Sep 72 (68)
Role of the Gut-Lung Axis and IL-1b Signaling in Sterile Inflammation Following Lung Ischemia Reperfusion Injury

Arun Prakash, MD, PhD; Judith Hellman, MD

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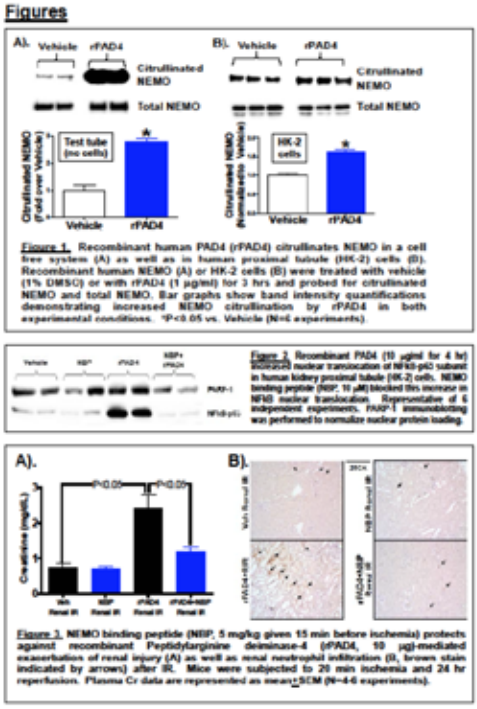
Introduction and General Purpose of Study: Ischemia reperfusion (IR) injury is a source of sterile inflammation that can complicate the clinical course of severely injured trauma patients in shock, as well as those undergoing organ transplantation, or thrombotic/embolic events. The lungs are a portal to the external environment and a barrier organ. As such, they are vulnerable to infectious and sterile insults that can be life threatening if their ability to deliver oxygen and eliminate CO2 is compromised. We previously reported that alveolar macrophages and the TLR4 signaling pathway are required early in the creation of sterile lung IR inflammation[1]. More recently, we have demonstrated a role for the intestinal microbiome in modulating this inflammatory process in vivo and in priming alveolar macrophages to inflammatory agonists, such as LPS and nigericin[2]. The current studies evaluate the role of IL-1b signaling in lung IR injury and further define potential mechanisms by which intestinal bacteria modulate the inflammatory responses of lung cell populations to IR.

Figures



Methods: We used an in vivo model of left pulmonary artery occlusion to examine the inflammation generated in mice either genetically deficient or pharmacologically inhibited in IL-1b release or signaling pathways. These include the ASCko, NLRP3ko, NLRC4ko, Caspase 1/11dko, IL-1Rko mice and wild-type mice treated with IL-1b neutralizing antibodies and caspase inhibitors. We also challenged alveolar macrophages and endothelial cells in vitro with colonic lumen filtrates from antibiotic treated and control mice to determine whether shed LPS and metabolites, such as butyrate and acetate were among the priming factor(s) affecting alveolar macrophages.

Results and Major Findings: Using knockout mice and inhibitor studies, we have determined that the inflammasome regulates lung IR-induced sterile inflammation. This was measured by detecting decreased IL-6 levels in select inflammasome knockouts compared to wild-type mice. Specifically, we demonstrated that the NLRP3 inflammasome, IL-1b release via caspase activation, and downstream IL-1b signaling are important factors in the generation of lung IR inflammation. Furthermore, we believe that the exponentially higher level of LPS in the colonic lumen filtrates from mice with a full complement of intestinal microbiota, along with the presence of low levels of short chain fatty acids, such as butyrate, may serve to prime alveolar macrophages and in turn results in IL-1b and downstream IL-6 production in the context of lung IR.

Conclusions: Taken together, our data supports the existence of an intriguing gut-lung axis of communication that modulates the lung IR sterile inflammatory process through inflammasome and IL-1 signaling pathways. This suggests that dysbiosis present in disease states can affect not only immune responses locally in the intestine but also remotely in the lung.

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CS/Organ Inj 60 (113)

Inhibition of Free Fatty Acid Receptor GPR40 Abolishes Cardioprotection Conferred by Intralipid in Two Rodent Models of Bupivacaine Cardiotoxicity and Ischemia Reperfusion Injury

Soban Umar, MD, PhD; Jingyuan Li, MD, PhD; Parisa Partownavid, MD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD

University of California, Los Angeles, Los Angeles, California

Introduction and General Purpose of Study: We have previously shown that Intralipid (ILP) protects the heart against ischemia/reperfusion injury and Bupivacaine cardiotoxicity. However the underlying mechanisms of ILP's cardioprotection is not fully understood. Free fatty acid receptor-1 or GPR40 is expressed in the heart and is activated by medium and long chain fatty acids. We explored whether cardioprotective effects of ILP are mediated, at least in part, through GPR40 in two animal models of I/R injury and Bupivacaine cardiotoxicity.

Methods: Bupivacaine cardiotoxicity: Sprague-Dawley rats were used. Continuous Echo and ECG were performed. In protocol-1 (n=3) rats received Bupivacaine bolus (10mg/kg, IV) to induce asystole. Resuscitation with ILP 20% (5ml/kg bolus, and 0.5ml/kg/min maintenance) and chest compressions were initiated. In protocol-2 (n=3) rats were pre-treated with GPR40-antagonist GW1100 (200uM, IV) 30-min before inducing asystole. Heart rate (HR) and ejection-fraction (EF) were measured before and 30-min after GW. In both protocols, HR, EF and fractional shortening (FS) were measured before asystole (baseline) and at 1, 5 and 10min after ILP.

I/R: Mice were anesthetized and hearts quickly removed and perfused on a Langendorff apparatus with Krebs Henseleit (KH) buffer. Aorta was clamped for 20 min to induce global ischemia at 370C, followed by 40 min reperfusion with KH (CTRL), with additional 1% ILP (ILP), or with 1% ILP together with GW (10μM, ILP+GW). A catheter was directly inserted into the left ventricle (LV) to measure LV systolic pressure (LVSP), LV end-diastolic pressure (LVEDP) and HR. The LV developed pressure (LVDP) was calculated as LVSP-LVEDP and rate pressure product (RPP) as HRxLVDP. The dP/dtmax and -dP/dtmin were calculated from recordings. The n=3-7/group and data were expressed as mean±SEM.

Results: Bupivacaine cardiotoxicity: In protocol-1, baseline HR and EF were 321±21 beats/min and 72.3±4.6%. Bupivacaine resulted in asystole and ILP improved HR gradually; HR was 86±13 at 1min (27% recovery), 216±10 at 5min (67% recovery), and 228±14 at 10min (71% recovery). LV function fully recovered within 5 min of ILP as EF and FS were similar to baseline (EF=72±5%, FS=42±4%). In protocol-2, there were no significant differences between HR and EF before (HR=316.6±3.3, EF=68.0±2.3%) and 30-min after GW (HR=330±5.7, EF=71.6±1.5%) excluding GW effects on hemodynamics. GW pre-treatment however prevented ILP rescue, with no recovery of cardiac function even after 10min.

I/R: ILP significantly improved RPP from 2349±1824 in CTRL to 10213±1217 in ILP. GW prevented protective effect of ILP since the RPP in ILP+GW was significantly lower than ILP (2186±674, n=7). LVDP was also lower in ILP+GW compared to ILP alone (22.6±3.9 in ILP+GW, 70.6±13.2 in ILP, 11.9±6.7 in CTRL, $p<0.01$ ILP+GW vs. ILP). ILP+GW also showed much lower LV dP/dtmax and LV dP/dtmin compared to ILP (dP/dtmax=749.1±14.6 in ILP+GW, 2127.4±408 in ILP, 338.4±248 in CTRL $p<0.01$ ILP+GW vs. ILP; dP/dtmin=-443±99 in ILP+GW, -1464±206 in ILP, -243±168 in CTRL, $p<0.01$ ILP±GW vs. ILP).

Conclusions: GPR40 is involved in cardioprotection mediated by ILP against Bupivacaine-induced cardiotoxicity and cardiac I/R injury, as pre-treatment with a selective GPR40 antagonist prevents ILP's rescue.

CS/Organ Inj/Sepsis 70 (48)

Therapeutic Effects of Microvesicles Derived From a Mouse Macrophage Cell Line (RAW264.7) in Severe Pneumonia in Mice

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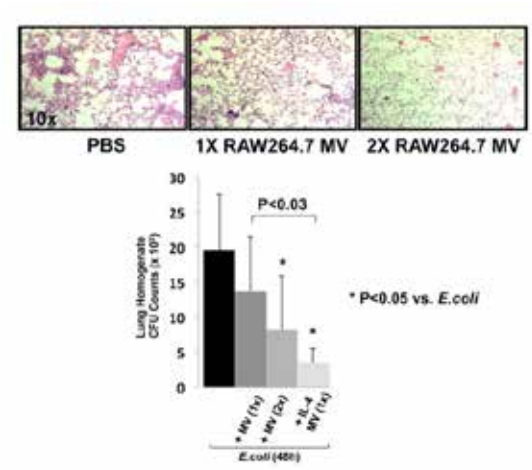
Introduction: We and others have demonstrated that human bone marrow derived mesenchymal stem or stromal cells (MSC) were effective in treating acute lung injury from endotoxin and bacterial pneumonia. Based in part due to these results, we are involved in an on-going Phase I/II clinical trial studying the use of human MSC in ARDS (NCT01775774)[1]. However, stem cell based therapy has potential risks such as long term iatrogenic tumor formation. We recently demonstrated that microvesicles (MV) released from human MSC were as effective as the parent stem cells as a therapeutic in severe bacterial pneumonia[2]. MVs are circular anuclear fragments of membrane (50-200 nM in size) constitutively released from multiple cell types. However, the amount of MVs needed to generate an equivalent therapeutic effect as MSCs was approximately 5-10x higher, making the production cost potentially prohibitive. In the current studies, to overcome this limitation of MV therapy, we hypothesized that MVs derived from a mouse macrophage cell line (RAW264.7) would reduce indices of acute lung injury in mice with severe bacterial pneumonia. Alveolar macrophages are among the primary cellular targets of MSCs or MSC MVs in acute lung injury, which is largely responsible for its therapeutic effects.



Methods: Severe bacterial pneumonia was induced in C57BL/6 male mice (10-12 wks, 25 gm) by the intra-tracheal instillation of 2 x 10(6) colony forming units (CFU) of Escherichia coli K1 strain bacteria. After 4h, either 1X (90 µl) or 2X (180 µl) of RAW264.7 MVs or phosphate buffered saline as a carrier control were administered intravenously; the dose refers to the MVs released by 9 or 18 x 10(6) serum starved RAW264.7 cells over 48 h respectively. At 24 or 48 h, a bronchoalveolar lavage (BAL) was performed and cytokines, total bacterial counts and protein levels in the BAL fluid were measured.

Results: MVs were isolated from the conditioned medium of serum starved RAW264.7 cells at 48 h using ultracentrifugation. Viability of RAW264.7 cells were >90%, excluding apoptotic bodies in the isolated MVs. By electron microscopy, RAW264.7 MVs appeared as small membrane bound vesicles 50-100 nm in size. Protein concentration of 10 µl RAW264.7 MVs was 0.9 ± 0.1 µg (N =3) , suggesting that the vesicular content was much smaller than previously seen with MSC MVs. Compared to E.coli pneumonia-injured mice, administration of RAW264.7 MVs significantly reduced the total influx of inflammatory cells, especially neutrophils, and protein levels in the injured alveolus, reflecting a decrease in lung protein permeability. RAW264.7 MVs, at the higher 2x dose, also reduced TNFÐ levels and total bacterial CFU counts at 48 h. MVs released from IL-4 preconditioned RAW264.7 cells to assume a M2 phenotype further decreased the bacterial count by an additional 50% (FIGURE).

Conclusions: Similar to MVs derived from MSCs, MVs derived from RAW264.7 cells were effective in severe bacterial pneumonia in terms of reducing inflammation, permeability and infection. Further studies are on-going to determine whether MSC can be immortalized to generate an unlimited supply of MSC MVs for therapy.

References

1. Lancet Respir Med 3:24-43, 2015.

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Basic Neuro/Inj 45 (152)
Microglia Exacerbate Neuronal Death after Cardiac Arrest

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Introduction: Following global ischemia during cardiac arrest (CA) and cardiopulmonary resuscitation (CPR), neurons characteristically do not die immediately, but rather in a delayed manner over days after resuscitation. Microglia (MG), the brain's resident immune cells, are rapidly activated after CA/CPR, before neuronal death occurs in both humans and in animal models. While it is likely that the microglial inflammatory response accelerates and exacerbates neuronal death, this causal relation has not been confirmed in vivo. We used a newly available genetically engineered mouse that allows selective ablation of brain resident MG to confirm that MG are indeed responsible for delayed neuronal death after CA/CPR.

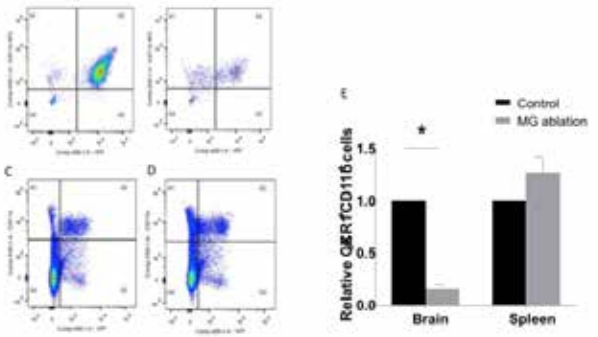

FIGURE 1. Representative flow cytometry analysis of brain (above) and spleen (below) tissue harvested from control mice (A, C) and microglia ablation mice (B, D). Dot plots in Q2 shows CX3CR1□EYFP+CD11b+ cells gated on CD45int, CD3Ð, CD19□. E: Quantification of data shown in (A□D). n = 5, 12, 2 and 4 respectively. Data are shown as mean ± SEM, *p < 0.05.

Methods: We used CX3CR1-CreER mice expressing tamoxifen-inducible Cre recombinase to drive diphtheria toxin receptor (DTR) expression in MG and peripheral macrophages (CX3CR1-CreER±/iDTR±). We induced Cre-recombination with a tamoxifen pulse 30 days before ablating cells that express DTR by diphtheria toxin (DT) injection. This delay allows for the short-lived peripheral macrophages to be completely turned over and replaced by non-DTR expressing cells, while the low-turnover MG maintain DTR expression, allowing selective ablation of MG by DT injection. We used CX3CR1-CreER±/iDTR-/- mice that do not express DTR as controls. Control mice received both tamoxifen and DT to exclude nonspecific drug effects. Mice were subjected to CA/CPR one day after final DT injection. CPR was initiated after 10 minutes of CA by injection of epinephrine and chest compressions at a rate of 300/minute. 3 days later, hippocampal tissue was harvested for quantification of neuronal death. We used flow cytometry analysis to confirm successful and selective ablation of MG. Brain and spleen were harvested one day after final DT injection. Tissues were dissociated to single-cell suspension by enzymatic digestion and mechanical disruption. Cells were stained with CD11b-APC, CD45-APC-eFluor® 780, CD19-PE, and CD3-PE-Cy7 antibodies. The CX3CR1+ CD11b+ population was assessed by flow cytometry (gated on CD45int, CD3-, CD19-). Group differences were evaluated using Chi-square test or Student's t-test, as appropriate. All data are presented as mean ±SD.

Results: DT injection markedly reduced the number of CX3CR1+CD11b+ MG in the brain by 84 ± 13% (P < 0.01) in CX3CR1-CreER±/iDTR± mice (Figure 1). In contrast, the number of CX3CR1+CD11b+ cells in the spleen was not affected. Mortality after CA/CPR was not different between mice after MG ablation and control mice (55% vs 50%, P=0.69). Neuronal death in hippocampal CA1 was significantly reduced after MG ablation (dead cell density 132±105 cells/mm2) vs control (427±333 cells/mm2, P = 0.02, n= 13 and 11, respectively).

Conclusions: DT injection 30 days after Cre recombination selectively depletes brain MG in CX3CR1-CreER±/iDTR± mice, while leaving peripheral CD11b+ cells intact. Specific deletion of MG reduces hippocampal neuronal death after CA/CPR, confirming that activated MG are major drivers of DND after CA/CPR. This novel observation strongly suggests that MG can be targeted to reduce neuronal death and improve neurologic function after CA/CPR.

References

1. Lancet Respir Med 3:24-43, 2015.
2. Am J Respir Crit Care Med 192:324-336, 2015.

Basic Neuro/Inj 36 (162)
Systemic HMGB1 Impairs Synaptic Plasticity after Surgery in Aged Rats

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Introduction: Postoperative neurocognitive disorders, encompassing postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), are common complications in the elderly patients following surgery or critical illness [1]. High-mobility group box 1 (HMGB1) is rapidly released after tissue trauma and contributes to monocytes activation, cytokine release and cell death [2]. Although HMGB1 has been implicated in neurocognitive disorders [3-6], its function in contributing to neuroinflammation remains unclear. Herein we assessed the role of HMGB1 after liver surgery in aged rats and explored the therapeutic potential of selective anti-HMGB1 antibody in preventing POD.

Methods: Aged Sprague Dawley rats (19-22 months) were randomly assigned as: (1) control with saline; (2) surgery + IgG; (3) surgery + anti-HMGB1. Treatments (1mg/kg) were given via tail vein right before surgical incision and 6 hr after surgery. A separate cohort of animals was used to detect His-tagged HMGB1 in the central nervous system (CNS). N-methyl-D-aspartate receptor (NMDAR) expression, phosphorylation of cyclic AMP response element binding (p-CREB), microglia activation and cognition were assessed in a model of partial hepatolobectomy under sevoflurane anesthesia.

Results: HMGB1 was significantly up-regulated in plasma on day 1 and 3 after partial hepatolobectomy in aged rats ($p < 0.05$). No evident change in cellular localization of HMGB1 in the hippocampus was noted. However, a significant increase of His-HMGB1 was detected in the CNS, suggesting a key role for systemic HMGB1 entering the brain. Treatment with anti-HMGB1 antibody reduced up-regulation of NMDAR subunits NR2A and NR2B in the hippocampus and restored levels of p-CREB after surgery ($p < 0.05$). Anti-HMGB1 also prevented Iba-1 immunoreactivity thus improving memory function and anxiety after surgery (figure 1).

Conclusion: Systemic HMGB1 exerts a pivotal role in postoperative neuroinflammation and neurotoxicity. These effects were effectively reversed by anti-HMGB1 treatment and this may inform on neuroprotective strategies for POD and other postoperative neurocognitive disorders.

References

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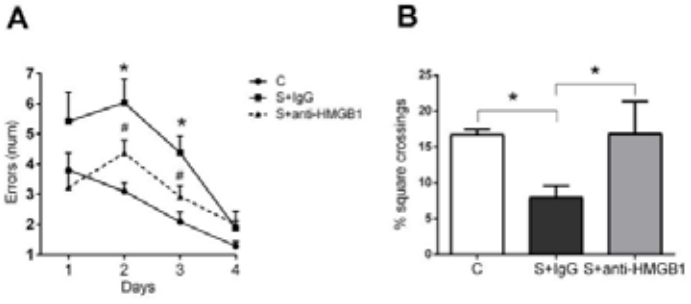

FIGURE 1: Anti-HMGB1 improves memory dysfunction and anxiety in aged rats.

We evaluated spatial memory in the Barnes maze. Rats who underwent liver surgery had significant memory impairments as detected by error numbers in reaching the correct target box (A). Treatment with anti-HMGB1 significantly improved postoperative memory dysfunction on both days 2 and 3 after surgery. (B) Anxiety was measure in an open field on postoperative day 3. Treatment with anti-HMGB1 antibody prevented postoperative anxiety as compared to S+IgG only. Results are expressed as mean ± SEM (n = 12). * $p < 0.05$ vs. C; # pÐ0.05 vs. S+IgG group by two-way repeated measures ANOVA for Barnes Maze and one-way ANOVA for open field. Abbreviations: C=control, S=surgery.

SAB Oral Session III
Friday, May 20, 2016 ▪ 8:00 am – 9:00 am

Moderators: Y.S. Prakash, MD, PhD, Mayo Clinic, Rochester, Minnesota, and Zhongchong Xie, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

	Basic Neuro/AA/NN 69 (38) **Using Social Network Analysis Tools to Assess the Effect of Isoflurane Anesthesia on Gene Networks in Rat Brain** **Helen F. Galley, PhD**; Nigel R. Webster, MBChB, PhD; Damon A. Lowes, BSc, MSc, PhD; Alessandro Moura, BSc, PhD *University of Aberdeen, Aberdeen, United Kingdom*	*Oral Presentation:* **SAB Oral Session (Part III)** Friday, May 20, 2016 8:00 – 9:00 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
JUNIOR FACULTY RESEARCH AWARD	**Pain 112 (101)** **The Analgesic Effects of Dopamine** **Norman E. Taylor, MD, PhD**[1]; JunZhu Pei, BS[2]; Ksenia Y. Vlasov, BA[2]; Jennifer A. Guidera, BA[1]; Ken Solt, MD[1]; Emery Brown, MD, PhD[1] *[1]Massachusetts General Hospital, Boston, Massachusetts, [2]Massachusetts Institute of Technology, Cambridge, Massachusetts* *See Page 58 for complete abstract*	*Oral Presentation:* **SAB Oral Session (Part I)** Thursday, May 19, 2016 8:15 am – 9:15 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 19, 2016 10:30 am – 12:00 pm
	CS 118 (114) **Pharmacodynamics and Pharmacokinetics of Novel GABA-A Receptor Alpha 4 Subunit Selective Ligands that Treat Bronchoconstriction** **Gene T. Yocum, MD**[1]; Yi Zhang, MD[1]; Gloria Forkuo, PhD[2]; Margaret Guthrie, BS[2]; Amanda Nieman, BS[2]; Rajwana Jahan, BSc[2]; Michael R. Stephen, PhD[2]; Douglas C. Stafford, PhD[2]; James M. Cook, PhD[2]; Alexander E. Arnold, PhD[2]; Charles W. Emala, MD[1] *[1]Columbia University, New York, New York; [2]University of Wisconsin-Milwaukee, Milwakee, Wisconsin*	*Oral Presentation:* **SAB Oral Session (Part III)** Friday, May 20, 2016 8:00 – 9:00 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
	CS/Organ Inj/Sep 84 (109) **The 'Meyer-Overton Quantum Underground' — Where Anesthetics Act to Prevent Consciousness** **Stuart R. Hameroff, MD**[1]; Travis J.A. Craddock, PhD[2]; Jack A. Tuszynski, PhD[3] *[1]The University of Arizonaof Arizona, Tucson, Arizona; [2]Nova Southeastern University, Fort Lauderdale, Florida; [3]University of Alberta, Edmonton, Alberta, Canada*	*Oral Presentation:* **SAB Oral Session (Part III)** Friday, May 20, 2016 8:00 – 9:00 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am

SAB Oral Session IV
Friday, May 20, 2016 ▪ 9:15 am – 10:15 am

Moderators: Y.S. Prakash, MD, PhD, Mayo Clinic, Rochester, Minnesota, and Zhongchong Xie, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts

RESIDENT TRAVEL AWARD	**CS 117 (140)** **Mitochondrial TRPV1 Regulates Endothelial Dysfunction in Diabetes** **Nana-Maria Wagner, MD**; Carl M. Hurt, MD, PhD; Honit Piplani, PhD; Stacy L. McAllister, PhD; Eric R. Gross, MD, PhD *Stanford University, Stanford, California* *See Page 57 for complete abstract*	*Oral Presentation:* **SAB Oral Session (Part IV)** Friday, May 20, 2016 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
MARGARET WOOD RESIDENT RESEARCH	**OC/Clin Studies 87 (151)** **A Novel Association Between High Density Lipoprotein Levels and the Risk of Acute Kidney Injury After Award Cardiac Surgery** **Loren E. Smith, MD, PhD**; Derek K. Smith, DDS; MacRae F. Linton, MD; Frederic T. Billings IV, MD, MSc *Vanderbilt University Medical Center, Nashville, Tennessee* *See Page 55 for complete abstract*	*Oral Presentation:* **SAB Oral Session (Part IV)** Friday, May 20, 2016 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
	CS 119 (81) **Impaired Relaxation of Airway Smooth Muscle in Mice Lacking the Cytoskeletal Regulatory Protein Gelsolin: A Potential Novel Target for Airway Relaxation** **Maya Mikami, MD, PhD, MPH**[1]; Jennifer Danielsson, MD[1]; Yi Zhang, MD[1]; Elizabeth Townsend, PhD[1]; Seema Khurana, PhD[2,3]; Charles W. Emala, MD[1] *[1]Columbia University, New York, New York,; [2]University of Houston, Houston, Texas; [3]Baylor College of Medicine*	*Oral Presentation:* **SAB Oral Session (Part IV)** Friday, May 20, 2016 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am
	Clin Studies 55 (72) **Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness** **Christopher G. Hughes, MD**; Timothy D. Girard, MD; James C. Jackson, PhD; Jennifer L. Thompson, MPH; E. Wesley Ely, MD; Pratik P. Panharipande, MD *Vanderbilt University, Nashville, Tennessee*	*Oral Presentation:* **SAB Oral Session (Part IV)** Friday, May 20, 2016 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 20, 2016 10:15 am – 11:45 am

Basic Neuro/AA/NN 69 (38)
Using Social Network Analysis Tools to Assess the Effect of Isoflurane Anesthesia on Gene Networks in Rat Brain

Helen F. Galley, PhD; Nigel R. Webster, MBChB, PhD1; Damon A. Lowes, BSc, MSc, PhD; Alessandro Moura, BSc, PhD

University of Aberdeen, Aberdeen, United Kingdom

Introduction: Most studies of effects of anesthesia on gene transcripts have compared differential expression profiles with and without anesthesia, but this approach neglects the interactions between the genes. We hypothesized that using network analysis tools originally developed for analyzing social networks, we would be able to identify the effects of isoflurane anesthesia on gene interactions in rat brain.

Methods: Male rats (n=10 per group) were randomized to either brief anesthesia with isoflurane in oxygen for 15min, or oxygen only, and 6h later brains were removed. cRNA targets for hybridization were prepared and hybridized to the Rat 230 2.0 Affymetrix Genechip®, and identified using biotin-streptavidin-phycoerythrin labeling. Fluorescence data were mined using standard clustering techniques and principal component analysis was undertaken. We used the GeneNet software package which computes the direct interaction between pairs of genes by the partial correlation matrix [1] and only genes where the expression profile changed by at least 2-fold were included. Network analysis was undertaken using techniques described for analysis of social networks [2].

Main Results: The Figure shows the topology of the networks in the two groups of rats. In controls 17 gene interactions were seen in rats which had been anesthetized, 3 of the genes were not expressed and the networks after anesthesia were completely different from non-anesthetized animals, with more interactions (edges) per gene (node) and more genes with 5 or more interactions (called hubs). In terms of measures of importance of each gene in the network, the median [range] closeness centrality, which is the average number of shortest paths needed for a given gene to reach every other gene, was 0.38 [0.30-0.53] in non-anesthetized and 0.06 [0-0.30] in anesthetized rats ($p<0.0001$, Mann Whitney test). The betweenness centrality, which indicates the % of shortest paths which go via each gene, was 6.7 [0-30.7]% in non-anesthetized controls and 53.4 [23.8-70.0]% in rats after anesthesia ($p<0.0001$).

Conclusions: These results show that even 6h after a very brief period of isoflurane anesthesia, gene networks in the brain were markedly affected in a manner which would enable a greater number of faster interactions with other genes. Network analysis, originally developed for describing social networks, has recently been applied to gene networks involved in antibiotic resistance [3] and inflammatory gene networks in coronary artery disease[4] but there are no reports of the effect of anesthesia on gene networks. Network analysis provides information on gene expression similarities in a tissue specific manner and enables identification of gene interactions under given conditions. Whilst the gene networks identified do not all involve genes previously associated with the molecular mechanisms of anesthesia, they represent novel targets for further investigation.

Funded by the British Journal of Anaesthesia/Royal College of Anaesthetists

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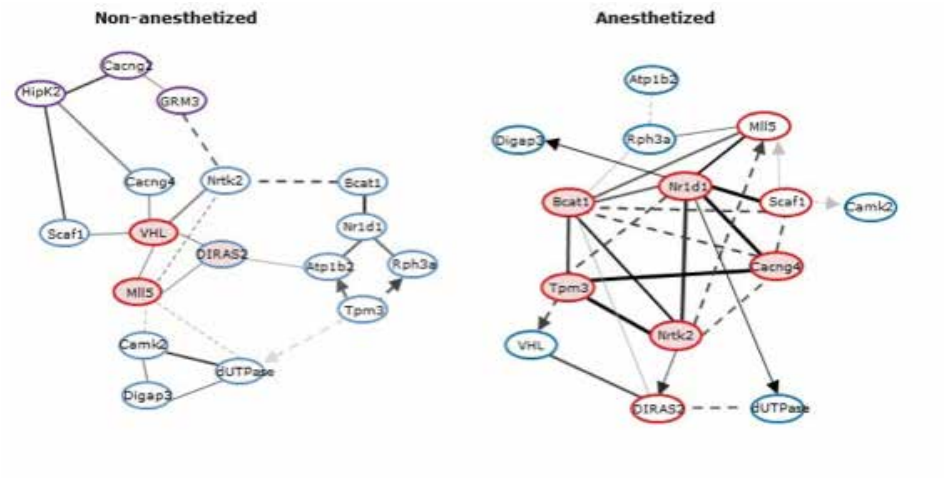


FIGURE Gene network topology in rat brains. Solid lines represent one gene enhancing the expression of the other, and dashed lines represent genes inhibiting another. Arrows indicate an inferred causal direction of interaction, otherwise direction cannot be inferred. The darkest and thickest lines indicate the strength of the connections. The red nodes (genes) are hubs, each with 5 or more edges. The nodes filled in pink form a clique, since each of genes interact directly with each other. The blue nodes have fewer than 5 edges and are less connected than the other nodes. Only 3 of the nodes seen in control rats were not seen in anesthetized rats (outlined in purple). Proteins assocated with the gene names and summary of functions are given below.

Atp1b2: ATPase, Na+/K+ transporting, beta 2 polypeptide. Responsible for establishing and maintaining electrochemical gradients of Na+ and K+ across plasma membrane.

Bcat1: Branched chain amino-acid transaminase 1, cytosolic. Catalyzes first reaction in catabolism of essential branched chain amino acids- leucine, isoleucine, valine.

Cacng2, Cacng4: Calcium channel, voltage-dependent, gamma subunit 2 or 4. Voltage-dependent calcium channel, functions as a transmembrane AMPA receptor regulatory protein.

Camk2: Calcium/calmodulin-dependent protein kinase II inhibitor 1. Modulates activity of a calcium-dependent protein kinase.

Diras2: DIRAS family, GTP-binding RAS-Like 2. Ras GTPases controlling MAP kinase activity.

Dlgap3: Discs, large (Drosophila) homolog-associated protein 3. Role in organization of synapses and neuronal cell signalling.

dUTPase: Deoxyuridine-triphosphatase. Involved in nucleotide metabolism and production of thymidine nucleotides.

HipK2: Homeodomain interacting protein kinase 2. Serine/threonine-protein kinase involved in transcription of p53 and transcriptional co-suppressor of HIF1A.

GRM3: Metabotropic glutamate receptor 3. Regulator of pre-frontal cortex neuroplasticity.

Mll5: Myeloid/lymphoid mixed-lineage leukemia 5. Key regulator of haematopoiesis and maintains expression of determination genes in quiescent cells.

Nr1d1: Nuclear receptor subfamily 1, group D, member 1. Transcription factor - negatively regulates expression of core clock proteins.

Ntrk2: Neurotrophic tyrosine kinase receptor, type 2. Involved in learning and memory by regulating shortterm synaptic function and long-term potentiation by mediating communication between neurones and glia.

Rph3: Rabphilin 3A homolog protein. Involved with synaptic vesicle trafficking and synaptic vesicle fusion for neurotransmitter release.

Scaf1: Serine arginine-rich pre-mRNA splicing factor. Role in pre-mRNA splicing.

Tpm3:Tropomyosin 3. Role in stabilizing non-muscle cell cytoskeleton actin filaments.

VHL Von Hippel Lindau tumour suppressor protein. Regulates angiogenesis, extracellular matrix formation and the cell cycle. Germ line mutation causes VHL disease, a hereditary cancer syndrome.

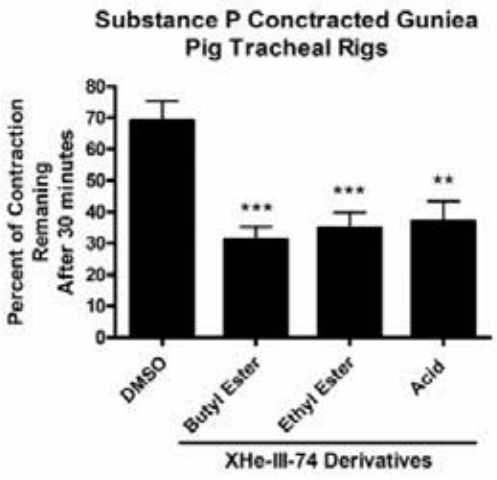
CS 118 (114)

Pharmacodynamics and Pharmacokinetics of Novel GABA-A Receptor Alpha 4 Subunit Selective Ligands that Treat Bronchoconstriction

Gene T. Yocum, MD[1]; Yi Zhang, MD[1]; Gloria Forkuo, PhD[2]; Margaret Guthrie, BS[2]; Amanda Nieman, BS[2]; Rajwana Jahan, BSc[2]; Michael R. Stephen, PhD[2]; Douglas C. Stafford, PhD[2]; James M. Cook, PhD[2]; Alexander E. Arnold, PhD[2]; Charles W. Emala, MD[1]

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

Introduction: We previously demonstrated that airway smooth muscle (ASM) cells express GABA-A receptors (GABA-ARs), which are best known for their role in inhibitory neurotransmission, and that GABA-AR ligands relax ASM. Among the GABA-AR Đ subunits, ASM cell GABA-ARs contain only Đ4 and Đ5. This provides the potential for selective pharmacologic targeting to avoid the sedative effects mediated by CNS GABA-ARs containing Đ1-3. XHe-III-74, a novel selective allosteric modulator of Đ4-containing GABA-ARs, relaxes ASM, but little is known about the pharmacokinetic properties or CNS side effect profile of this compound or its newly developed derivatives (i.e. XHe-III-74EE) and metabolites.



Methods: Guinea pig tracheal rings were contracted with 1 µM substance P and then exposed to 100 µM Xhe-III-74, XHe-III-74EE, or XHe-III-74A (XHe-III-74 metabolite) during continuous contraction force monitoring in organ baths. Mouse brain, lung, and blood concentrations of XHe-III-74EE and XHe-III-74A were determined over a 2 hours following intraperitoneal (IP) injection of 5 mg/kg. Finally, mouse sensorimotor coordination was tested using a rotarod 10 minutes after IP injection of concentration ranges of XHe-III-74EE, XHe-III-74A, diazepam (non-selective GABA-AR activator), and vehicle.

Results: XHe-III-74, XHe-III-74EE, and XHe-III-74A relaxed substance P-contracted guinea pig tracheal rings equally (approximately 50% relaxation of peak contraction compared to vehicle after 30 minutes, n=5-8, p<0.001). Following IP injection of XHe-III-74EE, there was significant lung penetration that peaked at 10 minutes (mean lung Cmax: 120.7 ng/ml). Brain concentration peaked at a mean Cmax of 84.8 ng/ml at 40 minutes. The brain concentrations of XHe-III-74A, both after XHe-III-74EE injection and direct XHe-III-74A injection, were undetectable. Despite detectable brain levels of XHe-III-74EE, no impairment was seen in sensorimotor performance after IP injection of 5 mg/kg (compared to an 80% decrease in performance following IP injection of 5mg/kg diazepam, n=8, p<0.001). However, significant impairment was seen after injection of 40 mg/kg XHe-III-74EE (p<0.01). No impairment was seen following XHe-III-74A injection at any concentration tested.

Discussion: XHe-III-74EE and XHe-III-74A relax ASM ex vivo with equal potency to the previously described XHe-III-74. Despite the ability of XHe-III-74EE to enter the CNS after IP injection of 5 mg/kg, no impairment of sensorimotor performance was seen at this concentration, unlike the benzodiazepine diazepam, supporting the potential to relax ASM while avoiding CNS sedation with subunit-selective GABA-AR ligands. Interesting, XHe-III-74A, the metabolite of XHe-III-74EE, does not appear to cross the blood brain barrier, making it another attractive therapeutic candidate.

CS/Organ Inj/Sep 84 (109)
The 'Meyer-Overton Quantum Underground' – Where Anesthetics Act to Prevent Consciousness

Stuart R. Hameroff, MD[1]; Travis J.A. Craddock, PhD[2]; Jack A. Tuszynski, PhD[3]

[1]The University of Arizonaof Arizona, Tucson, Arizona; [2]Nova Southeastern University, Fort Lauderdale, Florida; [3]University of Alberta, Edmonton, Alberta, Canada

Introduction: At the turn of the 20th century, Meyer and Overton discovered that potency of anesthetic gases correlated precisely with their solubility in non-polar, lipid-like regions akin to olive oil, e.g. pi electron resonance clouds. In the 1980s Franks and Lieb identified anesthetic binding in such regions inside proteins, e.g. near aromatic amino acid pi resonance groups. However anesthetic binding to various membrane proteins has failed to explain anesthetic action including loss of consciousness, whose nature remains unknown. Theorists since Schrodinger (1935) have related consciousness, and life, to biological quantum coherence, but the brain appeared too 'warm, wet and noisy' for seemingly delicate quantum effects. However ten years ago plant photosynthesis proteins were shown to utilize quantum coherence mediated through pi resonance groups in non-polar ('dry', not 'wet') regions, pumped by protein mechanical vibrations ('warm, noisy'). Quantum resonances are also found in cytoskeletal microtubules and their component protein 'tubulin' [(1-3)], and Eckenhoff's group has suggested through genomics, proteomics and optogenetics that microtubules mediate anesthetic action. Microtubule resonance spectral patterns [(1-3)] repeat in a scalar hierarchy of terahertz, gigahertz, megahertz, kilohertz and hertz (EEG) frequencies, apparently via electric and magnetic dipole oscillations among adjacent pi resonance clouds in aromatic amino acids. Molecular modeling [(4)] shows contiguous pi resonance groups traversing tubulin and microtubules, within which anesthetics bind. These quantum-friendly pi resonance channels have been dubbed the 'Meyer-Overton quantum underground', and we hypothesized [(5,6)] anesthetics act therein by dampening quantum oscillations.

Method/Results: Simulating a pair of pi resonance benzene rings separated by 3.7 angstroms as a model system, we calculated London dipole dispersion E (ionization 9.2 eV, polarizability 68 a.u.) for pi resonance oscillation at 68 terahertz (10^12 Hz) to be 4.4 x 10^-20 Joules, an energy barrier for terahertz oscillation. We then calculated effects of a halothane molecule (permanent dipole 1.41 Debye) placed 4.5 angstroms from the pi resonance rings, as occurs in tubulin. We found the presence of halothane increased oscillation threshold to 5.1 x 10^-20 Joules, a change likely able to dampen and slow terahertz oscillations, thereby dampening the brain's scalar hierarchy whose slow end is seen as EEG [(7)].

Conclusions: Anesthetic action, quantum coherence, the brain's scalar hierarchy and consciousness are likely to originate in a 'Meyer-Overton quantum underground' e.g. in non-polar pi resonance pathways within microtubules in dendrites and soma of brain neurons.

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CS 119 (81)

Impaired Relaxation of Airway Smooth Muscle in Mice Lacking the Cytoskeletal Regulatory Protein Gelsolin: A Potential Novel Target for Airway Relaxation

Maya Mikami, MD, PhD, MPH[1]; Jennifer Danielsson, MD[1]; Yi Zhang, MD[1]; Elizabeth Townsend, PhD[1]; Seema Khurana, PhD[2,3], Charles W. Emala, MD[1]

[1]Columbia University, New York, New York; [2]University of Houston, Houston, Texas; [3]Baylor College of Medicine

Introduction: Diverse classes of ligands have recently been discovered that relax airway smooth muscle (ASM) despite a transient increase in intracellular calcium concentrations [Ca2+]i [1-3]. These compounds are considered attractive novel therapeutics for bronchoconstrictive diseases and perioperative bronchospasm. However, the cellular mechanisms by which these agents induce relaxation is not well understood. Gelsolin is a calcium-activated actin severing and capping protein found in many cell types including ASM cells. Gelsolin also binds to phosphatidylinositol 4,5-bisphosphate (PIP2)[4] making this substrate less available for PLCb-mediated hydrolysis to inositol phosphate and diacylglycerol. An acute increase in [Ca2+]i exposes the actin-binding site of gelsolin, resulting in depolymerization of actin filaments. We hypothesized that gelsolin plays a critical role in ASM relaxation and mechanistically accounts for relaxation by ligands that transiently increase [Ca2+]i.

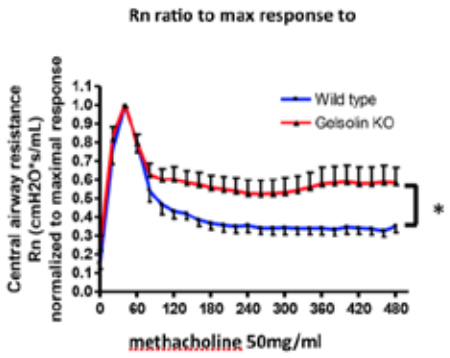

FIGURE: In vivo lung resistance measurements. Inhalation of a single concentration of methacholine caused an acute increase in airway resistance in both wild type and gelsolin knockout (KO) mice, but gelsolin KO mice exhibit impaired spontaneous reduction in central airway resistance (Rn) following inhalation of a single concentration of 50 mg/ml methacholine. n=5 in each group, *p<0.05.

Methods: Studies were approved by the local IACUC. Wild type and gelsolin knockout (KO) mice were tracheotomized and central airway resistance was measured after inhaled methacholine using the forced oscillation technique via Flexivent. Isolated tracheal rings were contracted in myograph organ baths with acetylcholine and then exposed to relaxing ligands known to induce transient increases in [Ca2+]i in addition to a classical relaxing ligand, a b2 adrenoceptor agonist. To further elucidate the cellular mechanisms, [Ca2+]i and [3H]-inositol phosphate (IP3) synthesis was measured in response to a Gq-coupled agonist in primary cultures of wild type and gelsolin KO mouse ASM cells.

Results and Major Findings: A single inhaled dose of 50 mg/ml methacholine increased lung resistance to a similar extent in wild type and gelsolin KO mice, but the subsequent spontaneous relaxation was less in gelsolin KO mice (n=6, p<0.05)(figure attached). Isolated tracheal rings from gelsolin KO mice studied ex vivo in myographs, showed impaired relaxation to both a b2-agonist and chloroquine (n=6, p<0.05), a known bitter taste receptor agonist which relaxes ASM despite inducing a transient increase in [Ca2+]i. [Ca2+]i and IP3 synthesis in response to the Gq-coupled ligand serotonin was increased in primary cultures of ASM cells from gelsolin KO mice compared to wild type (n=6 and 5, p<0.05 and p<0.01, respectively) possibly due to the absence of gelsolin binding to PIP2.

Conclusions: These findings suggest that the actin capping and severing protein gelsolin plays a critical role in ASM relaxation and that activation of gelsolin may contribute to relaxation induced by several classes of recently discovered ligands that relax ASM despite a transient increase in [Ca2+]i. By elucidating the mechanisms of gelsolin-mediated airway relaxation, we will have a better understanding of pathological bronchospasm and the response to medications in asthmatic/reactive airways. In addition, modulation of the expression of gelsolin itself, may be a novel therapeutic tool in future.

References

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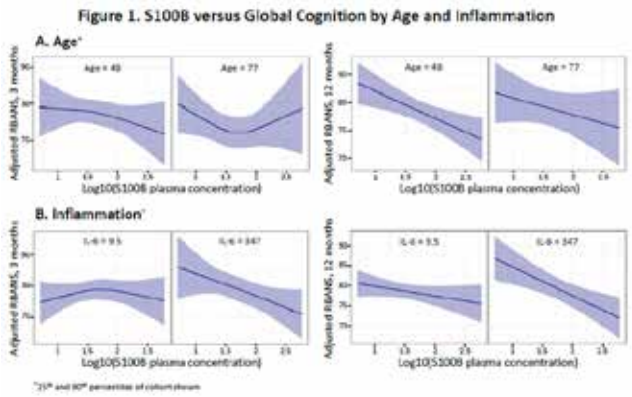
Clin Studies 55 (72)

Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness

Christopher G. Hughes, MD; Timothy D. Girard, MD; James C. Jackson, PhD; Jennifer L. Thompson, MPH; E. Wesley Ely, MD; Pratik P. Panharipande, MD

Vanderbilt University, Nashville, Tennessee

Introduction and General Purpose of the Study: Delirium in the hospital is one of the strongest predictors of cognitive impairment after critical illness.(1) Endothelial dysfunction may lead to delirium via perturbations in microvascular blood flow, release of biochemical mediators, or breakdown of the blood brain barrier (BBB).(2) Neuronal alterations from this acute insult may manifest as cognitive impairment in the long-term. We have shown that elevated plasma concentrations of endothelial activation and neurologic (BBB and brain) injury biomarkers are associated with prolonged delirium duration in critically ill patients.(3) The relationship of these biomarkers with cognitive impairment after critical illness has not been examined. We hypothesized that elevated plasma concentrations of endothelial activation (E-selectin and PAI-1), BBB injury (S100B), and brain injury (UCHL1 and BDNF) biomarkers would be associated with worse cognitive impairment after critical illness.



Methods: The BRAIN-ICU study enrolled adult patients within 72 hours of respiratory failure or shock admitted to a medical or surgical ICU. We measured plasma concentrations of E-selectin, PAI-1, S100B, UCHL1, and BDNF upon enrollment. At 3 and 12 months after hospital discharge, global cognition was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status.(4) We used multivariable linear regression to examine the independent associations of endothelial activation, BBB, and brain injury biomarkers with global cognition scores, adjusting for education, baseline cognition, comorbid disease, severity of illness, severe sepsis, delirium, and coma and allowing for interactions with age and systemic inflammation (IL-6 plasma concentration).

Results and Major Findings: Our study included 392 survivors of critical illness who underwent post-discharge cognitive assessment. The patients had a median age of 59 years and APACHE II score of 25, with 91% requiring mechanical ventilation, 65% having severe sepsis, and 76% developing delirium during the study. In general, higher S100B concentrations were associated with worse global cognition at both 3 and 12 months (overall P=0.057; P=0.005); these associations were modified by age and IL-6 such that the strongest associations were seen in younger patients and those with high inflammatory burden (Figure 1). Higher E-selectin (P=0.016) and UCHL1 (P=0.011) concentrations were associated with worse global cognition at 3 months but not 12 months and not modified by age or IL-6. No significant associations were found between PAI-1 and BDNF concentrations with global cognition.

Conclusions: These data support that BBB injury biomarkers are associated with long-term cognitive impairment after critical illness, in particular in younger patients and high inflammatory states. Endothelial activation and brain injury biomarkers may be associated with short-term cognitive impairment. Further confirmatory studies are needed, including serial evaluations of biomarker concentrations to assess whether these associations change in response to disease progression or medical therapy.

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Moderated Poster Discussions

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Category	Poster Board Numbers
Anesthetic Signaling and Genetics	9-13, 21
Clinical Studies (A)	22-25, 29-31, 56
Basic Neuro (Neuronal Injury) A	36-38, 43-47
Cell Signaling (A) Organ Injury	59-63, 124-126
Cell Signaling (B) Organ Injury (Sepsis)	70-77, 84
Clinical Outcomes (Big Data)	89-91, 93-95, 97-98

**Posters 14, 26, and 96 withdrawn*

Poster Presentations Schedule

Thursday, May 19, 2016, 10:30 am - 12:00 pm

Moderated Poster Discussion I: Anesthetic Cell Signaling and Genetics

Anesth Cell Signaling/Genetics 9 (142)
Genetic Risk Factors Contributing to Exertional Heat Illness in the UK Armed Forces

Lois Gardner, BSc (Hons), MSc[1]; Dorota M. Miller, PhD[1]; Daniel Roiz de Sa, MBBS[2]; Marie-Anne Shaw, PhD[1]; Philip M. Hopkins, MD[1]

[1]University of Leeds, Leeds, United Kingdom; [2]Institute of Naval Medicine, Alverstoke, Gosport, United Kingdom

Anesth Cell Signaling/Genetics 10 (143)
Pathway Analysis Highlights the Potential for Determining a Genetic Signature for Malignant Hyperthermia in Patient Blood Samples

Katie M. Nicoll Baines, BSc (Hons), MRes[1]; Dorota M. Mller, PhD[1]; Paul D. Allen, MD, PhD[2]; Marie-Anne Shaw, PhD[1]; Phil M. Hopkins, MD[1]

[1]University of Leeds, Leeds, United Kingdom; [2]University of California, Davis, Davis, California

JUNIOR FACULTY RESEARCH AWARD

Anesth Cell Signaling/Genetics 11 (154)
Gating of the Trek1 Tandem Pore Potassium Channel, a Molecular Signal Integrator and Anesthetic Target

Paul M. Riegelhaupt, MD, PhD[1], Marco Lolicato, PhD[2], Daniel Minor, PhD[2]

[1]Weill Cornell Medical College, New York, New York, [2]University of California, San Francisco, San Francisco, California

See page 59 for complete abstract

Anesth Cell Signaling/Genetics 12 (117)
The Differential Effects of Commonly Used Anesthetics on bBacterial Growth in Vitro

Koichi Yuki, MD; Sulpicio G. Soriano, MD

Boston Children's Hospital, Boston, Massachusetts

Anesth Cell Signaling/Genetics 13 (116)
Propofol Affects Neurodegeneration and Neurogenesis by Regulation of Intracellular Calcium Homeostasis

Huafeng Wei, MD, PhD[1]; Hui Qiao, MD[2]; Yun Li, MD[3]; Gongyi Ren, PhD[1]; Wenxian Li, MD[2]; Zhijan Fu, MD[3]

[1]University of Pennsylvania, Philadelphia, Pennsylvania; [2]The Eye Ear Nose and Throat Hospital of Fudan University, Shanghai, China; [3]Provincial Hospital Affiliated to Shandong University, Shandong, China

Anesth Cell Signaling/Genetics 21 (66)
Mutants of Cytochrome P450 Reductase Lacking Either Glycine 141 or Glycine 143 Have Decreased Ability to Support Cytochrome P450 Catalysis

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

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

Poster Presentations Schedule

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Basic Neuro (Neuronal Injury)

Basic Neuro/Inj 36 (162)
Systemic HMGB1 Impairs Synaptic Plasticity after Surgery in Aged Rats

Niccolo Terrando, BSc (Hons), DIC, PhD[1]; Wen Ouyang, MD[2]; Ting Yang, MD, PhD[1]; Jianbin Tong, MD, PhD[2]

[1]Duke University, Durham, North Carolina; [2]Third Xiangya Hospital, Hunan, China *See page 67 for complete abstract*

Basic Neuro/Inj 37 (156)
Purkinje Cell Death and Cerebellar Deficits Resulting from Experimental Cardiac Arrest and Cardiopulmonary Resuscitation

Nidia Quillinan, PhD; Guiying Deng, MD; Myriam Moreno-Garcia, BS; Richard J. Traystman, PhD; Paco S. Herson, PhD

University of Colorado School of Medicine, Aurora, Colorado

Basic Neuro/Inj 38 (155)
Sexually Dimorphic Estrogen Neuroprotection in Juvenile Mice Following Global Cerebral Ischemia

Richard J. Traystman, PhD; Guiying Deng, MD; Myriam Moreno-Garcia, BS; Paco S. Herson, PhD

University of Colorado School of Medicine, Aurora, Colorado

Basic Neuro/Inj 43 (103)
miR-29a and VDAC1 Regulate Mitochondrial Function and Cell Survival in Astrocytes from Cornu Ammonis-1 and Dentate Gyrus Following Injury

Creed M. Stary, MD, PhD[1]; Xiaoyun Sun, MD[1]; YiBing Ouyang, PhD[1]; Le Li, MD, PhD[2, 3], Rona G. Giffard, PhD, MD[1]

[1]Stanford University, Stanford, California; [2]Zhujiang Hospital, Guangzhup, China; [3]Southern Medical University, Guangzhou, China

Basic Neuro/Inj 44 (123)
Benzodiazepines Modulate Post-Traumatic Brain Injury Neurogenesis in Mice

Austin Peters, MD[1]; Laura Villasana, PhD[1]; Eric Schnell, MD, PhD[2]

[1]Oregon Health & Science University, Portland, Oregon; [2]Portland VA Health Care System, Portland, Oregon

Basic Neuro/Inj 45 (152)
Microglia Exacerbate Neuronal Death after Cardiac Arrest

Ines P. Koerner, MD, PhD; Mizuko Ikeda, MD, PhD

Oregon Health and Science University, Portland, Oregon *See page 66 for complete abstract*

Basic Neuro/Inj 46 (56)
Age-Related Up-Regulation of CTMP Promotes Cell Death in Older Rats after Ischemic Stroke

Zhiyi Zuo, MD, PhD; Jun Li, MD, PhD

University of Virginia, Charlottesville, Virginia

Basic Neuro/Inj 47 (52)
The Role of Heparanase in Subarachnoid Hemorrhage-Associated Neuroinflammation

Benjarat Changyaleket, MD; Hoa-Liang Xu, MD, PhD

University of Illinois at Chicago, Chicago, Illinois

Poster Presentations Schedule

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Cell Signaling/Organ Injury

CS/Organ Inj 59 (39)
Peptidyl Arginine Deiminase-4 Exacerbates Ischemic Acute Kidney Injury by Finding NEMO

HT Lee, MD, PhD; May Rabadi, PhD; Kevin Brown, BA; Mihwa Kim, PharmD

Columbia University, New York, New York

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CS/Organ Inj 60 (113)
Inhibition of Free Fatty Acid Receptor GPR40 abolishes Cardioprotection Conferred by Intralipid in Two Rodent Models of Bupivacaine Cardiotoxicity and Ischemia Reperfusion Injury

Soban Umar, MD, PhD; Jingyuan Li, MD, PhD; Parisa Partownavid, MD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD

University of California, Los Angeles, Los Angeles, California

See page 64 for complete abstract

CS/Organ Inj 61 (111)
Thoracic Epidural Anesthesia Prevents Ventricular Arrhythmias by Reducing Dispersion of Repolarization and Electrical Restitution during Myocardial Ischemia

Kimberly Howard-Quijano, MD, MS; Tatsuo Takamiya, MD; Wei Zhou, PhD; Jeff Ardell, PhD; Kalyman Shivkumar, MD, PhD; Aman Mahajan, MD, PhD

University of California, Los Angeles, Los Angeles, California

CS/Organ Inj 62 (134)
Multi-Frequency Oscillatory Ventilation: Effects on Regional Ventilation Heterogeneity and Carbon Dioxide Elimination in Canine Lungs

David W. Kaczka, MD, PhD[1]; Jacob Hermann, MS[1]; Merryn H. Tawhai, PhD[2]

[1]University of Iowa, Iowa City, Iowa; 2University of Auckland, Auckland, New Zealand

RESIDENT TRAVEL AWARD

CS/Organ Inj 63 (132)
Low Molecular Weight Hyaluronan Mediated Inflammation And Airway Hyperresponsiveness in Acid Aspiration Induced Acute Lung Injury in Mice

Weifeng Song, MD, PhD[1]; Zhihong Yu, MS[1]; Stavros Garantziotis, MD[2]; Sadis Matalon, PhD[1]

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CS/Organ Inj 124 (57)
Light Elicited Mechanisms in Organ Protection

Tobias Eckle, MD, PhD

University of Colorado Denver School of Medicine

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Poster Presentations Schedule, *continued from page 79*

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Cell Signaling/Organ Injury

CS/Organ Inj 125 (88)
Intralipid Protects Rat-Isolated Hearts against Ischemia-Reperfusion Injury through Nitric Oxide-Mediated Pathways

Matthias L. Riess, MD, PhD; Hunter F. Douglas, BS; Michele M. Salzman, BS

Vanderbilt University, Nashville, Tennessee

CS/Organ Inj 126 (93)
The Role of PDE4 in IL-8-dependent Inhibition of cAMP-stimulated Alveolar Fluid Clearance in a Murine Model of Trauma-Hemorrhage

Brant Wagener, MD, PhD; Angela Brandon, BS; Cilina Evans, BSN, RN; Jean-Francois Pittet, MD

University of Alabama at Birmingham, Birmingham, Alabama

Poster Presentations Schedule

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Cell Signaling, Organ Injury (Sepsis)

CS/Organ Inj/Sep (48)
Therapeutic Effects of Microvesicles Derived From A Mouse Macrophage Cell Line (RAW264.7) in Severe Pneumonia in Mice

Jae-Woo Lee, MD

University of California, San Francisco, San Francisco, California

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CS/Organ Inj/Sep 71 (112)
Cellular RNA and Synthetic microRNAs Induce Complement Activation and Tissue Inflammation via TLR Signaling

Wei Chao, MD, PhD[1]; Lin Zou[1]; Yan Feng, MD, PhD[1]; Wenling Jian, MD[2]

[1]University of Maryland, Baltimore, Maryland; [2]Massachusetts General Hospital, Boston, Massachusetts

CS/Organ Inj/Sep 72 (68)
Role of the Gut-Lung Axis and IL-1b Signaling in Sterile Inflammation Following Lung Ischemia Reperfusion Injury

Arun Prakash, MD, PhD; Judith Hellman, MD

University of California, San Francisco, San Francisco, California

See page 63 for complete abstract

CS/Organ Inj/Sep 73 (122)
Perioperative TLR4 Modulation in a Mouse Model of Surgical Trauma: A Systems-Wide Analysis by Single-Cell Mass Cytometry

Vivianne L. Tawfik, MD, PhD; Ed Ganio, PhD; Nima Aghaeepour, PhD; Martin Angst, MD; David J. Clark, MD, PhD; Brice Gaudiliere, MD, PhD

Stanford University, Stanford, California

CS/Organ Inj/Sep 74 (107)
Cholinergic Basal Forebrain Neurons Inhibit Systemic Inflammatory Response via Vagus Nerve during Sepsis

Ping Cui, PhD; XiangMing Fang, MD

First Affiliated Hospital, Hangzhou, China; Zhejiang University, Hangzhou, China

CS/Organ Inj/Sep 75 (139)
TRPM2 Regulates Phagosome Maturation and is Required for Bacterial Clearance in E. coli Induced Sepsis

Zhanqin Zhang, PhD[1, 3]; Qixing Cheng, PhD[2, 3]; Xiangming Fang, MD[1, 3]

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Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Cell Signaling, Organ Injury (Sepsis)

CS/Organ Inj/Sep 76 (108)
S1PR2 Contributes to Noncanonical Inflammasome Activation and Impairs the Outcome of Escherichia coli Sepsis

Fang Song, MSc; XiangMing Fang, MD

First Affiliated Hospital, Hangzhou, China; Zhejiang University, Hangzhou, China

CS/Organ Inj/Sep 77 (137)
Starvation-Induced Improvement in Long-Term Outcomes Following Sepsis in Drosophila Melanogaster

Ata M. Kaynar, MD, MPH[1]; Veli Bakalov, MD[1]; Amelie I.F. Cambriel[2]

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CS/Organ Inj/Sep 84 (109)
The 'Meyer-Overton Quantum Underground' - Where Anesthetics Act to Prevent Consciousness

Stuart R. Hameroff, MD[1]; Travis J.A. Craddock, PhD[2]; Jack A. Tuszynski, PhD[3]

[1]The University of Arizona, Tucson, Arizona; [2]Nova Southeastern University, Fort Lauderdale, Florida; [3]University of Alberta, Edmonton, Alberta, Canada

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Poster Presentations Schedule

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Clinical Studies

Clin Studies 22 (150)
Association between Availability of Videolaryngoscope for Tracheal Intubation and the Number of Emergency Tracheostomy in Perioperative Setting of a Large Academic Medical Center: A Retrospective Observational Study

Yandong Jiang, MD, PhD; Jonathan P. Wanderer, MD; Paul J. St. Jacques, MD; Min Fei, MD

Vanderbilt University, Nashville, Tennessee

Clin Studies 23 (170)
Increased Use of Inhaled Nitric Oxide in Single Ventricle Patients with Low Nasal Nitric Oxide Undergoing Congenital Heart Surgery

Phillip S. Adams, DO; Maliha Zahid, MD, PhD; Omar Khalifa, MD; Cecilia W. Lo, PhD

University of Pittsburgh, Pittsburgh, Pennsylvania

Clin Studies 24 (83)
Prediction of Imminent Deterioration of Children with Parallel Circulations Using Real-Time Processing of Physiologic Data

Ken Brady, MD; Craig Rusin, PhD; Sebastian Acosta, PhD; Eric Vu; Risa Myers, PhD; Daniel Penny, MD, PhD, MHa

Baylor College of Medicine, Houston, Texas

Clin Studies 25 (84)
Hypertension after Glenn Shunt Is Associated with Elevated Pulmonary Artery Pressure and Cerebrovascular Dysautoregulation

Ken Brady, MD; Antonio Cabrera, MD; Kathleen Kibler, CCP; Blaine Easley, MD; Michelle Goldsworthy, RN, BN; Dean Andropoulos, MD

Baylor College of Medicine, Houston, Texas

Clin Studies 29 (98)
An Ecg Algorithm Utilizing St Segment Instability for Detection of Cardiopulmonary Arrest in Single Ventricle Physiology

Eric Vu, MD; Craig G. Rusin, PhD; Dan J. Penny, MD, PhD, MHA; Ronald B. Easley, MD; Dean Andropoulos, MD, MHCM; Ken Brady, MD

Texas Children's Hospital, Houston, Texas; Baylor College of Medicine, Houston, Texas

Clin Studies 30 (99)
Review of Mobile ECMO Cases Performed by an Anesthesia/Cardiac Surgery Team

Jacob Gutsche, MD; William Vernick, MD

University of Pennsylvania, Philadelphia, Pennsylvania

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Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Clinical Studies

Clin Studies 31 (141)
Difference between Wrist and Ankle Actigraphy to Estimate Sleep-Wake Cycle in Critically Ill Patients

Nicholas C. Vigo, BS; Stephanie Principe, BA; David N. Yanez, PhD; Miranda Lim, MD, PhD; Kris Weymann, PhD, RN; Miriam Treggiari, MD, PhD

Oregon Health & Science University, Portland, Oregon

Clin Studies 56 (70)
Complexity of Preoperative Blood Pressure Dynamics: Possible Utility in Cardiac Surgical Risk Assessment

Balachundhar Subramaniam, MBBS, MD, MPH; Teresa Henriques, PhD; Madalena Costa, PhD; Ary L. Goldberger, MD; Murray L. Mittleman, MD, DrPH; Roger Davis, ScD

Beth Israel Deaconess Medical Center, Boston, Massachusetts

Poster Presentations Schedule

Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Clinical Outcomes (Big Data)

Clin OC 89 (171)
Exposure to Cardiopulmonary Bypass during Coronary Artery Bypass Surgery and Postoperative Delirium

Jason O'Neal, MD; Xulei Lui, MS; Matthew S. Shotwell, PhD; Andrew D. Shaw; Ashish Shah, MD; Frederic T. Billings, MD, MSCI

Vanderbilt University, Nashville, Tennessee

Clin OC 90 (62)
Interaction Effects of Multiple Complications on Postoperative Mortality in General Surgery

Minjae Kim, MD, MS; Guohua Li, MD, DrPH

Columbia University, New York, New York

Clin OC 91 (47)
Collaborative Health Outcomes Information Registry (CHOIR): Open Source Platform for a Learning Health System and Informing Therapeutic Development

Sean Mackey, MD, PhD; Ming Kao, PhD, MD; Beth Darnall, PhD; Susan Weber, PhD

Stanford University, Stanford, California

Clin OC 93 (78)
Epidemiology of Vasopressin Use among Adults with Septic Shock in the United States

Emily A. Vail, MD[1]; Hayley B. Gershengorn, MD[2,3]; May Hua, MD, MSc[1]; Allan Walkey, MD, MSc[4]; Hannah Wunsch, MD, MSc[5,6]

[1]Columbia University, New York, New York; [2]Albert Einstein College of Medicine, Bronx, New York; [3]Montefiore Medical Center, Bronx, New York; [4]Boston University, Boston, Massachusetts; [5]University of Toronto, Toronto, Ontario, Canada; [6]Sunnybrook Health Sciences Center, Toronto, Ontario, Canada

Clin OC 94 (92)
Effect of Care Fragmentation on Outcomes of Rehospitalizations after Critical Illness for Severe Sepsis Patients

May Hua, MD, MSc[1]; Michelle Ng Gong, MD, MSc[2]; Andrea Miltiades, MD[1]; Hannah Wunsch, MD, MSc[1,4]

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

Clin OC 95 (105)
Timing and Outcomes of Permanent Pacemaker Placement After Aortic Valve Replacement

Zachary A. Turnbull, MD; Virginia Tangel, MA; Matthew J. Alexander, BS; Christopher Chan; Cynthia A. Lien, MD; Natalia Ivascu, MD

Weill Cornell Medical College, New York, New York

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Thursday, May 19, 2016 ▪ 10:30 am - 12:00 pm

Moderated Poster Discussion I: Clinical Outcomes (Big Data)

Clin OC 97 (100)
Meta-Analysis of Temperature Reduction in Animal Models of Cardiac Arrest

Hannah Watson, MBChB, BMedSci[1]; Hilmer Olai[2]; Gustav Thornéus[2]; Malcolm MacLeod, MBChB, PhD, FRCP, Ed[4]; Hans Friberg[2, 3]; Jonathan Rhodes, PhD, MBChB, FRCA[4, 5]; Niklas Nielsen, MD, PhD[2]; Tobias Cronberg, MD, PhD[2]; Tomas Deierborg, PhD[2]

[1]South East Scotland Deanery, Edinburgh, Scotland; [2]Lund University, Lund, Sweden; [3]Skåne University Hospital, Lund, Sweden; [4]University of Edinburgh, Edinburgh, United Kingdom; [5]Western General Hospital, Edinburgh, United Kingdom

Clin OC 98 (128)
"Opt out" and Access to Anesthesia Care for Elective and Urgent Surgeries among US Medicare Beneficiaries

Eric Sun, MD, PhD[1]; Franklin Dexter, MD, PhD[2]; Thomas R. Miller, PhD, MBA[3]; Laurence C. Baker, PhD[4]

[1]Stanford University, Stanford, California; [2]University of Iowa, Iowa City, Iowa; [3]American Society of Anesthesiologists, Schaumburg, Illinois; [4]National Bureau of Economic Research, Cambridge, Massachusetts

Anesth Cell Signaling/Genetics 9 (142)
Genetic Risk Factors Contributing to Exertional Heat Illness in the UK Armed Forces

Lois Gardner, BSc (Hons), MSc[1]; Dorota M. Miller, PhD[1]; Daniel Roiz de Sa, MBBS[2]; Marie-Anne Shaw, PhD[1]; Philip M. Hopkins, MD[1]

[1]University of Leeds, Leeds, United Kingdom; [2]Institute of Naval Medicine, Alverstoke, Gosport, United Kingdom

Exertional heat illness (EHI) is a clinically important disorder in military personnel and is characterised by an inability to thermoregulate. The UK armed forces report an annual incidence of ~500 cases, ~140 of which are referred to the Institute of Naval Medicine (INM) for testing. EHI shares a similar clinical manifestation to malignant hyperthermia (MH) (1), a relationship which has also been reported at a genetic level (2). Interestingly, 35% of our UK military EHI cohort that demonstrate an abnormal thermoregulatory response during heat tolerance testing have in vitro contracture test (IVCT) results consistent with MH susceptibility (unpublished data). Variants in the ryanodine receptor type-1 gene (RYR1) only account for ~65% of MH susceptible individuals suggesting that additional loci are involved. Both MH and EHI have been attributed to a disruption of calcium homeostasis in skeletal muscle, which has helped guide our search for genetic variants contributing to both disorders.

Using a targeted next-generation sequencing approach we screened the coding region of 50 genes involved in calcium homeostasis and energy metabolism; a number of which are implicated in MH and related myopathies. Libraries of target DNA were created using the HaloPlex target enrichment system (Agilent technologies, Santa Clara, CA) and sequenced on the MiSeq® platform (Illumina Inc., USA). Our sample set comprised 62 EHI individuals, the majority of which were UK military personnel referred by the INM for an IVCT after failing two or more standardised heat tolerance tests. We also sequenced 10 family members from 3 available EHI families to investigate whether any variants co-segregated with IVCT phenotype.

Sixty-seven rare (minor allele frequency ~1%) and likely pathogenic (Combined Annotation Dependent Depletion(3), Polyphen2 and SIFT scores) non-synonymous variants were detected across 23 of the 50 target genes. Ten novel variants were detected across the EHI sequence dataset, six of which were annotated as potentially deleterious. The three EHI families each revealed a rare and potentially pathogenic variant that was concordant with positive IVCT responses (4), namely RYR1 p.Arg3534His, CACNA1S p.Ser606Asp and SCN4A p.Val730Met. These genes encode proteins that form either calcium or sodium release channels, which are fundamental in the process of skeletal muscle contraction. A high throughput assay has been designed to determine the frequency of all 67 variants in the UK MH population along with commercially available samples from the general population.

Our targeted sequencing strategy highlights the sensitivity of HaloPlex target enrichment to screen EHI patients for rare and potentially causative mutations. Of the 23 genes revealed in this analysis, 14 have been previously implicated in myopathic conditions. This approach will further our understanding of the genetic contribution to both EHI and MH, uncovering the molecular basis of these disorders and help us take the first steps towards genetic screening tests for military and preoperative use.

References

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2. JAMA 2001; 286: 168-9.

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Anesth Cell Signaling/Genetics 10 (143)

Pathway Analysis Highlights the Potential for Determining a Genetic Signature for Malignant Hyperthermia in Patient Blood Samples

Katie M. Nicoll Baines, BSc (Hons), MRes[1]; Dorota M. Mller, PhD[1]; Paul D. Allen, MD, PhD[2]; Marie-Anne Shaw, PhD[1]; Phil M. Hopkins, MD[1]

[1]University of Leeds, Leeds, United Kingdom; [2]University of California, Davis, Davis, California

Malignant Hyperthermia (MH) is a pharmacogenetic disorder presenting as a potentially fatal adverse drug reaction in otherwise healthy individuals during general anaesthesia. Susceptibility to MH is most commonly found to be the result of an inherited defect in the skeletal muscle ryanodine receptor gene RYR1. However studies on both UK and European pedigrees have highlighted the genetic complexity of this condition, suggesting that susceptibility to MH may be conferred by multiple interacting gene products.

The diagnosis of MH susceptibility by the in vitro contracture test (IVCT), uses a biopsied muscle sample to determine the presence of an abnormal reaction to halothane and caffeine. Individuals are only recommended for IVCT if there was been a clinical reaction or if they are a blood relative of someone proven to be susceptible. There are also guidelines for DNA-based screening, a process limited to searching for known functional mutations, but the genetic complexity of MH means this is not exhaustive.

Disease-related expression profiling, in conditions such as coronary artery disease and schizophrenia highlighted the potential for using peripheral blood for characterisation of expression profiles without using the tissue that is the primary focus of the disease process. We hypothesised that, despite the heterogeneity of the underlying defect in MH, there is a sufficiently homogeneous transcriptional response in skeletal muscle that is reflected in blood, to enable determination of those susceptible to MH.

Whole genome Affymetrix arrays were completed on 94 RNA samples derived from blood (39 MH normal: 18 male, 21 female; 55 MH susceptible: 31 male, 24 female), and 59 RNA samples derived from muscle (19 MH normal: 11 male, 8 female; 40 MH susceptible: 28 male, 12 female). Pre-processing, quality control, normalisation and annotation was completed using the 'Affy' package in R3.02. Normalised expression data was analysed by Akaike Information Criterion model comparison to determine those probes where MH phenotype (either susceptible or not) was a significant predictor variable, while controlling for effects of Age and Sex. A AIC of -2 was considered a suitable cut-off.

In muscle samples there were 4561 probe sets, equating to 3506 gene products, where MH phenotype was a significant factor; and in blood samples 2346 probe sets, equating to 1687 gene products. The 'nNOS signalling in skeletal muscle' pathway, detected by MetaCore©, showed differential expression of ACTB, DTNA, CALM1 and SNTB1 in muscle samples, while in blood samples SNTB2 expression (in the same pathway) differed. While differential gene expression common to these tissues was not identified, findings could indicate a role for this pathway in determining susceptibility to MH. The 'Role of HDAC and calcium/calmodulin-dependent kinase (CaMK) in control of skeletal myogenesis' pathway also showed genes exhibiting differential expression between MH susceptible and MH normal patients. Expression of CAMKK2, encoding calcium/calmodulin-dependent protein kinase 2, was significantly reduced in MH susceptible patients in both blood ($p<0.0001$) and muscle samples ($p=00072$). This gene could prove of use in developing a less invasive test for MH susceptibility.

Anesth Cell Signaling/Genetics 12 (117)
The Differential Effects of Commonly Used Anesthetics on Bacterial Growth In Vitro

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Introduction and General Purpose of the Study: It is a growing consensus that anesthetics are promiscuous molecules and work by directly interacting with a subset of ion channels in the central nervous system and modulating their functions [1, 2, 3]. For example, chloride channels (such as GABAA receptor), sodium channels or potassium channels (such as K2P channel) are presumably important anesthetic targets. Bacteria also possess various ion channels including potassium channels, sodium channels (NaChBac) and chloride channels (CLC chloride channels) [4]. Historically some of anesthetic structural research has been performed using bacterial ion channel [5]. Here we hypothesize that ion channels in bacteria may be affected by anesthetics. Because anesthetics are often given to patients with bacterial infection, understanding the effect of anesthetics on bacteria is important clinically. Therefore, we studied the impact of commonly used anesthetics (isoflurane, sevoflurane and propofol) on the growth of bacteria.

Methods: We tested both Gram negative bacteria (Escherichia coli, Pseudomonas aeruginosa) and Gram positive bacteria (Staphylococcus aureus and Enterococcus faecalis). Bacteria in the log-phase growth were cultured in tryptic soy broth (TSB) at 370C for 4 hours with or without isoflurane, sevoflurane or propofol at various concentrations. Isoflurane and sevoflurane were given in an airtight chamber. Samples are obtained at 1, 2 and 4 hours. Serial diluted samples were made and spread on agar for bacterial counting. % Growth was defined as [Bacterial count of sample exposed to anesthetics/bacterial count of control sample] x 100%. For propofol, DMSO containing solution (final concentration 0.1%) was used as a control. Data were shown as mean +/- S.D.

Results and Major Findings: Bacterial growth and anesthetics. We showed % Growth at 4 hours (Figure 1). We found that sevoflurane attenuated the growth of Escherichia coli as well as Staphylococcus aureus. However, sevoflurane did not attenuate the growth of Pseudomonas aeruginosa and Enterococcus faecalis. In contrast, propofol attenuated the growth of Pseudomonas aeruginosa and Enterococcus faecalis, but not Escherichia coli or Staphylococcus aureus. Isoflurane did not have a negative impact on the growth of bacteria.

Literature search: We performed the literature search of ion channels for each bacteria and summarized in Table 1. Although ion channels have been studied in bacteria, a comprehensive study of ion channels in individual bacteria waits future study.

Conclusions: Our results suggest that a structurally similar volatile anesthetics isoflurane and sevoflurane affect bacterial growth differently, and the effect of intravenous propofol is different. Although propofol reported interacts with multiple proteins, its anesthetic effect is primarily through GABAA receptor. Whether or not Pseudomonas aeruginosa and Enterococcus faecalis have homologous protein to GABAA receptor needs further study. The reduction of bacterial growth will be clinical benefit to patients and future directions should be to identify the underlying mechanism.

References

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Anesth Cell Signaling/Genetics 12 (117)
The Differential Effects of Commonly Used Anesthetics on Bacterial Growth In Vitro

Figure 1. % Growth of different bacteria under anesthetics

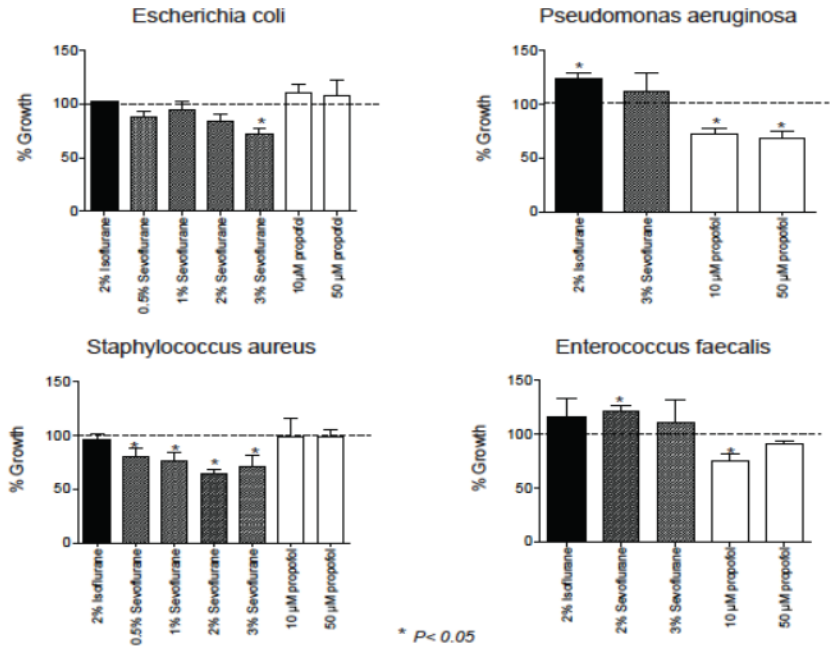

Table 1.

Bacteria strain	Ion channels
Escherichia coli	CIC chloride channel [6]
	Potassium channel [7]
Pseudomonas aeruginosa	Anion-selective channel [8]
Staphylococcus aureus	Potassium channel/ transporter [9]
Enterococcus faecalis	Potassium transporter? [10]

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Anesth Cell Signaling/Genetics 13 (116)

Propofol Affects Neurodegeneration and Neurogenesis by Regulation of Intracellular Calcium Homeostasis

Huafeng Wei, MD, PhD[1]; Hui Qiao, MD[2]; Yun Li, MD[3]; Gongyi Ren, PhD[1]; Wenxian Li, MD[2]; Zhijan Fu, MD[3]

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Background: Propofol is the most widely used intravenous anesthetic for general anesthesia. However, the effect of propofol on neurogenesis is still not clear. In this study, we investigated the effects of propofol on intracellular calcium homeostasis via activation of calcium release channels on endoplasmic reticulum (ER) membrane, i.e. the ryanodine and inositol 1,4,5-trisphosphate receptor (InsP3) receptor, and its role in propofol-mediated effects on autophagy, cell death and neurogenesis in human cortical neural progenitor cells (NPCs).

Methods: Cortical-derived NPCs from a human fetus were cultured and exposed to propofol at various concentrations and durations. Cell viability were measured by MTT reduction and lactate dehydrogenase release assays. NPCs proliferation was evaluated by bromodeoxyuridine incorporation. Autophagy activity was determined by measuring LC3 expression using Western Blot, in the presence or absence of autophagy flux inhibitor Bafilomycin, to differentiate the induction of autophagy from the impairment of autophagy flux. The effects of propofol on cytosolic calcium concentration ([Ca2+]c) were evaluated using dye Fura-2, in the presence or absence of the ryanodine receptor antagonist dantrolene, the InsP3 receptor antagonist xestospongin C, or the InsP3 production inhibitor lithium.

Results: Propofol dose- and time-dependently induced cell death, most robustly at 200 μM for 24 hrs, which could be inhibited by co-treatment of dantrolene or xestospongin C, but promoted by autophagy inducer rapamycin and autophagy flux inhibitor Bafilamycin. Propofol also dose- and time-dependently elevated the level of the autophagy biomarker LC3-II, which was further increased in the presence of bafilomycin but inhibited by dantrolene, suggesting an induction of autophagy via activation of ryanodine receptors by propofol. Propofol at a clinically relevant concentration (10 μM) stimulated NPCs proliferation but significantly impaired proliferation at a pharmacological concentration (200 μM), which could be inhibited by dantrolene or xestospongin C and potentiated by rapamycin. Propofol at 200 μM significantly increased [Ca2+]c, which could be inhibited partially by dantrolene, xestospongin C or lithium.

Conclusion: Propofol dose-dependently induced autophagy activity, cell damage and dual effects of both promoting and inhibiting neurogenesis in NPCs by differential activation of ryanodine or InsP3 receptor calcium channels. Propofol mediated cell damage is closely associated with its effects on autophagy.

Anesth Cell Signaling/Genetics 21 (66)

Mutants of Cytochrome P450 Reductase Lacking Either Glycine 141 or Glycine 143 Have Decreased Ability to Support Cytochrome P450 Catalysis

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Introduction: The majority of drugs used by anesthesiologists are metabolized by 20 of the 57 different human liver cytochrome P450 (P450). This means that only 20 proteins are major determinants of the efficacy, duration of action, and toxicity of the drugs used in the ~ 25 million anesthetics administered in the U.S. each year. The P450s are a superfamily of ubiquitous mixed-function oxygenases. P450 cleaves O2 with the assistance of electrons provided by P450 reductase (CYPOR) and inserts an atom of O into a hydrophobic substrate to enhance its water solubility and secretion by the kidney. CYPOR, which is required for P450 activity, has 2 flavin cofactors, FAD and FMN. NADPH transfers 2 electrons to FAD. FAD then transfers 1 electron at a time to FMN. The 2-electron-reduced FMN is the electron donor to P450. Each flavin cofactor exists in 3 oxidation states: oxidized (OX), 1-electron-reduced (semiquinone, SQ), and 2-electron-reduced (hydroquinone, HQ). It is the FMN HQ that reduces P450. To understand the biochemical and structural basis of the ability of FMN to reduced P450, we have deleted amino acids in a loop near the FMN that have been proposed to regulate electron transfer from FMN to P450. In the wild type protein, the conformation of the loop is different in the oxidized and reduced reductase. The loop does not contact the flavin ring in the oxidized form but rotates to an "up" position to hydrogen-bond (H-bond) to nitrogen 5 (N5) of the FMN SQ.

Methods: Two deletion mutant proteins, designated ΔGlycine141 (ΔGly141) and ΔGlycine143 (ΔGly143), were constructed by site-directed mutagenesis, expressed in E. coli, and purified. The mutant structures were determined in the oxidized and reduced state by X-ray crystallography. The biochemical properties of the mutants, including redox potential, rate of reduction by NADPH, rate of autoxidation, and catalytic activity with P450 were determined. Potentiometric methods and stopped-flow spectrophotometry under anaerobic conditions were employed.

Results and Discussion: The mutant lacking Gly 141 could not support P450 activity because it was thermodynamically (ox/sq couple -229 mV, sq/hq couple -53 mV) unable to reduce ferric P450 (-245 mV). Note that the more positive -53 mV sq/hq couple will be the most stable and least able to reduce P450. The altered potentials were due to the mutant's inability to form a stable H-bond with the N5 of the 1-electron-reduced SQ as occurs in the wild type (ox/sq -56 mV, sq/hq -249 mV). The crystal structure revealed that deleting Gly141 rigidified and shortened the loop which remained in contact with the flavin in both the OX and SQ form.

In contrast, the ΔGly143 mutant supported partial activity of P450. Crystallography revealed that the shortened loop of ΔGly143 was flexible and also did not form a stable H-bond with the FMN SQ in the presence of O2. However, the partial activity of ΔGly143 with P450 and its redox potential (ox/sq couple -240 mV, sq/hq -207 mV) indicated that a transient H-bond with the flavin N5 did indeed form. These results confirm the critical role of the sequence and length of a loop in controlling H-bond formation, redox potential, and ultimately the activity of CYPOR and drug metabolism.

Basic Neuro 37 (156)
Purkinje Cell Death and Cerebellar Deficits Resulting from Experimental Cardiac Arrest and Cardiopulmonary Resuscitation

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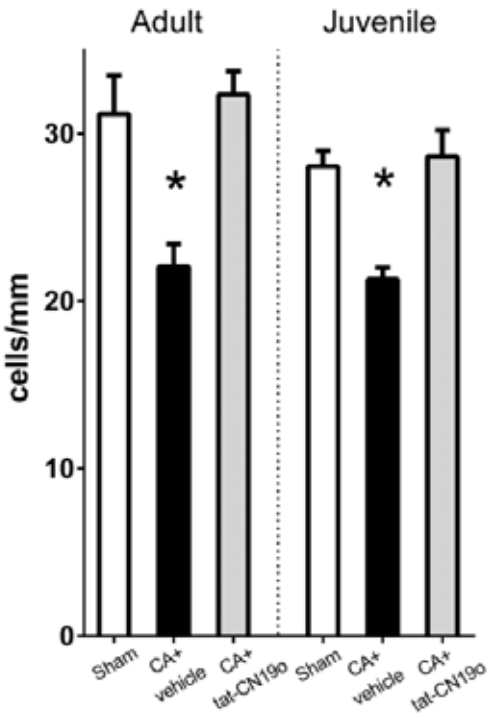
Objectives: Purkinje cell death in the cerebellum is a well-accepted consequence of global cerebral ischemia resulting from cardiac arrest and cardiopulmonary resuscitation (CA/CPR). However, the mechanisms of injury and consequences of Purkinje cell loss are poorly understood. The goal of this study was to assess Purkinje cell injury and cerebellar function in adult and pediatric mice following cardiac arrest and cardiopulmonary resuscitation. We also tested the hypothesis that calcium/calmodulin-dependent kinase (CAMKII) activation contributes to Purkinje cell death in pediatric and adult mice.

Methods: Pediatric (21-25 day old) and adult (8-12 week) male mice were subjected to 8 minutes cardiac arrest followed by cardiopulmonary resuscitation or sham surgery. Purkinje cells were labeled using anti-calbindin antibody and Purkine cell density was analyzed. To examine synaptic function, whole-cell voltage clamp recording on acute cerebellar slices was performed at 1 and 7 days after CA/CPR or sham. Excitatory postsynaptic currents (EPSCs) resulting from parallel (PF) or climbing fiber (CF) stimulation were recorded. To assess motor function rotarod and gait analysis was performed. Long-term depression (LTD), a form of synaptic plasticity was induced by simultaneous parallel and climbing fiber stimulation (1 Hz, 5 min).



Results: At 7 days following CA/CPR, Purkinje cell loss of 24% was observed in pediatric and 32% in adults. The novel CAMKII peptide inhibitor, tat-CN19o, provided significant protection against Purkinje cell loss in adults and pediatric mice compared to vehicle controls. Gait abnormalities were observed in adult and pediatric mice at 7 days after CA/CPR. Long-term depression, a characteristic reduction of synaptic strength of PF-EPSCs, was observed in adult and pediatric sham controls following PF+CF stimulation. LTD was absent in pediatric and adult mice at 24 hours after CA/CPR. At 7 after CA/CPR LTD was absent in adult mice, but had recovered in pediatric mice at 7 days after CA/CPR.

Conclusions: The results of this study suggest that CA/CPR results in significant Purkinje cell loss in pediatric and adult mice and that CAMKII activation contributes to cell death. Motor coordination impairments were observed in adult and pediatric mice following cardiac arrest and these impairments likely correlate with Purkinje cell death. In contrast, differences were observed in synaptic plasticity with pediatric mice showing enhanced recovery of LTD compared to adult mice. Therefore, future studies will be aimed at determining whether there are motor learning impairments that recover in pediatric, but not adult mice.

Basic Neuro/Inj 38 (155)

Sexually Dimorphic Estrogen Neuroprotection in Juvenile Mice Following Global Cerebral Ischemia

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Objectives: Pediatric cardiac arrest (CA) is a common and devastating condition which remains poorly understood. Mortality rates are extremely high and brain injury is the most common cause of death[1]. Epidemiologic studies in adults have suggested that females have better outcomes after CA when compared to males[2]. Numerous experimental studies in adult animal models have recapitulated this clinical data, showing that female animals exhibit significantly less brain injury following cerebral ischemia than males. The sex difference observed in experimental adult animals can be nearly completely explained by the high levels of estrogen in female animals, as removal of endogenous sex steroids (ovariectomy) increases female brain injury to male levels and estrogen replacement returns female injury to intact animal levels. Therefore, the focus of the current study is twofold, 1) assess gender difference in ischemic injury in pre-pubertal animals and 2) determine the influence of exogenous estrogen on pediatric brain injury.

Methods: Male and female pediatric mice (postnatal day 20-25) were subjected to 8 min cardiac arrest and cardiopulmonary resuscitation (CA/CPR). Mice were randomized to 17Ð-estradiol (E2) (0.1 mg/kg), E2+p39 MAPK inhibitor SB203580 (2 mg/kg) or vehicle administered 30 min after CPR (iv) and 3 days after resuscitation brains collected for histological analysis of hippocampal CA1 neuronal injury (H&E). Separate mice were used for Western blot analysis to evaluate the effect of CA/CPR and E2 treatment on phosphorylation of p38 MAPK, collected 24 hr after resuscitation. All data are expressed as mean±SEM. One-way ANOVA with Neuman Keuls post-hoc analysis of multiple-group comparisions performed and differences with $p<0.05$ considered significant.

Results: In contrast to previous studies using adult mice, no sex difference was observed in male and female pediatric mice (male: 49% ± 10% (n = 5) and female 62% ± 2% (n = 5, p=0.22). Female mice treated with E2 had significantly less neuronal damage (31% ± 6%; n=6; $p<0.05$). Surprisingly, E2 treatment of male juvenile mice had no effect on neuronal injury (56 ± 6%; n=6). Western blot analysis demonstrated that CA/CPR had no effect of phosphor-p38 MAPK levels, while estrogen increased phosphor-p38 MAPK levels in females. Finally, treatment with the p38 MAPK inhibitor (SB023580) prevented E2-mediated protection in female mice (54% ± 7%; n=5).

Conclusions: These data indicate that pre-pubertal juvenile mice do not exhibit sexually dimorphic neuronal injury following global cerebral ischemia, induced by CA/CPR. However, a single E2 dose administered at a clinically relevant timepoint provides robust neuroprotection, specifically in juvenile female mice. The E2 neuroprotection in female juvenile mice is likely mediated via upregulation of p38 MAPK signaling.

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Basic Neuro/Inj 43 (103)

miR-29a and VDAC1 Regulate Mitochondrial Function and Cell Survival in Astrocytes from Cornu Ammonis-1 and Dentate Gyrus Following Injury

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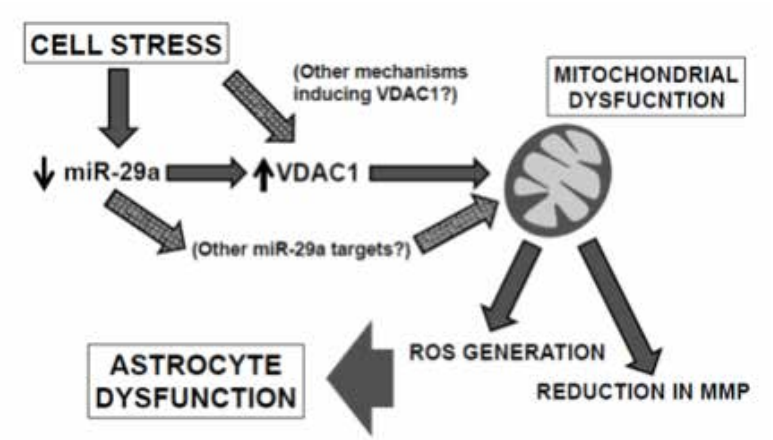
Neurons in the cornu ammonis 1 (CA1) region of the hippocampus are selectively vulnerable to transient cerebral ischemia, while neurons in the dentate gyrus (DG) are more resistant. This effect is mediated by local astrocyte function, and may be related to differences in subregional hippocampal expression of miR-29a. In the present study we investigated the role of miR-29a on cell survival in hippocampal astrocytes cultured selectively from CA1 and DG in response to extended glucose deprivation (GD) injury.



We observed that CA1 astrocytes exhibited lower resting mitochondrial membrane potential (MMP) and greater decrease in miR-29a following GD injury versus DG astrocytes. A reciprocal change was observed in expression of the mitochondrial voltage dependent cation channel-1 (VDAC1), a regulator of mitochondrial function and known target of miR-29a. Correspondingly, we observed a greater reduction in MMP and generation of reactive oxygen species (ROS) in CA1 astrocytes relative to DG astrocytes. In both CA1 and DG astrocytes, increasing levels of miR-29a with mimic decreased VDAC1 expression and ROS generation, preserved MMP, and improved cell survival following injury. Similarly, knockdown of VDAC1 expression with small interfering RNA resulted in improved survival from GD injury in both CA1 and DG astrocytes.

These findings suggest that the selective vulnerability of the CA1 to transient cerebral ischemia may be due in part to a greater reduction in miR-29a in CA1 astrocytes. This effect results in increased VDAC1-mediated disruption in mitochondrial function and dysfunction in CA1 astrocytes. These findings may provide a novel therapeutic intervention to preserve post-resuscitation hippocampal function following transient global cerebral ischemia.

Basic Neuro/Inj 44 (123)
Benzodiazepines Modulate Post-Traumatic Brain Injury Neurogenesis in Mice

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Introduction: Traumatic brain injury (TBI) affects millions of patients each year. Survivors can suffer from memory impairment, depression, seizures and loss of social independence. Previously, TBI was thought to result solely in neuronal loss. However, advancements in neuroscience have led to the discovery that certain regions of the brain possess some capacity to produce new neurons, known as neurogenesis. TBI has been shown to dramatically increase neurogenesis, specifically in the hippocampus. Because neurogenesis is modulated by GABAergic signaling, we investigated whether benzodiazepine administration would affect post-traumatic neurogenesis as it would have implications for the medical management of head injury patients.

Methods: In accordance with IACUC-approved protocols, POMC-GFP transgenic mice were subjected to a controlled cortical impact (CCI) model of TBI vs. sham (non-injury), with subsequent implantation of an osmotic drug pump containing diazepam or vehicle. Pumps were removed after 1 week. Neurogenesis was quantified via immunohistochemistry (IHC) of cells in the dentate gyrus of the hippocampus. At 2 weeks post-CCI, neurogenesis was evaluated via counting of GFP-positive newborn neurons; at 3 weeks post-injury, doublecortin and BrdU expression was evaluated.

Results: 2 week branch, POMC-GFP—Comparing vehicle-only groups, CCI increased neurogenesis vs sham (1.00 vs 1.72, N=9 each, p=0.004). In mice receiving diazepam after CCI, there was no difference in neurogenesis compared to sham groups (diazepam or vehicle). Additionally, in non-injured (sham) mice, there was no difference in neurogenesis with diazepam exposure (1.00 vs 1.03, N=9&7).

3 week branch, doublecortin and BrdU: In the vehicle-only groups, CCI again dramatically increased neurogenesis vs sham-injury (1.00 vs 7.11, N=6&8, p=0.005). In diazepam-treated groups, there was no difference in neurogenesis in CCI vs sham-injury. No difference in neurogenesis was observed between sham-vehicle and sham-diazepam mice.

Conclusions: CCI induces a robust neurogenic response in the dentate gyrus of the hippocampus, which appears to be profoundly inhibited by exposure to diazepam after injury. Possible mechanisms for this effect are related to GABAergic modulation of cell maturation or survival, or possibly via suppression.

Basic Neuro/Inj 46 (56)
Age-Related Up-Regulation of CTMP Promotes Cell Death in Older Rats after Ischemic Stroke

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Objective: Carboxyl-terminal modulator protein (CTMP) is an endogenous inhibitor of Akt, a prosurvival protein. It has been shown that global ischemia in young rats triggered the expression of CTMP in the hippocampal neurons and that this enhanced CTMP inhibited the Akt signaling, suggesting a role of CTMP in ischemic brain injury. Since aging is a risk for stroke and elderly patients and animals have a decreased brain ischemic tolerance, we designed this study to determine the role of CTMP in the aging-related decrease of brain ischemic tolerance.

Methods: The frontal cerebral cortex of 2-month and 20-month old Fischer 344 rats were harvested for Western blotting of CTMP and phosphorylated Akt. The frontal cerebral cortex of 2-month, 6-month and 10-month old Sprague-Dawley rats were also used for Western blotting of CTMP and phosphorylated Akt. Two-month and six-month old Sprague-Dawley rats were subjected to a 30-min middle cerebral artery occlusion (MCAO). The neurological outcomes including the neurological deficits, motor coordination and infarct volume were measured at 24 h after the reperfusion. In another experiment, the Akt inhibitor LY294002 and a viral vector carrying CTMP microRNA were injected into the brain cortex of 2-month and 6-month Sprague-Dawley rats before the MCAO.

Results: There was an age-related up-regulation of CTMP and a down-regulation of active Akt in the frontal cerebral cortex of Fischer 344 rats and Sprague-Dawley rats. LY294002 increased the infarct brain volume and worsened the neurological function of 2-month old rats. The neurological outcome of 6-month old rats was worse than that of 2-month old rats. This poor neurological outcome was attenuated by the viral vector carrying CTMP microRNA but not by the viral vector without CTMP microRNA. The viral vector carrying CTMP microRNA, but not the control viral vector, decreased CTMP and increased active Akt in the cerebral cortex of 6-month old rats.

Interpretation: These results suggest that a high level of CTMP and the subsequent inhibition of Akt signaling contribute to the aging dependent decrease of brain ischemic tolerance.

Basic Neuro/Inj 47 (52)
The Role of Heparanase in Subarachnoid Hemorrhage-Associated Neuroinflammation

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Objective: Our previous studies have indicated that the receptor of advanced glycation end-products (RAGE) plays an important role in mediating the cerebrovascular injury, neuroinflammation, and neurologic deficits following subarachnoid hemorrhage (SAH). In fact, blocking the RAGE signaling pathway by using a selective RAGE inhibitor led to a significant decrease in SAH-induced leukocyte trafficking, ameliorated cerebrovascular impairment, and restored neurologic functions. The expression of heparanase, another important pro-inflammatory mediator, has been shown to be up-regulated in the cortex after ischemic stroke and its function can be enhanced by the activation of RAGE signaling pathway. This study is designed to test the association between RAGE and heparanase in the neuroinflammatory reaction induced by SAH.

Material and Methods: The studies were conducted in Sprague-Dawley rats (~250 grams) which were divided into 3 groups: sham surgical control, vehicle (artificial CSF)-treated SAH, and SAH treated with a selective heparanase inhibitor (OGT2115). The treatment with OGT2115 or vehicle was initiated at 3 hours (h) after SAH via an intraventrical route. Neurological deficits were evaluated at 48 h post-SAH. Western blot analysis and immunohistological staining were used to determine protein expressions of both RAGE and heparanase in the brain cortex at 12 and 24 h post-SAH, while neuroinflammation (represented as leukocyte trafficking in pial venules) was monitored and assessed using intravital microscopy through the cranial window.

Results: The concurrent elevation in the expressions of both RAGE and heparanase was revealed at 12 and 24 h post SAH, suggesting a temporal relationship between RAGE and heparanase. Leukocyte trafficking also increases at 24 h in the vehicle-treated SAH group which was significantly suppressed in the presence of OGT2115. Moreover, OGT2115 treatment yielded a marked improvement in the neurological function compared to its vehicle-treated SAH control.

Conclusion: These data suggest that 1) a RAGE-dependent mechanism may account for the increase of heparanase expression in SAH, 2) heparanase asserts its role in SAH-induced neuroinflammation by enhancing leukocyte recruitment and 3) blocking heparanase activation provides a neuroprotective effect in SAH.

CS/Organ Inj 61 (111)

Thoracic Epidural Anesthesia Prevents Ventricular Arrhythmias by Reducing Dispersion of Repolarization and Electrical Restitution during Myocardial Ischemia

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Introduction: Autonomic nervous system imbalances are fundamental to the pathophysiology of ventricular arrhythmias. Thoracic epidural anesthesia (TEA) has been shown to reduce ventricular arrhythmias in patients however, the mechanism of this reduction in cardiac arrhythmias is not known. The goal of this study is to examine the effect of TEA on electrophysiological changes induced during acute myocardial ischemia and sympathetic stimulation. We hypothesize that spinal modulation of sympathoexcitation by TEA prevents ventricular arrhythmias by reducing dispersion of refractoriness and electrical restitution during myocardial ischemia.

Methods: Yorkshire pigs (n=17) were anesthetized, had thoracic epidural catheters placed at T1, and median sternotomy to expose the heart. A 56-electrode sock was placed over ventricles to obtain local electrograms for measurement of activation recovery intervals (ARIs), dispersion of repolarization (DOR), and electrical restitution (relationship of APD to diastolic intervals). ARI is an established surrogate for action potential duration. Increased DOR and steep electrical restitution are known to create an arrhythmogenic myocardial substrate and are precursors of ventricular tachycardias. In the ischemic group (n=8) acute ischemia was induced with 45 sec ligation of the left anterior descending coronary artery (LAD). ARI was recorded at baseline, with acute ischemia, and ischemia + left stellate ganglion stimulation (LSS); pre and post-TEA. In control group (n=9) ARI was recorded and restitution measured at baseline and + LSS; pre and post-TEA. (TEA: 0.5% bupivacaine 0.4mg/kg). Repeated measures ANOVA were used to compare measures between control and TEA conditions.

Results: In both ischemic and healthy groups, there was no significant difference between baseline global ARI with and without TEA. With acute ischemia, there was an expected reduction in ARI in the ischemic zone. However TEA attenuated this reduction in ARI with ischemia and blocked further sympathetic augmentation during LSS (% change pre-TEA vs. TEA: -5% vs. -3%, p=0.01). In normal controls, while there was no difference in baseline ARI, sympathoexcitation with LSS was attenuated and the magnitude of ARI shortening was reduced (pre-TEA vs. TEA: -7 ± 1 vs. -4 ± 1 %, p=0.01) Dispersion of repolarization, which increases with stellate ganglion stimulation, was also suppressed post-TEA in normal hearts. In addition, restitution curves which measure the arrhythmogenic potential of the myocardium demonstrated a reduction with TEA (maximum slope pre versus post-TEA: 0.9 to 0.7, p=0.02).

Conclusion: Thoracic epidural anesthesia reduces cardiac excitability induced by sympathetic stimulation. The results of this study show that TEA prevents ventricular arrhythmias by reducing dispersion of repolarization and electrical restitution during myocardial ischemia This suggests that the therapeutic anti-arrhythmic effects of TEA during acute ischemia are likely through spinal modulation of sympathetic reflexes at the thoracic level suppressing ischemia induced sympathoexcitation and reducing the arrhythmogenic myocardial substrate.

CS/Organ Inj 62 (134)

Multi-Frequency Oscillatory Ventilation: Effects on Regional Ventilation Heterogeneity and Carbon Dioxide Elimination in Canine Lungs

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Introduction: High frequency oscillatory ventilation (HFOV) relies on low tidal volumes cycled at supraphysiologic rates, producing fundamentally different mechanisms for gas transport and exchange compared with conventional mechanical ventilation. Despite the appeal of using low tidal volumes to mitigate the risks of ventilator-induced lung injury (VILI), HFOV has not improved mortality in most clinical applications. This may be due to distributing flows throughout the lung in a non-uniform and frequency-dependent manner, especially in the presence of mechanical heterogeneity[1]. However a recent experimental study demonstrated that HFOV using multiple simultaneous frequencies in mechanically heterogeneous lungs improved gas exchange and lung recruitment when compared to traditional single-frequency HFOV[2]. Thus the goal of this present study was to utilize computational modeling to elucidate the relationship between carbon dioxide (CO2) elimination and spectral content of multi-frequency oscillatory ventilation waveforms in heterogeneous lungs.

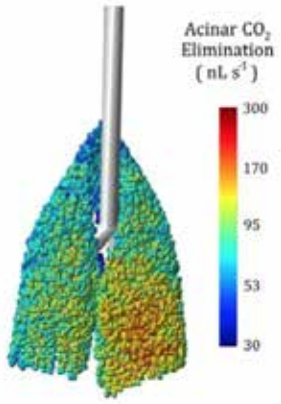

Figure 1. Canine lung model represented by cylindrical airways (grey) and terminal acini, colored according to individual rates of acinar CO_2 elimination during eucapnic ventilation at 11 Hz and 2.3 mL kg^{-1} tidal volume. Total CO_2 elimination at the airway opening is 4.6 mL kg^{-1} min^{-1}.

Methods: A computational model for simulating frequency-dependent distributions of flow in a canine airway tree was adapted to a three-dimensional airway network derived from a segmented thoracic CT scan of a supine dog [2]. Gas transport was simulated via direct alveolar ventilation, convective mixing at bifurcations, turbulent and oscillatory dispersion, and molecular diffusion. The volume amplitudes at each oscillatory frequency were iteratively optimized to attain eucapnea. Ventilation heterogeneity was assessed by the distributions of flow and CO2 elimination across all acini subtending the terminal airway segments in the model.

Results: HFOV reduced the total oscillatory volume required for eucapnic ventilation, at the expense of increased ventilation heterogeneity. However for certain pairs of oscillatory frequencies, simultaneous delivery of two frequencies reduced ventilation heterogeneity compared to either frequency alone. These pairs comprised frequencies characterized by dissimilar flow distributions with respect to each other, such that their superposition resulted in decreased portions of parenchymal tissue being exposed to over- or under-ventilation, with less potential for VILI.

Conclusion: Our computational model demonstrates that pairs of oscillatory frequencies yield eucapnic conditions with less potential for injurious ventilation compared to traditional single-frequency HFOV. This finding suggests that superposition of several simultaneous frequencies may minimize ventilation heterogeneity compared to single frequency oscillatory ventilation.

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CS/Organ Inj 124 (57)
Light Elicited Mechanisms in Organ Protection

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Background: Studies on human circadian rhythms suggest a role in metabolic adaptation during environmental stress and disease. Intense light, a key regulator of circadian rhythms, was found to mediate cardio- or lung-protection during myocardial ischemia or acute lung injury in mice, respectively. Following studies pointed us towards the light dependent circadian rhythm gene period 2 (Per2) as important player in these processes.

Methods: All animal and human studies had IACUC and IRB approval and were in accordance with the APS/ NIH guidelines. Studies on induction or stabilization of Per2 in mice or human subjects were assessed using real-time RT-PCR or western blotting. To study light elicited Per2 mechanisms during myocardial ischemia an in situ mouse model for ischemia and reperfusion injury of the heart was used[(1)]. In order to study light elicited Per2 mechanisms during lung injury a ventilator induced lung injury model was used [(2)]. To understand light elicited mechanisms in humans, we performed screening experiments using the SOMAscan or metabolomic profiling from plasma samples.

Results: One week of light exposure revealed increased Per2 protein expression in hearts and lungs of wild-type mice. Analogously, intense light therapy in human volunteers revealed increased Per2 levels in blood and buccal samples. Studies using 'blind' mice showed that light perception was necessary to mediate Per2 induction in the heart. Mechanistic studies revealed Per2 as significant regulator of metabolism and inflammation in mice and men.

Conclusions: Our murine studies indicate that light induced Per2 mediates organ protection in mice. Human studies reveal a robust Per2 induction in tissue samples following one week of intense light exposure. Studies on cell metabolism reveal Per2 as important regulator of many essential metabolic pathways. Future studies will have to test light therapy in patients (e.g. ceilings with daylight simulation) to either prevent or diseases associated with disruption of metabolic pathways [(3)].

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CS/Organ Inj 125 (88)
Intralipid Protects Rat-Isolated Hearts against Ischemia-Reperfusion Injury through Nitric Oxide-Mediated Pathways

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Introduction: Intralipid (ILP), an FDA-approved fat emulsion, attenuates myocardial ischemia-reperfusion (IR) injury when given before and/or after IR[1,2]. In an endothelial cell culture model, we have shown that ILP leads to increased levels of phosphorylated endothelial nitric oxide synthase (eNOS) and NO release. Here, we used rat isolated hearts and tested if ILP-induced cardioprotection is indeed mediated by NOS-derived NO.

Methods: Balanced Krebs solution containing 5 mM glucose (control) ± 1% Intralipid ± 100 μM of the nitric oxide synthase inhibitor NĐ-Nitro-L-arginine methyl ester (L-NAME) was used to perfuse Langendorff-prepared rat hearts for 35 min, followed by IR for 30/120 min, respectively. Coronary flow, left ventricular pressure and its derivatives before, during and after IR and infarct size were measured.

Results: L-NAME completely abolished functional improvement and infarct size reduction by ILP. DISCUSSION: Together with our previous findings, these results indicate a critical role of endothelial NO-release in ILP-induced cardioprotection against IR injury.

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CS/Organ Inj 126 (93)
The Role of PDE4 in IL-8-dependent Inhibition of cAMP-stimulated Alveolar Fluid Clearance in a Murine Model of Trauma-Hemorrhage

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Introduction: Stimulation of the beta2-adrenergic receptor (β2-AR) can increase cAMP-mediated alveolar fluid clearance (AFC) in both animals and humans. However, in patients with acute respiratory distress syndrome (ARDS), treatment with β2-agonists has failed in two phase III clinical trials [(1)]. Multiple studies have determined that the β2-AR is heterologously phosphorylated and internalized after activation of the interleukin-8 (IL-8) receptor or transforming growth factor-beta receptor in respiratory syncytial virus infection or trauma-hemorrhage (TH) [(2, 3)]. Inhibition of the β2-AR by these inflammatory mediators was phosphatidylinositol-3-kinase-dependent and led to decreased cAMP mobilization by β2-agonists. We hypothesized that inflammatory mediators induce β2-AR trafficking and signaling defects that can be reversed by rolipram, a phosphodiesterase (PDE) 4 inhibitor that increases cAMP levels. Roflumilast, a clinical PDE4 inhibitor, is used in chronic obstructive pulmonary disease and asthma as an adjunct to β2-agonist therapy.

Methods: In alveolar epithelial cells after exposure to IL-8, we determined the internalization and recycling of the β2-AR and the spatiotemporal mobilization of specific cAMP pools in response to β2-agonists. Furthermore, we used a murine model of TH (in which IL-8 is increased in the lung) to determine β2-AR-mediated AFC. Rolipram was used to determine whether PDE4 inhibition could prevent or reverse IL-8-dependent effects. All studies were approved by the IACUC at UAB.

Results: IL-8 exposure initiated internalization of the β2-AR and decreased Ð2-agonist-dependent cAMP mobilization in cytoplasmic pools. Furthermore, after internalization, the β2-AR did not recycle back to the cell surface. Pretreatment with rolipram prevents IL-8-mediated internalization of the β2-AR and altered mobilization of specific cAMP pools. Furthermore, after IL-8-dependent internalization of the β2-AR, treatment with rolipram restores recycling of the β2-AR. Finally, in a murine model of TH, treatment with rolipram after TH restores β2-AR-mediated AFC.

Conclusions: Our results provide a mechanism by which inflammatory mediators released during critical illness inhibit normal functioning of the β2-AR. Furthermore, we have revealed that pre- or post-treatment with a PDE4 inhibitor can reverse these effects. While this study focuses specifically on IL-8 effects and β2-AR-mediated AFC, these results are likely similar for other inflammatory mediators increased during critical illness and other organ systems in which β2-AR activation is vital for normal function such as the innate immune system and vascular smooth muscle.

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CS/Organ Inj/Sep 71 (112)
Cellular RNA and Synthetic microRNAs Induce Complement Activation and Tissue Inflammation via TLR Signaling

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Introduction: Severe sepsis induces massive activation of the complement system that includes the classical, lectin and alternative pathway (AP). Complement factor B (cfB) is an essential component of AP activation. It is recently reported that cfB is markedly up-regulated during sepsis and plays a critical role in cardiac dysfunction, acute kidney injury, and overall mortality in experimental polymicrobial sepsis (1). However, the mechanism leading to cfB production and AP activation during sepsis remains poorly understood. We hypothesize that RNA and miRNAs promotes cfB production through Toll-like receptors (TLRs) signaling pathway.

Methods: Polymicrobial sepsis was created by cecum ligation and puncture (CLP) in mice. Twenty-four hours later, blood was collected and plasma prepared. Plasma RNA was extracted using Trizol LS. Plasma miRNAs were analyzed using microRNA array and validated by qRT-PCR. Bone marrow-derived macrophages (Mϕ) from WT or TLR3-/-, TLR7-/-, MyD88-/- mice were treated with 10 µg/ml tissue RNA or 50 nM of miRNA mimics in the presence of lipofectamine for 18-24 hours. Medium cfB was analyzed by Western blot. Three mg RNase was injected i.p. 1 hour before and 12 hours after surgical procedures and cardiac cfB mRNA was determined by qRT-PCR. RNA (50 µg/mouse) or miRNA mimics (20 µg/mouse) were administered i.p. and lavage cfB was analyzed by Western blot 18 hours later.

Results: We found that the plasma cell-free RNA was significantly increased following CLP, and was closely associated with sepsis severity. qRT-PCR and miRNA array analysis revealed an increase in both bacterial RNA and multiple host microRNAs (miR-145, miR-146a, miR-122, miR-210) in the blood following CLP. In vitro, treatment with tissue RNA or synthetic miRNA mimics (miR-145, miR-146a, miR-122, miR-34a) induced a marked increase in cfB production and cytokine production in cardiomyocytes or macrophages. Genetic deletion of TLR7 or MyD88, but not TLR3, and inhibition of the MAP kinases (JNK and p38) or NF-kB abolished miRNA-induced cfB or cytokine production in Mϕ. In vivo, CLP led to a significant increase in splenic cfB gene expression, which was correlated with the plasma RNA or miRNA levels. Peritoneal injection of endogenous tissue RNA or miR-146a led to a rise in cfB expression and monocyte infiltration in the peritoneal space, which was attenuated in MyD88-KO or TLR7-KO mice, respectively.

Conclusions: We demonstrate that host cellular RNA and certain miRNAs are released into the circulation during polymicrobial sepsis. These cellular RNA and miRNA may function as extracellular mediators capable of activating cfB and cytokine production and promoting tissue inflammation through specific MyD88 and TLR7 signaling.

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CS/Organ Inj/Sep 73 (122)
Perioperative TLR4 Modulation in a Mouse Model of Surgical Trauma: A Systems-Wide Analysis by Single-Cell Mass Cytometry

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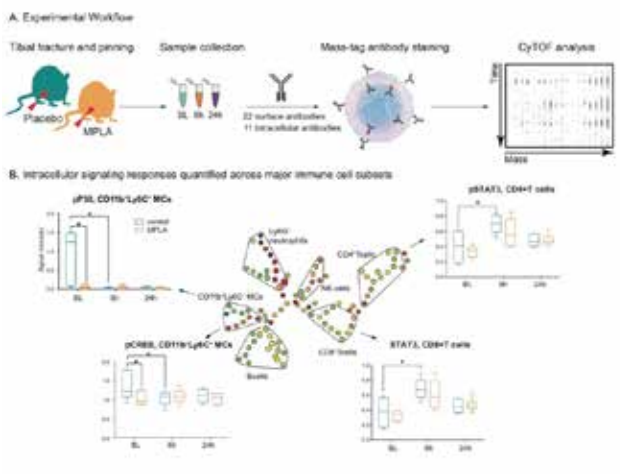
Introduction: Impaired recovery characterized by chronic post-surgical pain and difficulty with daily functioning affects 30% of patients and bears substantial economic costs. Recent advances in Enhanced Recovery After Surgery (ERAS) pathways highlight the significance of protracted surgical recovery. However the elements of these protocols that may improve recovery are uncertain. To identify patient-specific modifiers that may be targeted pre-operatively to improve surgical recovery, a precise understanding of the biological mechanisms that drive surgical recovery is critically needed.



Accumulating evidence from mouse and human models implicate the Toll-Like Receptor 4 (TLR4) signaling in essential aspects of the innate immune response to surgery. In a recent mass cytometry analysis of patients' immune system before surgery, activation of the MyD88 branch of the TLR4 signaling pathway in monocytes accounted for ~ 50% of inter-patient variability in recovery from pain and functional impairment. Here, we propose a novel high dimensional mass cytometry assay in a murine model of surgery to 1) establish a pre-clinical paradigm that recapitulates important components of the human immune response to surgery, 2) enable the systems-wide analysis of pharmacological manipulation of TLR4 signaling in vivo, and 3) demonstrate a causative link between TLR4 signaling in monocytes and functional recovery from surgery.

Methods: In order to positively modulate the immune response, we performed TLR4 priming of innate immune cells using the TLR4 agonist monophosphoryl lipid A (MPLA), a bacterial cell wall component that is used in several human vaccines. C57Bl6/J mice received intraperitoneal injections of MPLA 20 Î¼g or saline once daily for two consecutive days. Following MPLA injection, mice were subjected to tibial fracture and intramedullary pinning. Whole blood samples were collected before, then 6h or 24h after surgery. A panel containing 22 cell surface and 11 intracellular antibodies was utilized to quantify surgery-induced changes in cell frequency and associated intracellular signaling across all major immune cell subsets using mass cytometry (Figure 1).

Results: The systems-wide analysis of the murine immune response to surgery revealed cell-type specific immune features that remarkably mimicked human immune signatures of surgical recovery. Within the innate compartment, we found robust activation of STAT3 in lin-CD11b+LyC+ monocytes and the concomitant dephosphorylation of P38/CREB and NFkB, six hours after surgery. Interestingly, TLR4 priming with MPLA dramatically suppressed baseline P38, MAPKAPK2 and CREB phosphorylation in lin-CD11b+LyC+, while NFkB phosphorylation remained unchanged.

Conclusions: This study provides the foundation for a promising animal model to comprehensively study the effect of pre-operative TLR4-modulation on cellular mechanisms relevant to the human immune response to surgery. Further dissection of the individual cellular contributions will allow the development of interventions that can be translated back to humans to enhance recovery after surgery.

CS/Organ Inj/Sep 74 (107)
Cholinergic Basal Forebrain Neurons Inhibit Systemic Inflammatory Response via Vagus Nerve during Sepsis

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Introduction and General Purpose of the Study: Central nervous systemplays important roles in regulating innate immune responses via the vagus nerve, which was termed ascholinergic anti-inflammatory pathway[1]. Acetylcholine, as the principal neurotransmitter of vagus nerve, can activate the ±7 nicotinic acetylcholine receptor subunit (±7nAChR), and then inhibit pro-inflammatory cytokines, and finally improve survival in murine sepsis[2,3]. The cholinergic neurons in the basal forebrain constitute an important component of the neuromodulatory system controlling brain states[4]. However, its exact role in the cholinergic anti-inflammatory pathway remains unclear. In this study, we hypothesized thatBF modulates systemic inflammatory response in sepsis via controlling the peripheral vagus nerve.

Methods: ChAT-ChR2-EYFP transgenic mice (ChAT mice) were treated by photostimulation to activate ch-BF neurons according to a scheduled protocol. Sepsis was induced by cecal ligation and puncture (CLP) in both ChAT mice and wild-type littermates. Mice were sacrificed at 3, 12 or 36 hours after the surgery. In some experiments, mice were first implemented left cervical vagotomy, and then performed CLP as previous. Characterization of splenic lymphocytes and cytokine levels in the plasma and spleens were evaluated.

Results and Major Findings: After light stimulation of BF, TNF-α and IL-6 levelsin serum and spleen of ChAT mice were significantly decreased at 3 and 12 hours after CLP compared with those inwild-type controls. And IL-10 levels showed no significant difference. However, after selective left cervical vagotomyin ChAT mice, TNF and IL-6 levels were significantly increased when compared with the sham controls. Additionally, stimulation of the cholinergic basal forebrain neurons lead to alterations in splenic immune cell population, which presentedwith higher percent of B lymphocytesand lower percent of T cells in the ChAT mice.

Conclusions: The basal forebrain can regulate systemic inflammatory response through activating peripheral vagus nerve. The cholinergic basal forebrain neurons play important roles in the inhibition of the systemic inflammatory response during sepsis.

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CS/Organ Inj/Sep 75 (139)
TRPM2 Regulates Phagosome Maturation and is Required for Bacterial Clearance in E. coli Induced Sepsis

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Introduction and General Purpose of the Study: The transient receptor potential melastatin 2 (TRPM2) channel is a nonselective, Ca2+-permeable cation channel abundantly existed in macrophages[1]. TRPM2 knockout (Trpm2−/−) mice showed exacerbated bacterial load and high mortality during polymicrobial sepsis, which might result from an inefficient bacterial killing in Trpm2−/− macrophages[2,3]. However, the regulation mechanism of TRPM2 in degradation of engulfed bacteria in macrophage remains unknown.

Methods: Trpm2+/+ and Trpm2−/− mice were intraperitoneal (i.p.) injection of Escherichia coli (E. coli) to induce peritonitis. The survival rate and bacterial burden were assessed. The phagosome maturation process in Trpm2−/− peritoneal macrophages were studied. Ionomycin was used to restore cytosolic Ca2+ concentration of peritoneal macrophages derived from Trpm2−/− mice. The impacts of elevated Ca2+ concentration on bacterial clearance of macrophages and survival rate of Trpm2−/− mice were further clarified.

Results: Trpm2−/− mice had increased mortality (85 vs.54.5%, P = 0.009) as well as aggravated bacterial burden during E. coli–induced sepsis. Infection of Trpm2−/− peritoneal macrophages with E. coli resulted in dampened recruitment of the lysosomal marker protein LAMP-1. The maturation of phagosomes isolated from Trpm2−/− peritoneal macrophages were attenuated as judged by reduced accumulation of early endosome marker EEA1 while normal acquisition of Rab5. Restoring cytosolic Ca2+ concentration via ionomycin treatment facilitated EEA1 recruited to Rab5 and phagosomal localization of LAMP-1. Transfusion of ionomycin treated peritoneal macrophages improved bacterial clearance and survival of Trpm2−/− mice challenged with E. coli (23.1 vs. 64.3 %, P=0.027).

Conclusions: TRPM2 plays a critical role in phagosome maturation by regulating EEA1 recruitment and hence functions in maintaining host defense against invading bacteria.

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CS/Organ Inj/Sep 76 (108)
S1PR2 Contributes to Noncanonical Inflammasome Activation and Impairs the Outcome of Escherichia coli Sepsis

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Introduction and General Purpose of the Study: Sepsis is still a threat in hospital with high mortality rates [1]. Absence of the noncanonical inflammasome caspase-11 was found to protect mice from lipopolysaccharide (LPS)-induced endotoxic shock[2, 3]. However, the regulators of caspase-11 are still unknown. The objective of this study was to investigate whether S1PR2 contributes to noncanonical inflammasome activation and its molecular mechanisms.

Methods: In vivo, Noncanonical inflammasome pathway was studied after S1pr2+/+ or S1pr2-/- mice subjected to LPS-induced endotoximia. Caspase-11 expression in spleen, lung and liver, and the inflammatory response were examined. In vitro, we compared the level of active caspase-11 and its downstream caspase-1, IL-1β levels and pyroptosis in the primary peritoneal macrophages from S1pr2+/+ and S1pr2-/- mice, which are stimulated by LPS or Escherichia coli. We further examined the phosphorylation of STAT1. JTE-013, an inhibitor of S1PR2 was also utilized to reconfirm the above results from genetic deletion of S1pr2 peritoneal macrophages in vitro and target S1PR2 for therapeutic intervention in vivo.

Results and Major Findings: S1pr2-/- mice that underwent LPS-induced endotoximia at 12 hours had lower expression of caspase-11 compared with that from S1pr2+/+ mice. In addition, the serum level of IL-1Î² and lung damage was also decreased in S1pr2-/- mice. Activation of the caspase-11 pathway stimulated with Escherichia coli in S1pr2-/- macrophage was significantly reduced, both at mRNA and protein levels. Downstream of caspase-11, caspase-1, IL-1β and pyroptosis were decreased as well in S1pr2-/- macrophage. Furthermore, we found that deficiency of S1PR2 inhibited caspase-11 signaling pathway by reducing the phosphorylation of STAT1. Pharmaceutical inhibition of S1PR2 with JTE-013 could also inhibit the phosphorylation of STAT1 and the activity of caspase-11 signaling. In vivo, JTE-013 improved the outcome of sepsis from intraperitoneal injection of Escherichia coli.

Conclusions: Our results indicated that S1PR2 contributes to caspase-11 activation and impairs the outcome of Escherichia coli sepsis. Interventions targeting S1PR2 signaling may serve as promising therapeutic approaches for sepsis.

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CS/Organ Inj/Sep 77 (137)
Starvation-Induced Improvement in Long-Term Outcomes Following Sepsis in Drosophila Melanogaster

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Introduction: Multiple organ failure, wasting, increased morbidity, and mortality following acute illness complicates the health span of patients surviving sepsis. Persistent inflammation has been implicated, and it is proposed that insulin signaling contributes to persistent inflammatory signaling during the recovery phase after sepsis. However, mechanisms are unknown and suitable pre-clinical models are lacking [1-16]. We used recently developed a Drosophila melanogaster model of sepsis [17] to explore effects of starvation and starvation mimetic drugs (Metformin and 2-deoxy-D-glucose (DG)) on chronic outcomes of sepsis like sustained inflammation, impaired metabolic disturbance, and changes in lifespan.

Methods: We used wild-type (WT) and NF-?B-luc reporter male Drosophila melanogaster 4–5 days of age (unmanipulated). We infected Drosophila with Staphylococcus aureus (infected without treatment) or pricked with aseptic needles (sham). Subsets of insects were treated with oral linezolid after the infection (infected with antibiotics). Starvation group were exposed to starvation prior to infection and starvation-mimetic were also fed to flies prior to infection. We assessed rapid iterative negative geotaxis (RING) in all the groups as a surrogate for neuromuscular functional outcome up to 96 h following infection. We harvested the flies over the 7-day course to evaluate bacterial burden, inflammatory and metabolic pathway gene expression patterns, NF-?B translation, and metabolic reserve. We also followed the lifespan of the flies.

Results: Our results showed that when treated with antibiotics, flies had improved survival compared to infected without treatment flies in the early phase of sepsis up to 1 week (81 %, p?0.001). However, the lifespan of infected with antibiotics flies was significantly shorter than that of sham controls (p?0.001). Among infected with antibiotic sepsis survivors, we observed persistent elevation of NF-?B in the absence of any obvious infection as shown by culturing flies surviving sepsis. In the same group, geotaxis had an early (18 h) and sustained decline compared to its baseline. Geotaxis in infected with antibiotics sepsis survivors was significantly lower than that in sham and age-matched unmanipulated flies at 18 and 48 h. Expression of antimicrobial peptides (AMP) remained significantly elevated over the course of 7 days after sepsis, especially drosomycin (5.7-fold, p?0.0145) on day 7 compared to that of sham flies. Infected with antibiotics flies had a trend towards decreased Akt activation, yet their glucose stores were significantly lower than those of sham flies (p?0.001). Once starved 6 hours before infection, infected with treatment flies demonstrated significantly better survival 1 week after infection and longer life-span. Flies pretreated with Metformin or DG also demonstrated similar improvement in survival 1 week after infection. Sepsis survivors had increased lactate levels and LDH activity by 1 week, whereas ATP and pyruvate content was similar to that of the sham group.

Conclusions: Using Drosophila sepsis model, we successfully reversed mortality in sepsis surviving flies by preventing metabolic shift following sepsis instead of traditional interventions on immune system or pathogens.

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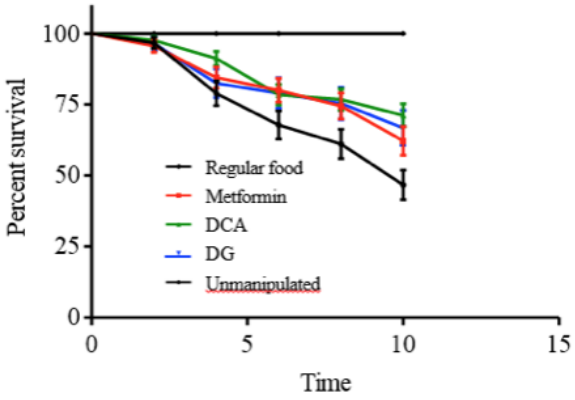
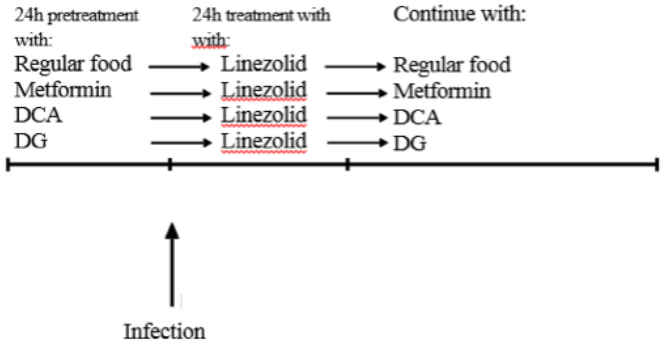
Starvation-Induced Improvement in Long-Term Outcomes Following Sepsis in Drosophila Melanogaster





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Clin Studies 22 (150)

Association between Availability of Videolaryngoscope for Tracheal Intubation and the Number of Emergency Tracheostomy in Perioperative Setting of a Large Academic Medical Center: A Retrospective Observational Study

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Introduction: Difficult mask ventilation and difficult tracheal intubation occur under anesthesia[1] and share common risk factors. "Cannot intubate, cannot ventilate" is a rare but catastrophic event. When it occurs, rescue by emergency surgical airway is recommended if return of effective spontaneous breathing is not feasible. As technology advances, videolaryngoscope has become readily available and there is study demonstrating its advantages[2]. However, it remains unknown if the availability of videolaryngoscope leads to a reduction in the need for emergency surgical airways. The aim of this study is to assess the trend of the incidence of emergency tracheostomy in the perioperative setting and the utilization, a surrogate of availability, of videolaryngoscopy for tracheal intubation.

Methods: After IRB approval, data were collected from 2008-2015 from the Perioperative Data Warehouse at Vanderbilt University Medical Center. Billing codes and procedure codes were used to identify emergency tracheostomy cases. All identified cases underwent a manual review of the electronic medical records. We identified the number of general anesthetics where either an endotracheal tube or laryngeal mask airway was inserted. Additionally, we determined the number of intubations performed with videolaryngoscopy over the same time period.

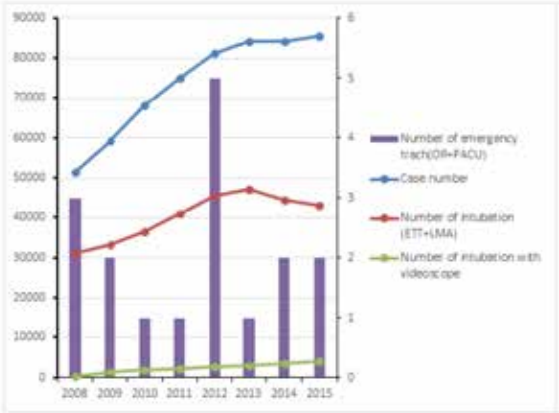

FIGURE 1: Number of emergency tracheostomy, total anesthestic cases, cases intubated with endotracheal tube (ETT) or insertion of laryngeal mask airway (LMA) and cases intubated with videolaryngoscopy. The units of Y-axis are cases/year on the left side for total cases of anesthesia, cases intubated with ETT or insertion of LMA and cases intubated with videolarygoscopy and cases/year on the right for emergency tracheostomy.

Results: A total of 17 cases of emergency tracheostomy were identified in the perioperative setting, operating room and post operation care unit. During this period, the number of general anesthetic cases with either intubation or laryngeal mask airway placement increased from 51,445 per year to 85,618. The number of endotracheal intubations increased from 31,182 to 43,330, while the utilization of videolaryngoscope for tracheal intubation increased from 391 to 3,988. The number of emergency tracheostomy ranged from 1 to 5 cases per year (Figure 1).

Conclusion: Our results do not show a correlation between the utilization of videolaryngoscopy and the number of emergency tracheostomy in perioperative setting. Increased utilization of videolaryngoscopy has not obviated the need for emergency tracheostomy in perioperative setting. Therefore, skill and equipment for establishing a surgical airway should be maintained in the perioperative setting.

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Clin Studies 23 (170)
Increased Use of Inhaled Nitric Oxide in Single Ventricle Patients with Low Nasal Nitric Oxide Undergoing Congenital Heart Surgery

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Introduction: Cardiopulmonary bypass impairs endogenous production of nitric oxide (NO) leading to increased pulmonary vascular resistance (PVR) and associated increased stress on an already vulnerable ventricle [1]. Supplemental inhaled NO (iNO) decreases PVR and has improved post-bypass mortality [1]. We hypothesized nasal NO (nNO), which can be sampled in a quick, easy, non-invasive bedside test, may be a biomarker for endogenous NO homeostasis, thus patients with low nNO undergoing cardiac surgery may be predicted to have increased perioperative iNO use.

Methods: With institutional review board approval, 132 congenital heart disease patients undergoing cardiac surgery were consented into the study. Nasal NO was obtained using an Eco Physics CLD 88sp NO analyzer. Patients were categorized as having normal or low nNO based on established cutoff values[2, 3]. Charts were reviewed for perioperative iNO administration. All health care providers were blinded to the study.

Results: Sixty-four patients had low nNO (48.5%). Of these, 35 patients (54.7%) received perioperative iNO compared to 21/68 (30.9%) patients with normal nNO (p=0.006, OR 2.7 [1.3-5.5]) (Table 1). There were significantly more single ventricle physiology (SV) patients in the low nNO group (29/64 vs. 16/68, p=0.008). Subgroup analysis showed the incidence of receiving perioperative iNO was significantly higher in SV patients with low nNO than in SV patients with normal nNO (21/29 [72.4%] vs. 5/16 [31.2%], p=0.007, OR 5.8 [1.5-21.9]). There was no significant difference in iNO use between SV and two-ventricle (2V) patients with normal nNO (5/16 vs. 16/52, p=1), but there was a difference in the low nNO groups (21/29 vs. 14/35, p=0.01).

Table 1.

	Did not receive iNO	Received iNO	p	OR
All pts, low nNO (%)	29 (45.3)	35 (54.7)	0.006	2.7 (1.3-5.5)
All pts, normal nNO (%)	47 (69.1)	21 (30.9)		
SV, low nNO (%)	8 (27.6)	21 (72.4)	0.007	5.8 (1.5-21.9)
SV, normal nNO (%)	11 (68.8)	5 (31.2)		
Low nNO, SV (%)	8 (27.6)	21 (72.4)	0.01	3.9 (1.4-11.3)
Low nNO, 2V (%)	21 (60)	14 (40)		
Normal nNO, SV (%)	11 (68.8)	5 (31.2)	1	1 (0.3-3.4)
Normal nNO, 2V (%)	36 (69.2)	16 (30.8)		

Table showing increased odds of receiving iNO perioperatively for patients with low nNO.

Key: pts - patients, iNO - inhaled nitric oxide, nNO - nasal nitric oxide, SV - single ventricle physiology, 2V - two-ventricle physiology

Conclusions: SV patients with low nNO undergoing cardiac surgeries are more likely to receive perioperative supplemental iNO. Patients with normal nNO and 2V patients with low nNO are less likely to receive perioperative iNO. These findings suggest that nNO sampling obtained at the bedside can help identify patients who can benefit from supplemental iNO for their cardiac procedure. By mitigating delays in treatment with iNO, this may help improve postsurgical outcome by preventing severe hemodynamic derangements due to NO deficiency.

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Clin Studies 24 (83)

Prediction of Imminent Deterioration of Children with Parallel Circulations Using Real-Time Processing of Physiologic Data

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Introduction: Sudden death is common in patients with hypoplastic left heart syndrome and comparable lesions with parallel systemic and pulmonary circulation from a common ventricular chamber. Acute deterioration can manifest as shock, hypoxemia, and cardiorespiratory arrest. It is hypothesized that overt clinical extremis is preceded by subtle changes in physiologic dynamics. Using high-resolution multi-parameter physiologic recordings, we developed a predictive algorithm for clinical deterioration in newborns with single ventricle physiology after their first stage of surgical palliation.

Methods: Twenty-one episodes of critical deterioration were identified in 13 of 25 infants with hypoplastic left heart syndrome or related lesions with parallel circulation. A predictive multi-parameter algorithm was developed using high resolution and continuous physiologic data obtained after stage I palliation and before stage II palliation. Critical deterioration was defined as the need for CPR or endotracheal intubation. A classification model was constructed from primary (visible to the provider at the bedside monitor) and derived (not visible in primary monitoring) parameters that were significantly associated with critical deterioration. The classification model was optimized to discriminate pre-arrest physiology from stable physiology. When normalized to global data in the cohort, a real-time estimate of the risk for acute deterioration is rendered.

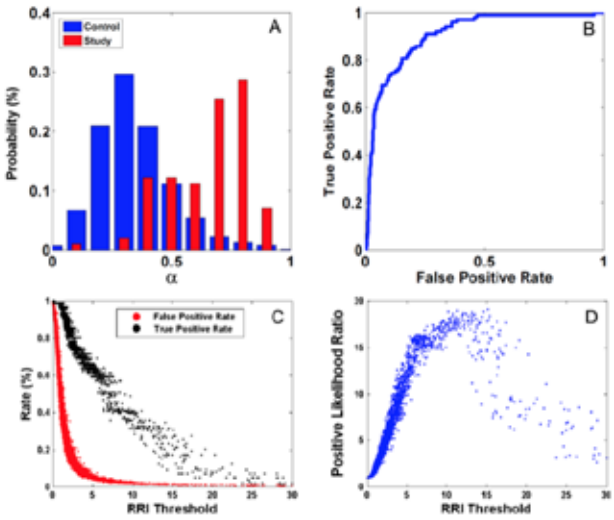

FIGURE: Performance of the optimized logistic regression model. (A) Histogram of the optimized classification algorithm for the control and study data sets projected on the axis of optimal separation (Ð). (B) The receiver operating characteristic curve for the optimized classification algorithm (ROC Area=0.91). (C) The true positive and false positive rates for the optimized classification model as a function of the RRI threshold. (D) The positive likelihood ratio as a function of the RRI threshold. The positive likelihood ratio is the sensitivity divided by 1-specificity and represents the likelihood of a true event being detected compared to a false positive.

Results: The following variables [coefficient; p value] were included in the final model classifying the state of stability from imminent deterioration: heart rate [1.06; <0.001], respiratory rate variability [-0.46; <0.001], SpO2 [-0.32; <0.001], ST segment variability [0.16; 0.017], V1 ST segment value [-0.12, 0.045], heart rate variability [-0.10; 0.052]. The resulting multivariate predictor was both sensitive and specific for detecting impending critical deterioration one to two hours in advance of overt extremis (ROC Area = 0.91, 95% CI = 0.88-0.94).

Conclusions: Automated, intelligent analysis of standard physiologic data in real time can detect signs of clinical deterioration too subtle for the clinician to observe without the aid of a computer. We present an example of a real-time predictive analytic that may serve as an early warning indicator of cardiac arrest in patients with single ventricle physiology. The predictive metric presented and the method used to derive it warrant further investigation and validation in a new, prospective cohort.

Clin Studies 25 (84)

Hypertension after Glenn Shunt Is Associated with Elevated Pulmonary Artery Pressure and Cerebrovascular Dysautoregulation

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Background: Hypertension occurs commonly after palliation of single ventricle anatomy with cavo-pulmonary anastomosis. Given that cephalic venous pressure is elevated by the anastomosis, it is not known if hypertension after cavo-pulmonary anastamosis results in impaired or intact cerebrovascular hemodynamics.

Methods: An observational study was performed to continuously record mean arterial blood pressure (ABP) cavo-pulmonary pressure (PAP), transcutaneous CO2 (TCO2) and near-infrared spectroscopy derived measures of cerebral oximetry (rSO2), and a relative cerebral blood volume index (BVI) in subjects admitted to a tertiary intensive care unit after cavo-pulmonary anastamosis. Autoregulation was continuously measured as the hemoglobin volume index (HVx), a moving correlation between ABP and BVI.[1] Physiologic variables were tested for co-linearity with ABP to test the hypothesis that hypertension is associated with dysautoregulation. Inconsistently repeated measures of HVx, rSO2, and PAP in single subjects obtained from continuous monitoring were analyzed for associations with ABP using linear regression with generalized estimation of equations.[2]

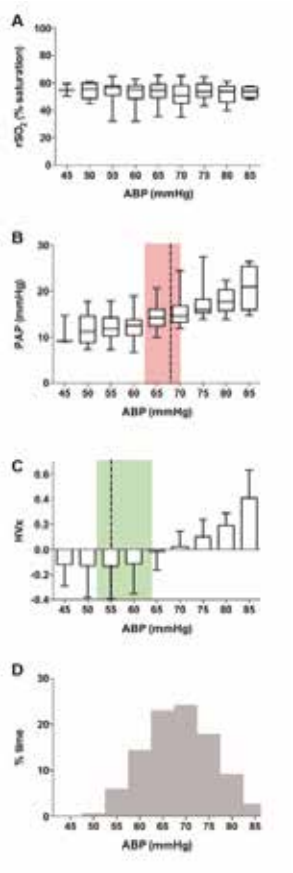

FIGURE: High arterial blood pressure (ABP) after Glenn shunt is associated with elevated pulmonary artery pressure (PAP) and dysautoregulation. A) Cerebral oximetry (rSO2) was not associated with ABP in this cohort. B) Hypertension was associated with elevated PAP. A non-linear increase in PAP with increase in ABP was observed. Individual subject cutoffs for increased PAP/ABP are shown with a vertical dashed line and vertical red shading at 68 mmHg [IQR 62 - 70 mmHg]. C) Hypertension was associated with increased hemoglobin volume index (HVx), signifying dysautoregulation. Individual subject optimal ABP for autoregulation are shown with a vertical dashed line and green shading at 55 mmHg [IQR 51 - 64 mmHg]. D) The % time at each ABP for the aggregate recordings are presented.

Results: Hypertension in this cohort of 16 subjects post cavopulmonary anastomosis is associated with both elevated PAP ($p<0.01$) and positive HVx (dysautoregulation; $p<0.01$). No association was observed between TCO2 and either PAP or HVx. Neither ABP nor TCO2 were associated with rSO2. A cutoff ABP was identified for each subject by piecewise regression, above which PAP rose precipitously. The median cutoff was 68 mmHg [IQR 62 - 70 mmHg]. Curve fit of HVx as a function of ABP identified optimal ABP for autoregulation in 14/16 subjects. HVx optimized at a median ABP of 55 mmHg [IQR 51 - 64 mmHg].

Conclusion: Hypertension after cavopulmonary anastomosis is not an adaptive mechanism to preserve cerebral perfusion. Rather, it is associated with both dysautoregulation, and elevated cephalad venous pressure.

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Clin Studies 29 (98)

An ECG Algorithm Utilizing St Segment Instability for Detection of Cardiopulmonary Arrest in Single Ventricle Physiology

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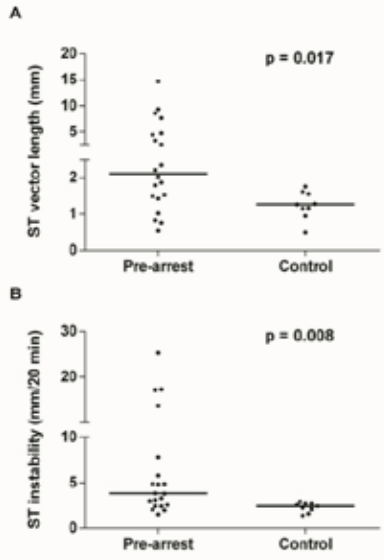
Introduction: We evaluated ST segment monitoring to detect clinical deterioration in infants with single ventricle anatomy, a population where nonspecific ST segment changes frequently limit detection of cardiac ischemia or strain. The interstage period is high-risk for cardiopulmonary arrests and requires close monitoring. We proposed a signal processing algorithm for ST segment instability and hypothesized that instability is associated with arrests. Comparison was made between our algorithm and unprocessed ST segment monitoring.

Methods: A retrospective observational study was conducted at Texas Children's Hospital's 21-bed cardiovascular intensive care unit (CVICU) and 36-bed step-down unit (SDU). All single ventricle patients receiving stage 1 and 2 palliation surgery from January 2013 to January 2014 were included. High fidelity ECG signals (240 Hz) captured from bedside CVICU and SDU monitors were recorded.

Clinical deterioration data was collected over the 4-hour time window prior to arrest. Control data was collected from subjects with no history of interstage arrest using the 4-hour time window prior to CVICU discharge. Raw and absolute value of ST segments were compared between groups. A 3-dimensional ST segment vector was created using 3 quasi-orthogonal leads (II, aVL, and V5). Magnitude and instability of this continuous vector were compared between groups. Predictive performances of the ST metrics were assessed with receiver operator characteristics.

Results and Major Findings: Twenty rapid response events resulting in cardiopulmonary arrests (pre-arrest) were recorded in 13 subjects, and 9 subjects had no interstage cardiopulmonary arrest (control). The median interstage length was 141 days [IQR: 94-175] and overall interstage survival rate was 90%. There were no differences in study population characteristics between study and control group, including shunt type (Blalock-Taussig vs Sano), except for gestational age at birth: 38.2 weeks [36.8-38.9] vs 39 weeks [39-39.1] ($p = 0.007$), respectively.



When comparing unprocessed ST segment values, there was no difference between pre-arrest and control groups. However, the mean absolute values of ST segments were increased in leads I, II, III, and aVF in the pre-arrest group compared to the control group ($p < 0.05$). Utilizing the signal processing algorithm, there was an increase in ST vector magnitude (2.1 mm [1.4 - 4.6 mm] vs. 1.3 mm [1.1 - 1.6 mm], $p = 0.02$) and instability (3.8 mm/20 min [2.4 - 25.4] vs 2.4 mm/20 min [1.8 - 2.7], $p = 0.008$) in the pre-arrest group. ST vector magnitude and instability discriminated the pre-arrest state from control with areas under the receiver operator characteristic curves of 0.78 and 0.81, respectively.

Conclusions: In single ventricle patients, increased ST instability was associated with rapid response events requiring intervention for cardiopulmonary arrest. In a population where the ST segment is confounded by arrhythmias and the lack of a baseline, this signal processing technique may be a noninvasive method for the early detection of cardiac ischemia or strain. With continued development, the ST instability algorithm may be incorporated into advanced predictive monitoring techniques and improve the perioperative care of the single ventricle patient.

Clin Studies 30 (99)
Review of Mobile ECMO Cases Performed by an Anesthesia/Cardiac Surgery Team

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Introduction: Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is increasingly being used as rescue therapy in patients with acute, severe lung disease as a bridge to recovery. Safe and effective delivery of ECMO should be performed by high volume regional centers with a mobile team available 24/7 for patients with severe respiratory disease too unstable to transport.[1] An anesthesia team partnered with cardiac surgeons to lead the organization of a multi-disciplinary mobile ECMO team and the infrastructure to support a 24/7 service. This study analyzed the outcomes of the mobile cases performed by this team.

Methods: A multi-disciplinary mobile team was created that included representatives from cardiac and critical care anesthesiology, perfusion services, and cardiovascular surgery for the development of a mobile ECMO program to serve a tri-state region. This team screened all consults from outside hospitals to determine need for mobile ECMO. Following Institutional Review Board approval, all patients referred for mobile ECMO for acute pulmonary insufficiency from January 1st 2015 to December 31st 2015 were retrospectively entered into a database. The only data collected for outside referrals declined for ECMO or deemed inappropriate for transfer from the outside hospital was age, sex and reason for exclusion. Patient characteristics, medical comorbidities, ICU and hospital length of stay where collected on all other patients.

Results: A total of 106 consults (7 from the study hospital and 99 from outside hospitals) were received by the mobile ECMO physicians for consideration of either ECMO support or transfer to our tertiary center for a higher level of care. Twenty-one patients were deemed appropriate ECMO candidates but were considered too unstable to transport without ECMO support. In these cases the mobile team was activated and cannulation was performed at the referring hospital. All patients underwent transesophageal echocardiography by a member of the mobile team to confirm that cardiac function was sufficient to allow implementation of veno-venous ECMO without the need for cardiac support with veno-arterial ECMO. Most of the mobile ECMO cases were performed in the referring hospital's operating room with flouroscopic guidance of catheter insertion (15/21), but the remaining six were performed at the bedside with transesophageal echocardiography guided catheter insertion. One patient sustained a pulseless electrocardiographic arrest (PEA) during ECMO implementation in the setting of severe respiratory acidosis and hypoxemia and was placed briefly on veno-arterial ECMO. Most patients were able to be weaned from ECMO (76%, 16/21). The mean duration of ECMO for patients successfully weaned from ECMO was 11 days (range 2-32). The mean hospital length of stay following mobile ECMO for patients surviving to discharge was 22 days (range 10-43). The survival to hospital discharge of these patients was 66.7% (14/21).

Conclusions: Insertion and management of mobile ECMO should be performed by a team of experienced personnel with the training for both the implementation and subsequent medical management during transport. Cardiac and critical care anesthesiologists familiar with cannula insertion and ECMO management can lead mobile ECMO teams and perform successful cannulation as part of a multi-disciplinary team. The survival of patients placed on mobile ECMO for lung disease in our program was superior to the national average published by the Extracorporeal Life Support Organization (58% survival to transfer or discharge). [2]

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Clin Studies 31 (141)
Difference between Wrist and Ankle Actigraphy to Estimate Sleep-Wake Cycle in Critically-Ill Patients

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Introduction: It is recognized that critically-ill patients suffer from disruption of circadian rhythms and sleep loss while in the ICU, and circadian dysregulation may play an important role in the pathogenesis of ICU-acquired delirium.[1] Actigraphy, a watch accelerometer worn on the wrist that measures activity, has been used as a tool for monitoring activity and sedation in the ICU.[2] However, movement in critically-ill patients can be limited due to the use of physical restraints that may reduce the range of motion at the wrist. We sought to determine if detection of movement at the upper or lower extremity is representative of the actual patient activity and which of the two locations has a higher correlation with a nursing reported sleep diary.

Methods: We conducted a prospective observational study, enrolling patients receiving mechanical ventilation and admitted to the cardiovascular ICU after elective surgery. Upon ICU admission, patients had actigraphy recordings initiated at the wrist and ankle for a duration of 24 hours. Concurrently, we collected a hourly nursing observation sleep diary during the same recording interval. Wrist and ankle actigraphy was used to determine the proportion of total sleep time in 24 hours occurring during nighttime (defined as 22:00 to 05:59), total sleep time in 24 hours, and arousal index (number of arousals/hour) during night time.

Results: 10 patients were enrolled (2 female, 8 male, mean age 64.4, SD: 11.4). From the actigraphy data collection, total sleep time at night was 354 minutes (SD: 354) at the wrist and 402 minutes (SD: 86) at the ankle. Total sleep time during the 24 hour recording period was 672 minutes (SD: 271) at the wrist and 883 minutes (SD: 278) at the ankle. The mean arousal index was 5.8 (SD: 3.5) at the wrist and 2.7 (SD: 1.7) at the ankle. Of patients with complete nursing logs (n=6), total sleep time at night was 288 minutes (SD: 248) and total sleep time in 24 hours was 480 minutes (SD: 197). The proportion of total sleep time in 24 hours occurring at night was 53% based on wrist recordings, 58% based on ankle recordings, and 75% based on nurse observation. There was no correlation between wrist actigraphy and nurse sleep diary (correlation coefficient 0.56), while there was a higher correlation between ankle actigraphy and nurse sleep diary (correlation coefficient 0.80).

Conclusions: There were substantial discrepancies between actigraphy recordings at the wrist and ankle, compared with the nurse observation. While sleep measured at the ankle seemed to overestimate nurse-reported sleep, there was a stronger correlation between the nurse sleep observation and the ankle recordings. These preliminary data suggest that when comparing actigraphy to the nursing sleep diaries, although ankle actigraphy overestimates sleep at night, ankle recordings might be more representative of nursing observation than wrist activity data. These data also confirm previous findings that ICU patients' sleep patterns can be disrupted at night and that a substantial amount of sleep occurs during the daytime.

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Clin Studies 56 (70)
Complexity of Preoperative Blood Pressure Dynamics: Possible Utility in Cardiac Surgical Risk Assessment

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Introduction and General Purpose of the Study: Cardiovascular surgical procedures are increasingly being performed on elderly patients, motivating the need for novel indices of individual risk. We explored the utility of using complexity measures to extract physiologic information contained in the preoperative beat-to-beat dynamics of arterial blood pressure (ABP). Such measures probe integrated system capacity to respond to stressors. Here we sought to determine if decreased ABP complexity is associated with increased estimated risk as obtained from two standard instruments: the Society of Thoracic Surgeons' (STS) Risk of Mortality and Morbidity and the European System for Cardiac Operative Risk Evaluation (EuroSCORE II).

Methods: ABP waveforms were recorded during the preoperative period using a radial artery catheter from 143 patients (mean age=66yrs; range: [24-92]) undergoing major cardiac surgical procedures. Beat-to-beat systolic, diastolic, mean and pulse arterial pressure time series were extracted from the continuous waveforms and pre-processed to remove outliers. For each blood pressure signal we computed the mean and the standard deviation (SD) of the time series, and two measures of complexity based on the multiscale entropy (MSE) method: i) a complexity index, which quantifies the information content of the signal over a range of scales, in this work from scales 2 to 5 (CI2-5), and ii) an adjusted complexity index (aCI), which measures how close the MSE profile is from random uncorrelated noise. Briefly, the MSE measures quantify the degree of irregularity of a time series over a range of time scales, reflecting the system resilience, this is, the capacity system to adapt to novel stimuli. Complexity is highest in heathy systems and degrades with pathology and senescence. The Spearman correlation coefficients between the signal measures (two-sided for mean and SD and one sided for both complexity indexes) and the risk indices were calculated.

Table 1 - Spearman correlation coefficients between ABP measures and risk indices.

	STS risk				EuroSCORE II			
	Diastolic	MAP	Systolic	PP	Diastolic	MAP	Systolic	PP
Conventional Measures								
Mean	-0.20*	-0.03	0.16	0.30***	-0.24***	-0.10	0.07	0.25***
SD	0.03	-0.02	-0.05	0.12	-0.01	-0.03	-0.04	0.11
Dynamical Measures								
CI_{2-5}	-0.20*	-0.25***	-0.18*	-0.16	-0.18*	-0.20**	-0.20**	-0.18*
aCI	-0.30****	-0.29***	-0.23**	-0.14	-0.34****	-0.34****	-0.32****	-0.26****

p-values: * <0.05; ** <0.01; *** <0.005; **** <0.001

MAP – Mean Arterial Pressure; PP – Pulse Pressure; SD – Standard Deviation; CI_{2-5} – Complexity Index from scales 2 to 5; aCI – Adjusted Complexity Index from scale 1 to 5.

Results and Major Findings: A high correlation was found between the STS and EuroSCORE II risk indices (rs = 0.83). The correlation between the risk indices and the ABP measures: mean, SD, CI2-5 and aCI are presented in Table 1. While no significant correlation was found between the SD and the risk indices, the mean of the diastolic and pulse pressure showed a significant correlation, i.e., lower values of mean diastolic and higher values of mean pulse pressure were associated a higher risk score of mortality. Also, a significant negative correlation was found between the two complexity measures and both the risk indices, except for the pulse pressure measures and the STS risk index.

Conclusion: These findings suggest that lower BP complexity may provide a new marker of cardiovascular instability, warranting future studies to investigate whether the incorporation of dynamical indices into current risk assessment tools is useful.

Clin OC 89 (171)
Exposure to Cardiopulmonary Bypass during Coronary Artery Bypass Surgery and Postoperative Delirium

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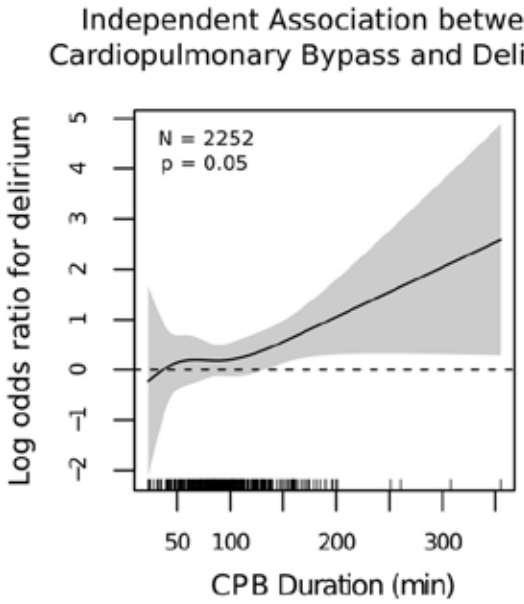
Introduction: Up to 50% of patients over 60 years of age develop delirium following cardiac surgery[1]. ICU delirium may lead to long-term cognitive impairment similar to Alzheimer's disease[2]. Cardiopulmonary bypass (CPB) alters perfusion, lyses erythrocytes, and induces a significant inflammatory response that may increase the risk for delirium, although to date, no studies have examined the association between CPB and postoperative delirium in patients receiving coronary artery bypass surgery. We hypothesized that CPB during coronary artery bypass surgery would correlate with an increased odds of delirium.

Methods: We reviewed clinical data from two prospectively collected databases at our medical center, the Cardiac Surgery Perioperative Outcomes Database and the Society of Thoracic Surgeons (STS) Database, and included all patients who underwent elective on-pump coronary artery bypass grafting or elective off-pump coronary artery bypass grafting cardiac surgery from November 1, 2009 to June 30, 2015. Patient who also had valve surgery or other procedures were excluded. Delirium was defined as any positive confusion assessment method for the intensive care unit (CAM-ICU) exam following surgery during the ICU course. ICU standard practice directs bedside nurses to perform a CAM-ICU twice per 12 hour shift. We performed logistic regression to isolate the association between CPB exposure (use and duration) and the incidence of delirium from potential confounders and risk factors for delirium, including a history of cerebrovascular disease, history of cardiac surgery, and age.



Results: Two thousand two hundred and fifty-two patients underwent elective coronary artery bypass surgery during the study period. Four hundred and twelve of these (18.3%) were exposed to CPB and 1840 (82.7%) were not. Delirium was diagnosed in 442 patients (19.6%). Median age in the cohort was 63 years, 23.3% were female, 79.0% had hypertension, 17.4% had cerebrovascular disease, and 3.2% had a history of cardiac surgery. CPB use and duration were associated with an increased odds of postoperative delirium (p=0.05). The association with CPB was strongest with longer CPB durations. For example, relative to off-pump procedures, the odds of delirium were greater by 58% (95% CI: [6%, 84%]) among patients who were exposed to CPB for 140 minutes (90th percentile of CPB duration), but only 18% (95% CI: [-29%, 100%]) greater among those on CPB for 54 minutes (10th percentile) (Figure).

Conclusions: CPB was associated with increased odds of delirium in patients undergoing coronary artery bypass surgery. Future studies are needed to examine potential mechanisms of this association.

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Clin OC 90 (62)
Interaction Effects of Multiple Complications on Postoperative Mortality in General Surgery

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Introduction: Perioperative complications increase the risk of short-term mortality in critically ill surgical patients. We previously demonstrated that synergistic interactions exist between acute kidney injury (AKI), acute respiratory failure (ARF), and sepsis/septic shock to increase the risk of perioperative mortality[1]. However, synergistic relationships between these and other perioperative complications may also exist but are not well established.

Methods: Multicenter, retrospective cohort study of patients undergoing intraabdominal general surgery in the American College of Surgeons National Surgical Quality Improvement Program (2005-2011). Eight major postoperative complications were evaluated: 1) ARF, 2) AKI, 3) sepsis/septic shock, 4) stroke, 5) cardiac arrest, 6) myocardial infarction (MI), 7) deep vein thrombosis/pulmonary embolus, and 8) transfusion. We separately modeled each of the 28 combination of two complications in a Cox model of 30-day mortality, adjusting for comorbidities and other risk factors. Additive interaction was assessed with the relative excess risk due to interaction (RERI)[2]. Interactions exist when the effect of a complication on perioperative mortality varies with the presence or absence of a second complication, with a positive RERI indicating that the increase in mortality risk with a complication is greater when a second complication also occurs. A Bonferroni correction was applied for multiple comparisons (α=0.05/28=0.0018).

Results: We analyzed 422,827 records. Seven combinations of complications demonstrated positive additive interactions (Table): sepsis/cardiac arrest (RERI 76.5; p<0.0001), ARF/AKI (RERI 55.2; p<0.0001), AKI/sepsis (RERI 37.7; p<0.0001), ARF/stroke (RERI 30.3; p<0.0001), AKI/MI (RERI 28.6; p=0.0006), sepsis/stroke (RERI 28.6; p=0.0002), and ARF/sepsis (RERI 20.4; p<0.0001). In addition, one combination demonstrated negative additive interaction: ARF/cardiac arrest (RERI -81.6; p=0.0002). The remaining 20 combinations did not demonstrate additive interactions.

Conclusions: Interaction effects exist between certain complications to increase the risk of short-term mortality. ARF, AKI, sepsis, and stroke were most likely to be involved in positive interactions. Further research into the mechanisms for these effects will be necessary to develop strategies to minimize the compounding effects of multiple complications in the perioperative period.

References

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Table. Relative excess risk due to interaction for combinations of two perioperative complications in patients undergoing intraabdominal general surgery. Adjusted Cox proportional hazards models were used on data from the American College of Surgeons National Surgical Quality Improvement Program, 2005-2011.

	Acute Respiratory Failure		Acute Kidney Injury		Sepsis/Septic Shock		Stroke		Cardiac Arrest		Myocardial Infarction		DVT/PE	
	RERI	95% CI	RERI	95% CI	RERI	95% CI	RERI	95% CI	RERI	95% CI	RERI	95% CI	RERI	95% CI
Acute Kidney Injury	55.2 *	[46.2, 64.3]												
Sepsis/Septic Shock	20.4 *	[16.8, 24.0]	37.7 *	[31.0, 44.4]										
Stroke	30.3 *	[15.3, 45.3]	18.2	-[3.0, 39.3]	28.6 *	[13.7, 43.5]								
Cardiac Arrest	-81.6 *	-[125.0, -38.1]	22.9	-[14.6, 60.4]	76.5 *	[38.1, 114.9]	-61.6	-[111.5, -11.7]						
Myocardial Infarction	7.74	[0.61, 14.9]	28.6 *	[12.3, 45.0]	9.80	[2.24, 17.4]	20.0	-[0.81, 40.5]	-41.2	-[70.5, -11.8]				
DVT/PE	2.32	-[2.80, 7.44]	2.97	-[5.19, 11.1]	-1.66	-[4.93, 1.60]	-1.66	-[4.93, 1.60]	-18.6	-[51.3, 14.1]	7.85	[0.44, 15.3]		
Transfusion	-2.46	-[5.12, 0.20]	0.25	-[3.95, 4.45]	2.06	[0.07, 4.06]	-1.73	-[6.43, 2.97]	-34.3	-[59.4, -9.26]	1.86	-[1.49, 5.20]	-1.28	-[2.78, 0.22]

DVT, deep vein thrombosis; PE, pulmonary embolus; RERI, relative excess risk due to interaction; CI, confidence interval.
Bonferroni adjusted p-value for significance is 0.0018.
*P<0.0018

Clin OC 91 (47)
Collaborative Health Outcomes Information Registry (CHOIR): Open Source Platform for a Learning Health System and Informing Therapeutic Development

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Introduction: The Institute of Medicine (IOM) in Relieving Pain in America report (2011) called for the development of national patient registries to support the development of learning healthcare systems. In particular for the management of patients with chronic pain, the IOM has called for national patient outcome registries that can support point-of-care decision making and large-scale assessment of safety and effectiveness of therapies.

Methods: In answer to the call from the IOM, we developed the Collaborative Health Outcomes Information Registry (CHOIR), an open-source web application to assess patients and to support clinic staff with integrating the pain registry into the clinic workflow. Patient assessment features are designed for use on mobile devices with touch interfaces (smart phones and tablets), while also supporting desktop web browsers. Key technologies used include Java, Oracle database, Google Web Toolkit, jQuery Mobile, AngularJS, and Bootstrap.

Results: Since roll-out in August 2012 and the subsequent slow ramp-up, over 8,000 unique patients have completed surveys, with over 150,000 NIH PROMIS assessments including Global Health (Physical and Mental), Mood (Depression, Anxiety, Anger), Function (Fatigue, Physical Function), Sleep (Sleep Disturbance, Sleep-Related Impairment), Social (Emotional Support, Instrumental Support, Satisfaction with Roles and Activities, Social Isolation, and Ability to Participate in Social Activities). Surveys were completed at home via email link, or at the Pain Clinic, using computers, iPads, Android tablets, and Chrome notebooks. We have extended CHOIR to other academic centers and other clinical specialties (e.g. GI Medicine, Headache, Orthopedics, Pediatric Pain).

Discussions: In conclusion, we have created an open source, extensible platform CHOIR (Collaborative Health Outcomes Information Registry) that enables rapid definition and deployment of data capture tools. This represents a successful partnership between the NIH and Stanford with funding from most of the NIH Institute Directors.

Conclusions: Future works include the expansion of survey items, into additional disease areas, dissemination of code, as well as networked registry build-out.

Clin OC 93 (78)
Epidemiology of Vasopressin Use among Adults with Septic Shock in the United States

Emily A. Vail, MD[1]; Hayley B. Gershengorn, MD[2, 3]; May Hua, MD, MSc[1]; Allan Walkey, MD, MSc[4]; Hannah Wunsch, MD, MSc[5, 6]

[1]Columbia University, New York, New York; [2]Albert Einstein College of Medicine, Bronx, New York; [3]Montefiore Medical Center, Bronx, New York; [4]Boston University, Boston, Massachusetts; [5]University of Toronto, Toronto, Ontario, Canada; [6]Sunnybrook Health Sciences Center, Toronto, Ontario, Canada

Rationale: Vasopressin may be used to treat vasodilatory hypotension in septic shock, but it is not recommended by guidelines as a first-line agent; little is known about how often it is currently used to treat septic shock. We assessed patient and hospital-level usage patterns among US hospitals.

Methods: Analysis of adults admitted to US hospitals with septic shock (defined by Angus criteria for severe sepsis and receipt of at least one day of vasopressor treatment) in the Premier Perspective database (July 2008-June 2013). Primary outcome was administration of vasopressin, alone or in combination with other vasopressors, on at least one day of hospital admission. We performed multilevel mixed-effects logistic regression with hospitals as a random effect to identify factors associated with use of vasopressin, and calculated the adjusted median odds ratio (AMOR) to summarize variation in vasopressin use across cohort hospitals; quotients of Akaike information criteria (AIC) were used to compare relative contributions of patient and hospital-level characteristics and hospital of admission to the observed variability.

Results: Among 584,421 patients with septic shock in 532 hospitals, 106,994 (18.3%) received vasopressin; 5.7% of all patients receiving vasopressin received vasopressin alone, and the rest were in combination with other vasopressors (up to 5 vasopressors in 15 different combinations). Compared with patients who received other vasopressors alone or in combination, receipt of vasopressin was associated with higher in-hospital mortality (55.7% versus 23.9%, $p<0.001$) and hospital length of stay (16.5±20.8 versus 14.5±16.9 days, $p<0.001$). Among study hospitals, a median of 11.7% of patients with septic shock received vasopressin (range 0% to 69.7%). Patient-level factors determined the majority of observed variation in vasopressin use (quotient of AICs 0.56) when compared with individual hospitals (0.37) and hospital-level characteristics (0.001). The AMOR was 2.65 (95% CI 2.48-2.84) which means that patients admitted to hospitals with high rates of vasopressin use were 2.65 times more likely to receive vasopressin than identical patients admitted to hospitals with low rates of vasopressin use.

Conclusions: One fifth of patients in septic shock receive vasopressin, but rarely as a single vasopressor. Vasopressin use varied due to patient-level factors but the likelihood of receiving vasopressin was also very strongly associated with the specific hospital to which each patient was admitted. Further work is necessary to determine whether observed variation in vasopressin administration impacts patient outcomes.

Clin OC 94 (92)
Effect of Care Fragmentation on Outcomes of Rehospitalizations after Critical Illness for Severe Sepsis Patients

May Hua, MD, MSc[1]; Michelle Ng Gong, MD, MSc[2]; Andrea Miltiades, MD[1]; Hannah Wunsch, MD, MSc[1, 4]

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

Background: Approximately 15% of intensive care unit (ICU) survivors are re-hospitalized within 30 days of hospital discharge. Given their medical complexity, a lack of continuity of care may adversely affect outcomes for the sickest of these patients. Thus, we sought to determine whether outcomes during re-hospitalization differ for ICU patients with severe sepsis when they are re-hospitalized at a different hospital versus the hospital of the index ICU stay.

Methods: Retrospective cohort study of ICU patients with severe sepsis who were re-hospitalized within 30 days of hospital discharge in 2008-2011 in New York State. We compared mortality during re-hospitalization using hierarchical logistic regression. Secondary outcomes included length of stay and costs during re-hospitalization.

Results: Of 11,916 ICU patients with severe sepsis who were re-hospitalized within 30 days of discharge, 3,601 patients (30.2%) were re-hospitalized at a different hospital than that of the index ICU stay. Patients had an increased risk of death if re-hospitalized at a different hospital (17.1% versus 13.8% for index hospitals, aOR 1.15 [1.01-1.31], p=0.04). Length of stay and costs were not different for survivors of re-hospitalization at a different hospital (adjusted rate ratio 1.04 [0.98-1.11], p=0.16, mean difference in total cost $996.84 [-$887.57 to $2881.26], p=0.30]), but were decreased for patients who died (adjusted rate ratio 0.83 [0.70-0.99], p=0.04, mean difference in total cost -$11,566.96 [-$21,480.44 to -$1653.47], p=0.02).

Conclusions: Over a quarter of critically ill patients with severe sepsis were re-hospitalized at a different hospital than that of the index ICU stay. This care fragmentation was associated with increased mortality as well as decreased length of stay and costs for patients who died during re-hospitalization. Further research is needed to better understand whether preventing care fragmentation may improve outcomes.

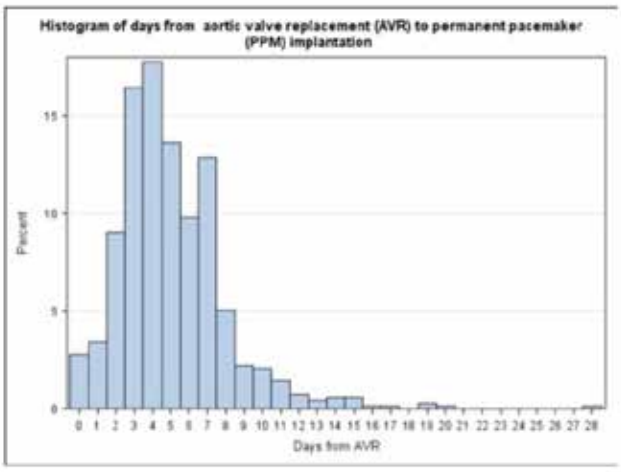
Clin OC 95 (105)
Timing and Outcomes of Permanent Pacemaker Placement after Aortic Valve Replacement

Zachary A. Turnbull, MD; Virginia Tangel, MA; Matthew J. Alexander, BS; Christopher Chan; Cynthia A. Lien, MD; Natalia Ivascu, MD

Weill Cornell Medical College, New York, New York

Background: Traditionally, permanent pacemaker (PPM) implantation after aortic valve surgery (AVR) has occurred at 7 days, yet guidelines allow for PPM implantation at the physician's discretion. Clinical studies suggest PPM implantation can occur as early as 5 days post-AVR, though there is considerable variation. Given this incongruity in clinical practice and recommendations, we sought to identify practice patterns of PPM placement in a large patient population and evaluate the effect of placement timing on outcomes following AVR. We hypothesize earlier implantation of PPM will result in lower mortality and 30-day readmission rates.

Methods: We analyzed hospitalizations of uncomplicated patients (age ≥ 18 years) from 2007 - 2011 in California, Florida, and New York utilizing the State Inpatient Database, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Selection criteria included heart block (ICD-9: 426.0-426.9, excluding 426.81 and 426.82) or supraventricular arrhythmias (ICD-9: 427.0-427.42, 427.6) after AVR. Uncomplicated patients included those without selected cardiovascular, pulmonary, neurological, or infectious diseases, nor intraoperative complications. Stepwise multivariable logistic regression models were used to identify significant factors associated with 30-day readmission such as the patients' demographic characteristics, clinical characteristics measured by the Deyo index, and hospital volume.



Results: A total of 674 patients met study criteria. Thirty-two percent (n = 214) received a PPM by post-operative day (POD) 3, 50% (n = 334) by POD 4, 63% (n = 426) by POD 5, and 86% (n = 579) by POD 7. Median time to PPM was 5 days (Q1: 3, Q3: 7). Overall, 15% of the population were readmitted within 30 days post-AVR. Controlling for age, race, Deyo index, and hospital volume, patients that received a PPM >5 days post-AVR had increased odds of 30-day readmission compared to those receiving a PPM <5 days (OR = 1.61, 95% CI: 1.03-2.52; p = 0.04). Due to the small number of deaths, data on mortality could not be fully analyzed.

Conclusions: Relative to historical practice and recommendations of clinical studies, PPMs are being implanted early following AVR. Here we identified that uncomplicated patients receiving a PPM within 5 days post-AVR showed improvements in 30-day readmissions compared to later PPM placement. Given the vast variability of clinical practice across the United States, further research is needed to truly understand the impact of early PPM after AVR and to establish an algorithm for optimal timing of PPM implantation.

Clin OC 97 (100)
Meta-Analysis of Temperature Reduction in Animal Models of Cardiac Arrest

Hannah Watson, MBChB, BMedSci[1]; Hilmer Olai[2]; Gustav Thornéus[2]; Malcolm MacLeod, MBChB, PhD, FRCP, Ed[4]; Hans Friberg[2, 3]; Jonathan Rhodes, PhD, MBChB, FRCA[4, 5]; Niklas Nielsen, MD, PhD[2]; Tobias Cronberg, MD, PhD[2]; Tomas Deierborg, PhD[2]

[1]South East Scotland Deanery, Edinburgh, Scotland; [2]Lund University, Lund, Sweden; [3]Skåne University Hospital, Lund, Sweden; [4]University of Edinburgh, Edinburgh, United Kingdom; [5]Western General Hospital, Edinburgh, United Kingdom

Introduction: In Europe, attempted resuscitation in out-of-hospital cardiac arrest is estimated to have an incidence close to 40 per 100,000 inhabitants per year(1). Targeted Temperature Management (TTM) of 32-34 degrees Celsius has been the standard treatment for out-of-hospital cardiac arrest since clinical trials in 2002 showed benefits to survival and neurological outcome(2,3). Recently this treatment has been challenged by another clinical trial showing no difference in outcome between TTM of 33 and 36 degrees Celsius for unconscious survivors of out-of-hospital cardiac arrest(4).

Aims: The objectives of this meta-analysis are to assess the quality of individual preclinical studies investigating temperature reduction in animal models of cardiac arrest. This will allow exploration of the experimental evidence for TTM to highlight any translational gaps and allow provision of methodological considerations for future experimental research and clinical trials.

Methodology: The protocol underwent peer-review prior to completion. A defined search strategy was used in Embase and PubMed with no restrictions on date or language of publication. Abstract analysis was conducted using CAMARADES software. Each abstract was reviewed against defined exclusion and inclusion criteria allowing full-text review of all included articles. Data analysis was then completed. There were multiple reviewers at each protocol stage. The preclinical evidence will be assessed on study quality, efficacy, design factors and also a modified STAIR criteria(5). Specifically, efficacy will be reported as histological outcome, neurobehavioural outcome or mortality.

Summary: The literature review highlighted 12,245 abstracts; following this process, 1471 of these articles underwent full-text review. Around 15% of the full-text review articles met the strict inclusion criteria allowing progression onto full data analysis.

To date there has been no preclinical meta-analysis investigating the effects of temperature reduction in relation to global ischaemia. Work of this nature has relevance to researchers and clinicians alike, with anaesthetists and intensivists often having pivotal involvement in patient care. On completion of this meta-analysis the authors believe that the results will be influential in evidence provision for further clinical trials with the overall aim of improving neurological outcome in this high-risk patient cohort.

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Clin OC 98 (128)
"Opt out" and Access to Anesthesia Care for Elective and Urgent Surgeries among US Medicare Beneficiaries

Eric Sun, MD, PhD[1]; Franklin Dexter, MD, PhD[2]; Thomas R. Miller, PhD, MBA[3]; Laurence C. Baker, PhD[4]

[1]Stanford University, Stanford, California; [2]University of Iowa, Iowa City, Iowa; [3]American Society of Anesthesiologists, Schaumburg, Illinois; [4]National Bureau of Economic Research, Cambridge, Massachusetts

Introduction: In 2001, the Centers for Medicare and Medicaid Services (CMS) issued a rule allowing US states to "opt out" of the regulations requiring physician supervision of nurse anesthetists, in an effort to increase access to anesthesia care. Since then, 17 states have decided to "opt out" of the Medicare regulations requiring supervision of nurse anesthetists. Whether "opt out" has successfully increased access remains unknown.

Methods: Using Medicare administrative claims data, we examined whether "opt out" reduced the distance traveled by patients, a common measure of access,1-3 for patients undergoing total knee arthroplasty, total hip arthroplasty (THA), cataract surgery, colonoscopy/sigmoidoscopy, esophagogastroduodenoscopy, appendectomy, or hip fracture repair. In order to reduce bias, we performed a two-step analysis in which we first examined whether "opt out" was associated with a reduction in the percentage of patients traveling outside of their zip code for a given procedure. We then examined the effect of "opt out" on the actual distance traveled for patients who traveled outside of their home zip code. In addition, we examined whether "opt out" was associated with an increase in the use of anesthesia care for cataract surgery, colonoscopy/sigmoidoscopy, or esophagogastroduodenoscopy. Our analysis used a difference-in-differences approach with a robust set of controls to minimize confounding.

Table 1: "Opt out" And Procedure Travel Distance, 1999-2012

	% Patients Traveling Outside Home Zip Code	Change in Travel Distance (km)
Total Knee Arthroplasty	0.143 (-1.38, 1.66) p=0.850	0.821 (-1.61, 3.25) p=0.501
Total Hip Arthroplasty	-2.67 (-4.61, -0.727) p=0.008	2.18 (-3.32, 7.67) p=0.430
Cataract Surgery	0.353 (-0.295, 1.00) p=0.279	0.258 (-0.681, 1.20) p=0.584
Colonoscopy/Sigmoidoscopy	0.755 (-1.29, 2.81) p=0.463	-0.169 (-1.95, 1.61) p=0.849
Esophagogastroduodenoscopy	-0.505 (-1.51, 0.496) p=0.303	0.422 (-2.72, 3.56) p=0.788
Appendectomy	0.903 (-6.43, 8.24) p=0.806	-7.46 (-18.3, 3.38) p=0.173
Hip Fracture Repair	0.108 (-2.46, 2.67) p=0.933	-1.50 (-5.06, 2.07) p=0.404

Table 1 presents the results of two sets of analyses examining the effect of "opt out" on the distance traveled to obtain the given procedure. The first column show the estimated effect of "opt out" on the probability that a patient had to travel outside of their zip code in absolute (percentage point) terms. The second effect shows the effect of "opt out" on the average distance traveled by patients who traveled outside of their zip code. Both sets of analyses incorporate a variety of controls including zip code effects, year effects, and controls for patient demographics and comorbidities. 95% confidence intervals shown in parentheses are adjusted for clustering at the state level.

Results: "Opt out" did not reduce the percentage of patients who traveled outside of their home zip code except in the case of THA (2.67 percentage point reduction, p=0.008, Table 1). For patients travelling outside of their zip code, "opt out" had no significant effect on the distance traveled across any of the procedures we examined, with point estimates ranging from a 7.5 kilometer decrease for appendectomy (95%CI -18, 3.0; p=0.173) to a 2.2 kilometer increase (95%CI -3.3, 7.7; p=0.430) for THA. There also was no significant effect on the use of anesthesia for esophagogastroduodenoscopy, appendectomy, or cataract surgery. Sensitivity analyses considered alternative specifications (such as the minimum distance traveled among patients residing in a given zip code), and they similarly demonstrated that "opt out" had no effect on access to anesthesia care.

Conclusions: "Opt out" does not seem to be associated with increased access to anesthesia care for several common procedures.

Moderated Poster Discussions

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Category	Poster Board Numbers
Education	1-8
Clinical Management	15-20, 27-28
Neuro Clinical	32-35, 39-42
Clinical Studies (B)	49-55
Basic Neuro (Anesth Action, Neural Networks)	57-58, 64-69
Clinical Studies (Outcomes)	78-83, 85-88
Basic and Clinical Pain	92, 99-105, 112
Basic Neuro (Neuronal Injury)	106-111, 113-115
Cell Signaling (C)	116-123

**Poster 48 withdrawn*

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Basic Neuro (Anesth Action, Neural Networks)

Basic Neuro/AA/NN 57 (169)
Electroencephalographic Correlates of Hypnosis Independent of Drug Effect

Andrew R. McKinstry-Wu, MD; Andrzej Wasilczuk, BS; Max Kelz, MD, PhD
University of Pennsylvania, Philadelphia, Pennsylvania

Basic Neuro/AA/NN 58 (115)
Electrical Stimulation of the Ventral Tegmental Area Restores the Ability to Perform a Touchscreen-Based Visual Discrimination Task in Rats Sedated with Isoflurane

Ken Solt, MD, Jonathan D. Kenny, Norman E. Taylor, MD, PhD, Justin T. Lee, MEng, Jennifer A. Guidera, AB, Emery Brown, MD, PhD
Massachusetts General Hospital, Boston, Massachusetts

Basic Neuro/AA/NN 64 (67)
Sex Dependent Mitochondrial Respiratory Impairment and Oxidative Stress in a Rat model of Neonatal Hypoxic-Ischemic Encephalopathy

Gary Fiskum, PhD; Tyler Demarest, MS
University of Maryland, Baltimore, Maryland

Basic Neuro/AA/NN 65 (102)
Novel Neuro-Restorative Strategy to Improve Memory Function after Global Cerebral Ischemia

Paco S. Herson, PhD; Robert M. Dietz, MD, PhD; James E. Orfila, PhD; Guiring Deng, MD; Nidia Quilinan, PhD; Richard J. Traystman, PhD
University of Colorado School of Medicine, Aurora, Colorado

Basic Neuro/AA/NN 66 (45)
Elevated Serum TNF-alpha Levels Lead to Abnormal Cortical Synaptic Dynamics in a Mouse Model for Neuroinflammation: Could Cytokines Play a Similar Role in Postoperative Cognitive Dysfunction?

Scott M. Hayes, MD; Guang Yang, PhD; Christopher Parkhurst, PhD; Wenbiao Gan, PhD
New York University, New York, New York

Basic Neuro/AA/NN 67 (149)
Isoflurane Inhibits Excitatory Neurotransmission in the Anesthetic Hypersensitive Mouse Mutant, NDUFS4(KO)

Pavel I. Zimin, PhD[1,2]; Phil G. Morgan, MD[1,2]; Margaret M. Sedensky, MD[1,2]
[1]Seattle Children's Research Institute, Seattle, Washington; [2]University of Washington, Seattle, Washington

Basic Neuro/AA/NN 68 (159)
Isoflurane Differentially Inhibits Firing Correlations among Parvalbumin Interneurons versus Pyramidal Neurons in Mouse Frontal Cortex

Andrew Hudson, MD, PhD
University of California, Los Angeles, Los Angeles, California

Basic Neuro/AA/NN 69 (38)
Using Social Network Analysis Tools to Assess the Effect of Isoflurane Anesthesia on Gene Networks in Rat Brain

Helen F. Galley, PhD; Nigel R. Webster, MBChB, PhD1; Damon A. Lowes, BSc, MSc, PhD; Alessandro Moura, BSc, PhD
University of Aberdeen, Aberdeen, United Kingdom
See page 70 for complete abstract

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Basic Neuro (Neuronal Injury)

Basic Neuro/Inj 106 (77)
Lidocaine Inhibited Glioma Cell Proliferation via TRPM7 Channels

Jun Lin, MD, PhD[1]; Tiandong Leng, MD, PhD[2]; Zhigang Xiong, MD, PhD[2]

[1]State University of New York at Stony Brook, Stony Brook, New York; [2]Morehouse School of Medicine, Atlanta, Georgia

Basic Neuro/Inj 107 (94)
The Underlying Mechanism of Sevoflurane-Induced Cognitive Impairment

Yuanlin Dong, MS, MD[1], Fang Fang, MD, PhD[1], Lining Huang, MD, PhD[1], Sulpicio G. Soriano, MD[2], Guanghong Xu, MD, PhD[1], Zhongcong Xie, MD, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts, [2]Boston Children's Hospital, Boston, Massachusetts

Basic Neuro/Inj 108 (96)
Olfactory Impairment and Postoperative Cognitive Dysfunction

Ce Zhang, MD, PhD[1]; Mian Peng, MD, PhD[1]; Yuanlin Dong, MD, MS[1]; Deborah Culley, MD[2, 3]; Gregory Crosby, MD[2, 3]; Zhongcong Xie, MD, PhD[1]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Brigham and Woman's Hospital, Boston, Massachusetts; [3]Harvard Medical School, Cambridge, Massachusetts

Basic Neuro/Inj 109 (147)
Selective Alkylphenol Anesthetic Binding to Gabaa Subunits in Native Neuronal Tissue

Kellie A. Woll, BS; Roderic G. Eckenhoff, MD

University of Pennsylvania

Basic Neuro/Inj 110 (158)
Protecting Mitochondrial Function by Reducing miRNA-210 Facilitates Immature Neuron Survival after Injury

Rona G. Giffard, PhD, MD; Xiaoyun Sun, MD; Yibing Ouyang, PhD; Ludmila A. Volobuoeva, PhD

Stanford University, Stanford, California

Basic Neuro/Inj 111 (106)
Targeting α5GABAA Receptors to Treat Memory Impairment after Traumatic Brain Injury

Sinziana Avramescu, MD, PhD, FRCPC[1, 2]; Heping Sheng, BSc[1]; Dian-Shi Wang, MD, PhD[1]; Beverley A. Orser, MD, PhD, FRCPC[1]

[1]University of Toronto, Toronto, Ontario, Canada; [2]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Basic Neuro/Inj 113 (71)
Carbon Monoxide and Isoflurane-induced Neurodegeneration in the Developing Brain

Richard J. Levy, MD, FAAP[1]; William Supplee, BS[2]; Aili Wang, MD[1]

[1]Columbia University, New York, New York; [2]New Jersey Medical School, Newark, New Jersey

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Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Basic Neuro (Neuronal Injury)

Basic Neuro/Inj 114 (82)
Ketamine Modulates GSK-3β-Disc1 Interaction in a Rat Model of Anesthetic-Induced Developmental Neuroapoptosis

Sulpicio G. Soriano, MD[1,2]; Jia-ren Liu, MD, PhD[1]; Xiao-hui Han, RN[1]

[1]Boston Children's Hospital, Boston, Massachusetts; [2]Harvard Medical School, Cambridge, Massachusetts

Basic Neuro/Inj 115 (121)
Genetics of Isoflurane-induced Neurotoxicity

Philip G. Morgan, MD; Margaret M. Sedensky, MD

University of Washington, Seattle, Washington

Poster Presentations Schedule

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Cell Signaling

CS 116 (73)
Cytoskeletal Perturbing Drugs and Their Effect on Cell Elasticity

David M. Eckmann, PhD, MD; Martha E. Grady, PhD; Russell J. Composto, PhD

University of Pennsylvania, Philadelphia, Pennsylvania

RESIDENT TRAVEL AWARD

CS 117 (140)
Mitochondrial TRPV1 Regulates Endothelial Dysfunction in Diabetes

Nana-Maria Wagner, MD[1]; Carl M. Hurt, MD, PhD[1]; Honit Piplani, PhD[1]; Stacy L. McAllister, PhD[1]; Eric R. Gross, MD, PhD[1]

[1]Stanford University, Stanford, California

See page 57 for complete abstract

CS 118 (114)
Pharmacodynamics and Pharmacokinetics of Novel GABA-A Receptor Alpha 4 Subunit Selective Ligands that Treat Bronchoconstriction

Gene T. Yocum, MD[1]; Yi Zhang, MD[1]; Gloria Forkuo, PhD[2]; Margaret Guthrie, BS[2]; Amanda Nieman, BS[2]; Rajwana Jahan, BSc[2]; Michael R. Stephen, PhD[2]; Douglas C. Stafford, PhD[2]; James M. Cook, PhD[2]; Alexander E. Arnold, PhD[2]; Charles W. Emala, MD[1]

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

See page 72 for complete abstract

CS 119 (81)
Impaired Relaxation of Airway Smooth Muscle in Mice Lacking the Cytoskeletal Regulatory Protein Gelsolin: A Potential Novel Target for Airway Relaxation

Maya Mikami, MD, PhD, MPH[1]; Jennifer Danielsson, MD[1]; Yi Zhang, MD[1]; Elizabeth Townsend, PhD[1]; Seema Khurana, PhD[2,3]; Charles W. Emala, MD[1]

[1]Columbia University, New York, New York; [2]University of Houston, Houston, Texas; [3]Baylor College of Medicine

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CS 120 (54)
Modulation of Human Myometrial Anoctamin-1 Attenuates Aontractile Agonist-Induced F-Actin Formation

George Gallos, MD; Thomas R. Pfeiffer, MD

Columbia University, New York, New York

CS 121 (51)
Opposite Effects of Dexmedetomidine and Midazolam on Lung Cancer Cell Biology In Vitro

Daqing Ma, MD, PhD, FRCA; Chunyan Wang, PhD; Akshay Date, BSc; Hailin Zhao, PhD

Imperial College London, London, United Kingdom

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Moderated Poster Discussion II: Cell Signaling

CS 122 (146)
Opsin 3 and 4 Mediate Blue Light-Dependent Pulmonary Vasorelaxation

Dan E. Berkowitz, MD; Daijiro Hori, MD; Gautam Sikka, MD; Xin Yun, PhD; Lakshmi Santhanam, PhD; Larissa Shimoda, PhD

Johns Hopkins University, Baltimore, Maryland

CS 123 (50)
Contribution of Mitochondrial Oxidative Stress in the Formation of Endothelial-Derived Microvesicles

Julie K. Freed, MD, PhD; Matthew J. Durand, PhD; Brian R. Hoffman, PhD; John C. Densmore, MD; Andrew S. Greene, PhD; David D. Gutterman, MD

Medical College of Wisconsin, Milwaukee, Wisconsin

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Clinical Management

Clin Manag 15 (55)
Raman Spectroscopy Differentiates Each Neuraxial Tissue: A Novel Method for Epidural Needle Placement?

T. Anthony Anderson, PhD, MD[1,2]; Jeon Woong Kang, PhD[3]; Peter So, PhD[3]; Ramachandra Dasari, PhD[3]; Tatyana Gubin[3]

[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Harvard Medical School, Cambridge, Massachusetts; [3]Massachusetts Institute of Technology, Cambridge, Massachusetts

Clin Manag 16 (168)
Real Time Compliance Solutions in a Disparate Electronic Medical Record System

Zachary A. Turnbull, MD; Matthew J. Alexander, BS; Peter Fleischut, MD; Amanda Carr, BS; Bohdan Hawryluk, MS; Hugh C. Hemmings, MD, PhD

Weill Cornell Medical College, New York, New York

Clin Manag 17 (172)
Proposed Anesthetic Management for Embolization of an Antenatal Hepatocellular Adenoma

Asma Asif, MD; Ami Attali, MD

Henry Ford Health System, Detroit Michigan

Clin Manag 18 (40)
Intracardiac Thrombosis Associated with Cardiopulmonary Bypass: Index Case and Review of Case Reports

Brittney Williams, MD; Andrew Crabbe, MD; Zachary Kon, MD; Michael Mazzeffi, MD; Kenichi Tanaka, MD

University of Maryland, Baltimore, Maryland

Clin Manag 19 (76)
Autonomic Dysreflexia in a Patient with a Recent Cervical Spine Injury Resistant to Conventional Therapy

Elvera L. Baron, MD, PhD[1]; Gebriel Bonilla, MD[2]; Elizabeth A.M. Frost, MD[1]

[1]Mount Sinai Hospital, New York, New York; [2]Elmhurst Hospital Center, Queens, New York

Clin Manag 20 (119)
Neonatal Intensive Care to Operating Room Handovers: What We Have Learned from Observation

Amanda N. Lorinc, MD; David A. Roberts, MD; Jason M. Glagle, PhD; J. Maria Sullivan, RN; Dan J. France, PhD; Matthew B. Weinger, MD

Vanderbilt University, Nashville, Tennessee

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Moderated Poster Discussion II: Clinical Management

Clin Manag 27 (124)
Surveying ICU Nurses Regarding Perspectives on Patient Communication

Miriam A. Madsen, MEng, MD[1]; Leigh R. Hochberg, MD, PhD[1,2,3]; Stephen O. Heard, MD[1]; J. Matthias Walz, MD[1]

[1]University of Massachusetts, Worchester, Massachusetts; [2]Brown University, Providence, Rhode Island; [3]Providence VA Medical Center, Providence, Rhode Island

Clin Manag 28 (126)
Designing a Novel Manual Communication System for Mechanically Ventilated ICU Patients

Miriam A. Madsen, MEng, MD[1]; Leigh R. Hochberg, MD, PhD[1,2,3]; Stephen O. Heard, MD[1]; J. Matthias Walz, MD[1]

[1]University of Massachusetts, Worchester, Massachusetts; [2]Brown University, Providence, Rhode Island; [3]Providence VA Medical Center, Providence, Rhode Island

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Neuro Clinical

Neuro Clin 32 (104)
Cerebral Hyperemia Following Circulatory Arrest in Humans

Warren J. Levy, MD
University of Pennsylvania, Philadelphia, Pennsylvania

Neuro Clin 33 (173)
Tissue Damage Induced Perioperative Inflammation is Associated with a Greater Risk of Postoperative Delirium in Elderly Patients Undergoing Spine Surgery: A Prospective Observational Study

John G. Gaudet, MD
Columbia University, New York, New York

Neuro Clin 34 (174)
Perioperative Anesthetic and Surgical Risk Factors Associated with Postoperative Delirium In Elderly Patients Undergoing Elective Spine Surgery: A Prospective Observational Study

John G. Gaudet, MD
Columbia University, New York, New York

Neuro Clin 35 (175)
EEG Slowing and the Recovery from Postoperative Delirium

Ben Julian A. Palanca, MD, PhD, MSc; Ginika Apakama, MD; Nan Lin, PhD; Troy Wildes, MD; Michael S. Avidan, MBBCh
Washington University in St. Louis, St. Louis, Missouri

Neuro Clin 39 (41)
Differential Synaptic Actions of Isoflurane on Hippocampal and Cortical Connections

Bruce M. MacIver, MSc, PhD
Stanford University, Stanford, California

Neuro Clin 40 (42)
Chaos Analysis Provides a More Sensitive and Accurate Measure for Loss of Consciousness Compared to Frequency Domain Measures of EEG Signals

Bruce M. MacIver, MSc, PhD
Stanford University, Stanford, California

Neuro Clin 41 (160)
Dexmedetomidine Sedation Disrupts Local and Global Communication in Large-Scale Brain Networks

Oluwaseun Johnson-Akeju, MD, MMSc[1]; Javeria Hashmi, PhD[2];Marco Loggia, PhD[1,3]; Emery Brown, MD, PhD[1]
[1]Massachusetts General Hospital, Boston, Massachusetts; [2]Dalhousie University, Halifax, Canada; [3]Harvard Medical School, Cambridge, Massachusetts

Neuro Clin 42 (90)
Anterior Insula Suppression at Loss of Volitional Behavioural Response

Catherine E. Warnaby, MPhys, PhD[1]; Marta Seretny, MD[1]; Saad Jbabdi, PhD[1]; Richard Rogers, MD[1]; Jamie Sleigh, MD[2]; Irene Tracey, DPhil[1]; Roisin Ni Mhuicheartaigh, MB BCh, MRCPI, FFARCSI, DPHIL[1]
[1]University of Oxford, Oxford, United Kingdom; [2]University of Auckland, Auckland, New Zealand

Poster Presentations Schedule

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Education

Edu 1 (133)
ReMind: Reducing Delirium and Improving Patient Satisfaction with a Perioperative Mindfulness Intervention

Lauren Lisann, BS[1]; Francesco Pagnini, PsyD, PhD[2]; Ellen Langer, PhD[3]; Stacie Deiner, MD[1]

[1]Icahn School of Medicine at Mount Sinai, New York, New York; [2]Catholic University of Milan, Milano, Italy; [3]Harvard University, Cambridge, Massachusetts

Edu 2 (157)
Seeing Through the Eyes of the Intubating Anesthesiologist: Google Glass to Improve Patient Safety during Airway Training

Karthik K. Kura, MD; Glenn Mann, MD; Michael H. Andreae, MD

Montefiore Medical Center, Bronx, New York

Edu 3 (75)
Faculty and Resident Perceptions of Anesthesiology Milestones: Do We Share A Similar Mental Model of Milestones Achievement?

Regina Y. Fragneto, MD[1]; Amy DiLorenzo, MA[1]; John Mitchell, MD[2]; Susie Martinelli, MD[3]; Matthew McEvoy, MD[4]; Randall Schell, MD, MACM[1]

[1]University of Kentucky, Lexington, Kentucky; [2]Beth Israel Deaconess Medical Center, Boston, Massachusetts; [3]University of North Carolina, Chapel Hill, North Carolina; [4]Vanderbilt University, Nashville, Tennessee

Edu 4 (69)
Addition of Focused Critical Care Transthoracic Echocardiography (FoTE) Learning into an Existing Anesthesiology Residency Training Program: a Prospective Study

Victoria Sokoliuk, DO; Nibras Bughrara, MD; Tanya Richvalsky, DO; Kevin Roberts, MD; Scott Groudine, MD

Albany Medical Center, Albany, New York

Edu 5 (120)
Critical Errors in Rarely Performed Procedures up to 5 Years after Training among 105 Surgeons

Colin Mackenzie, MD[1]; Kristy Pugh, MS[2]; Guinevere Granite, PhD[2]; Hegang Chen, PhD[1]; Adam Puche, PhD[1]; Samuel Tisherman, MD[1]

[1]University of Maryland, Baltimore, Baltimore, Maryland; [2]Shock Trauma Anesthesiology Research Center, Baltimore, Maryland

Edu 6 (166)
Is Pediatric Dental Surgery Under General Anesthesia a Teachable Moment?

Helen H. Lee, MD, MPH; Anne Koerber, DDS, PhD; Chuck LeHew, PhD; David Avenetti, DDS, MPH

University of Illinois at Chicago, Chicago, Illinois

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Moderated Poster Discussion II: Clinical Management

Edu 7 (165)
Practice Patterns and Outcomes of Older Anesthesiologists

Elizabeth L. Whitlock, MD, MSc[1]; Adrian Liau, PhD[2]; Lee-lynn Chen, MD[1]; Jeana E. Havidich, MD, MS[3]; Richard P. Dutton, MD, MBA[4]

[1]University of California, San Francisco, San Francisco, California; [2]University of Iowa, Iowa City, Iowa; [3]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; [4]United States Anesthesia Providers, Fort Lauderdale, Florida

Edu 8 (44)
Work Habits are Valid Component of Anesthesia Resident Evaluations Based on Faculty Anesthesiologists' Daily Written Comments

Franklin Dexter, MD, PhD[1]; Danielle Masursky, PhD[2]; Debra Szeluga, MD, PhD[1]; Bradley J. Hindman, MD[1]

[1]University of Iowa, Iowa City, Iowa; [2]State University of New York at Oswego, Oswego, New York

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Clinical Studies

Clin Studies 49 (60)
Evaluation of the Vios Medical Wireless Monitoring System – Initial Report of a Clinical Pilot Study

Chennapragada Sridevi, MD[1]; Prasad Sistla, ME[1]; Varun Varma, BS[2]; Amit Patel, MBA[2]; Melissa Cohen, BS[3]; Kumar Belani, MBBS, MS[3]

[1]Care Hospital Foundation, Hyderabad, India; [2]Vios Medical, St. Paul, Minnesota; [3]University of Minnesota, Minneapolis, Minnesota

Clin Studies 50 (46)
Reduction in Cryoprecipitate Waste in the Pediatric Cardiovascular Operating Room: A Goal-Directed Transfusion Algorithm Based on Rotational Thromboelastometry

Erin A. Gottlieb, MD[1]; Julie Nicholson, RN[2]; Matthew James, MD[1]; Dani Gleason, JD[2]; Sara Sommers, MBA[2]

[1]Baylor College of Medicine, Houston, Texas; [2]Texas Children's Hospital, Houston, Texas

Clin Studies 51 (65)
A Comparison of the Effectiveness of Two Commonly Used Two-Handed-Mask Ventilation Techniques on Unconscious Apneic Obese Adults: A Non-Inferiority Trial

Mark J. Rice, MD; Min Fei, MD; James L. Blair, MD; David A. Edwards, MD; Yandong Jiang, MD, PhD

Vanderbilt University, Nashville, Tennessee

Clin Studies 52 (59)
Barriers to Hepatitis C Virus Epidemiology in Anesthesia Care Workers

Mark J. Rice, MD[1]; Douglas B. Coursin, MD[2]; James D. Chappell, MD[1]; Kirk J. Hogon, MD, JD[2]

[1]Vanderbilt University, Nashville, Tennessee; [2]University of Wisconsin, Madison, Wisconsin

Clin Studies 53 (91)
System-Wide Modulation of Patients Immune Response to Surgery by Pre-Operative Immune-Enhancing Nutrients

Brice Gaudilliere, MD, PhD; Nima Aghaeepour, PhD; Edward Ganio, PhD; Hope Lancero, PhD; Martha Tingle, RN; Martin Angst, MD

Stanford University, Stanford, California

Clin Studies 54 (80)
Delirium Risk Factors in Critically Ill Children

Heidi A.B. Smith, MD, MSCI[1]; Molly Gangopadhyay, MD[2]; D. Catherine Fuchs, MD[1]; Jennifer Thompson, MPH[1]; E. Wesley Ely, MD[1]; Pratik P. Pandharipande, MD[1]

[1]Vanderbilt University, Nashville, Tennessee; [2]Columbia University, New York, New York

Clin Studies 55 (72)
Association of Endothelial and Neurologic Injury Biomarkers with Cognitive Impairment after Critical Illness

Christopher G. Hughes, MD; Timothy D. Girard, MD; James C. Jackson, PhD; Jennifer L. Thompson, MPH; E. Wesley Ely, MD; Pratik P. Panharipande, MD

Vanderbilt University, Nashville, Tennessee

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Moderated Poster Discussion II: Clinical Studies (Outcomes)

Clin Studies/OC 78 (63)
The Effect of Vasopressor Infusion During Spine Surgeries in Prone Position on Renal Function

Emily C. Farrin, MD; Natalya Makarova, MS; Zeyd Ebrahim, MD; Edward Benzel, MD; Iain Kalfas, MD; Ehab Farag, MD

Cleveland Clinic, Cleveland, Ohio

Clin Studies/OC 79 (85)
Mortality in Hospitalized Non-Traumatic Subarachnoid Hemorrhage Patients

Michael M. Todd, MD; Emine Mayman, PhD; David Hasan, MD; Santiago Ortega, MD; Bradley Hindman, MD; James Torner, PhD

University of Iowa Carver, Iowa City, Iowa

Clin Studies/OC 80 (125)
Pathophysiology of Perioperative Acute Coronary Syndromes: A Coronary Angiographic Investigation

Srikar Rao, MD; Paul M. Lavigne, MD; Amit P. Amin, MD, MSc; Mohamed A. Helwani, MD, MSPH; Peter Nagele, MD, MSc

Washington University in St. Louis, St. Louis, Missouri

Clin Studies/OC 81 (127)
Anomalous Billing by Health Care Providers: Evidence from Anesthesia

Eric C. Sun, MD, PhD[1]; Richard P. Dutton, MD, MBA[2]; Anupam B. Jena, MD, PhD[3]

[1]Stanford University, Stanford, California; [2]U.S. Anesthesia Partners, Fort Lauderdale, Florida; [3]Harvard University, Cambridge, Massachusetts

Clin Studies/OC 82 (131)
High-Sensitivity Cardiac Troponin for the Diagnosis of Perioperative Myocardial Injury and Infarction: A Comparison of Different Approaches

Peter Nagele, MD, MSc; Jamie Brown, MD; Srikar Rao, MD; Eslam Samaha, MD

Washington University in St. Louis, St. Louis, Missouri

Clin Studies/OC 83 (145)
The Relationship between Intraoperative Hypotension, Defined by Reduction from Baseline or Absolute Thresholds, and Myocardial Injury after Non-Cardiac Surgery: A Retrospective Cohort Analysis

Vafi Salmasi, MD; Kamal Maheshwari, MD, MPH; Dongsheng Yang, MA; Edward J. Mascha, PhD; Daniel I. Sessler, MD; Andrea Kurz, MD; Asha Singh, MD

Cleveland Clinic, Cleveland, Ohio

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Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Clinical Studies (Outcomes)

Clin Studies/OC 85 (163)
Low Health Literacy is a Predictor of Hospital Admission, Length of Stay and Other Hospital Quality Outcomes

Jesse M. Ehrenfeld, MD, MPH; Warren S. Sandberg, MD, PhD; Maxim Terekhov, MS; Sunil Kripalani, MD

Vanderbilt University, Nashville, Tennessee

Clin Studies/OC 86 (164)
Ace Inhibitors and Angiotensin Antagonists Were Not Associated With Decrease in Incidence of Postoperative Delirium in Surgical ICU Patients

Jagan Devarajan, MD; Jing You, MS; Argalious Maged, MD, MBA; Ali Sakr Esa Wael, MD, PhD; Daniel Sessler, MD; Ehab Farag, MD

Cleveland Clinic, Cleveland, Ohio

MARGARET WOOD RESIDENT RESEARCH AWARD

Clin Studies/OC 87 (151)
A Novel Association Between High Density Lipoprotein Levels and the Risk of Acute Kidney Injury After Award Cardiac Surgery

Loren E. Smith, MD, PhD; Derek K. Smith, DDS; MacRae F. Linton, MD; Frederic T. Billings IV, MD, MSc

Vanderbilt University Medical Center, Nashville, Tennessee

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Clin Studies/OC 88 (167)
Frequency, Severity and Location of Perioperative Hypoxemia in Patients with No Respiratory Disease

Ana Fernandez-Bustamante, MD, PhD; Karsten Bartels, MD; Leslie Jameson, MD; Angela Moss, MS; Ken Bullard, MS^3

University of Colorado School of Medicine, Aurora, Colorado

Friday, May 20, 2016 ▪ 10:15 am – 11:45 am

Moderated Poster Discussion II: Basic and Clinical Pain

Pain 92 (110)
Adeno-associated Viral (AAV) Vectors Expressing the Wild Type Mouse Carbonic Anhydrase-8 (Car8) Gene Inhibits Chronic Inflammatory Nociception and Regulates Calcium Signaling

Eugene S. Fu, MD; Gerald Z. Zhuang, PhD; Diane M. Erasso, PhD; Roy C. Levitt, MD

University of Miami, Miami, Florida

Pain 99 (95)
Physicians Dispense More Opioid Than Needed To Treat Same Day Surgery Pain: A Prospective Pediatric Cohort Study

Myron Yaster, MD; Shuna Gao, BA; Paul Vozzo, BA; Aaron Hsu, BS, MHS; Constance L. Monitto, MD; Benjamin H. Lee, MD, MPH

Johns Hopkins University, Baltimore, Maryland

Pain 100 (87)
Remotely Triggered On-Demand Adjustable Local Anesthesia

Daniel S. Kohane, MD, PhD; Alina Rwei, BS; Changyou Zhan, PhD

Boston Children's Hospital, Boston, Massachusetts

Pain 101 (177)
Acute and Subacute Postoperative Pain after Partial and Total Mastectomy: Association with Prospectively Assessed Psychosocial and Psychophysical Variables

Kristin L. Schreiber, MD, PhD[1]; Nantthasorn Zinboonyahgoon, MD[2]; Rob R. Edwards, MD[1]

[1]Brigham and Women's Hospital, Boston, Massachusetts; [2]Oregon Health Sciences University, Portland, Oregon

Pain 102 (176)
Sp1-like Transcription Factor Inhibitor Mithramycin – A, Reverses Platinum – Induced Pain Behaviors in Mice

Mark A. Schumacher, MD, PhD; Kayla Sheehan, BA; Keisuke, MD, PhD; Gabriella Rader, BA; Manohar Sharma, PhD; Helge Eilers, MD

University of California, San Francisco, San Francisco, California

Pain 103 (136)
Development of a Functional Connectivity Tool for Identifying Pain

James W. Ibinson, MD, PhD; Christopher J. Becker, MS; Keith M. Vogt, MD, PhD

University of Pittsburgh, Pittsburgh, Pennsylvania

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Moderated Poster Discussion II: Basic and Clinical Pain

Pain 104 (53)
Modulation of Long-Term Auditory Memory by Acute Pain, Including During Sedation with Midazolam and Dexmedetomidine

Keith M. Vogt, MD, PhD[1]; James W. Ibinson, MD, PhD[1]; Joshua Tremel, BS[1]; Lynne M. Reder, PhD[2]; Julie A. Fiez, PhD[1]

[1]University of Pittsburgh, Pittsburgh, Pennsylvania; [2]Carnegie Mellon University, Pittsburgh, Pennsylvania

Pain 105 (49)
Stem Cells Reversed Morphine Tolerance and Opioid-induced Hyperalgesia

Jianguo Cheng, MD, PhD; Zhen Hua, MD, PhD; LiPing Liu, MD, PhD; Kathleen Cheng; Jun Shen, MD; Yan Yin, MD

Cleveland Clinic, Cleveland, Ohio

JUNIOR FACULTY RESEARCH AWARD

Pain 112 (101)
The Analgesic Effects of Dopamine

Norman E. Taylor, MD, PhD[1]; JunZhu Pei, BS[2]; Ksenia Y. Vlasov, BA[2]; Jennifer A. Guidera, BA[1]; Ken Solt, MD[1]; Emery Brown, MD, PhD[1]

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

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Basic Neuro/AA/NN 57 (169)
Electroencephalographic Correlates of Hypnosis Independent of Drug Effect

Andrew R. McKinstry-Wu, MD; Andrzej Wasilczuk, BS; Max Kelz, MD, PhD

University of Pennsylvania, Philadelphia, Pennsylvania

Introduction: In the continuing effort to develop a method to independently assess consciousness and unconsciousness, a number of novel electroencephalographic (EEG) correlates of hypnosis have been proposed in human and animal models. These correlates have been shown to correlate well with behavioral markers of hypnosis, but whether these metrics are a direct reflections of changes in arousability or are instead changes from direct drug concentration effect is unknown. Here, we employ an engineered mouse, lacking dopamine-beta-hydroxylase (Dbh -/-) with increased anesthetic sensitivity to decouple drug concentration from arousal state in order to evaluate the validity of specific EEG correlates of hypnosis.

Methods: Mice were implanted with 28 transcranial electrodes spaced from 3 mm anterior to bregma to 4.5 mm posterior to bregma, spanning 2.3 mm laterally in either direction, 2 cervical EMGs, and 2 thoracic EMGs. After a 2 week recovery, mice were tethered to head caps and placed in a sealed, temperature-controlled chamber. Isoflurane was ramped from 0 to 1.0% and back to 0% in 0.2% increments, 40 minutes per step, while continuously recording EEG and EMG. Data was acquired using 32 channel headstages (Intan Technologies, Los Angeles, CA) through an acquisition board based on open source designs provided by Open-Ephys (openephys.org) and imported for analysis into Matlab (Mathworks. Natick, Massachusettes.)

Results: Mutant mice (n=5) and heterozygote littermates (n=5) displayed divergent EEG responses to identical concentrations of isoflurane, reflective of previously described differences in behavioral responses between the two genotypes (Hu).[1] Differences were noted in delta power between the two groups at multiple concentrations of isoflurane during induction and emergence. These changes, as well as the previously published behavioral responses to given concentrations of isoflurane, were analyzed in parallel to each genotype's global coherence (Cimenser),[2] stability (Solovey),[3] and frontal-parietal feedback (Ku),[4] per published protocols.

Conclusions: Patterns of behavioral divergence between mutant and heterozygote littermates at a given anesthetic concentration held for EEG analysis, suggesting such differences are true divergences in hypnosis, rather than a behavioral confound.

References

1. Hu, F. et al. Hypnotic Hypersensitivity to Volatile Anesthetics and Dexmedetomidine in Dopamine Ð-Hydroxylase Knockout Mice. Anesthesiology 117, 1006 (2012).
2. Cimenser, A. et al. Tracking brain states under general anesthesia by using global coherence analysis. Proc. Natl. Acad. Sci. U.S.A. 108, 8832-7 (2011).
3. Solovey, G. et al. Loss of Consciousness Is Associated with Stabilization of Cortical Activity. J. Neurosci. 35, 10866-77 (2015).
4. Ku, S.-W., Lee, U., Noh, G.-J., Jun, I.-G. & Mashour, G. Preferential Inhibition of Frontal-to-Parietal Feedback Connectivity Is a Neurophysiologic Correlate of General Anesthesia in Surgical Patients. PLoS ONE 6, (2011).

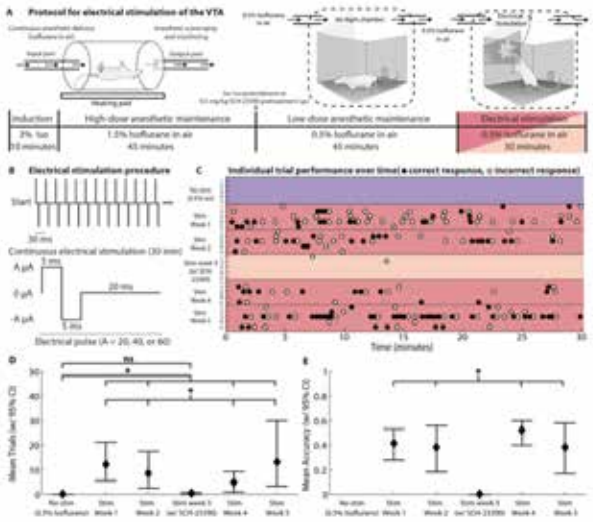
Basic Neuro/AA/NN 58 (115)

Electrical Stimulation of the Ventral Tegmental Area Restores the Ability to Perform a Touchscreen-Based Visual Discrimination Task in Rats Sedated with Isoflurane

Ken Solt, MD; Jonathan D. Kenny; Norman E. Taylor, MD, PhD; Justin T. Lee, MEng; Jennifer A. Guidera, AB; Emery Brown, MD, PhD

Massachusetts General Hospital, Boston, Massachusetts

Introduction: Electrical stimulation of the VTA restores righting in anesthetized rats[1]. It is unknown whether VTA stimulation also restores cognitive function. In this study rats were trained to perform a touchscreen-based visual discrimination task to test if VTA stimulation restores task performance during isoflurane (ISO) sedation.



Methods: Male Sprague-Dawley rats (n=8) were used in these IACUC approved experiments. Rats were first trained to perform a visual discrimination task[2]. The chamber was in a sealed enclosure with ports for gas in/outflow and sampling. Two images were presented simultaneously on a touchscreen, and rats were trained to complete trials by touching the correct image for a food reward. During each 30-minute session, rats were able to initiate a new trial 30 sec after completion of a previous trial. After reaching >85% correct responses for at least 3 consecutive days, the animals underwent stereotaxic implantation of bipolar stimulation electrodes in the VTA. The rats recovered for at least 7 days, and then were re-introduced to the testing chambers. Three weeks after surgery, the animals recovered to their baseline performance level. A dose-response was then performed by exposing them to steady-state ISO (0.1-0.5%) while performing the cognitive task. The rats were only exposed to a single dose of ISO once per week.

After establishing that 0.5% ISO reliably extinguished task performance, once a week (for 5 weeks) the rats underwent electrical VTA stimulation during steady-state 0.5% ISO sedation, and task performance was assessed. During week 3, the D1 dopamine receptor antagonist SCH-23390 (0.5 mg/kg i.p.) was administered before VTA stimulation. Fig. A shows the anesthesia protocol used to ensure steady-state ISO, while Fig. B shows the waveform characteristics of electrical stimulation. Cognitive performance was assessed by: 1) number of trials completed per session, and 2) overall accuracy (percent correct). After completing all experiments, histological analysis of electrode placement was performed. The electrode tip was in the VTA in 5/8 animals. Only these animals were used for analysis.

Results: The trials completed by each rat over time are shown in Fig. C (black circles= correct responses, white=incorrect responses). At 0.5% ISO, all rats were heavily sedated, rarely moved, and performed no trials. However, during VTA stimulation 5/5 rats performed the task despite continuous 0.5% ISO (weeks 1,2,4,5). Administration of SCH-23390 prior to VTA simulation (week 3) reversibly abolished task performance. Figs. D and E show number of trials and accuracy (mean with 95% CIs) for each week. Although VTA stimulation during ISO sedation restored task performance, mean accuracy was not restored to baseline.

Conclusions: At a dose of ISO insufficient to induce loss of righting (0.5%) the ability of rats to perform a visual discrimination task was reliably extinguished, suggesting that this many be a useful endpoint for loss of cognitive function. VTA stimulation restores task performance but not accuracy, and this effect is likely mediated by dopamine. Activation of this dopamine circuit may provide a novel target to treat POCD.

References

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2. Learning and Memory 2008;15:516

Basic Neuro/AA/NN 64 (67)
Sex Dependent Mitochondrial Respiratory Impairment and Oxidative Stress in a Rat model of Neonatal Hypoxic-Ischemic Encephalopathy

Gary Fiskum, PhD; Tyler Demarest, MS

University of Maryland, Baltimore, Maryland

Introduction: Increased male susceptibility to long-term cognitive deficits is well described in clinical and experimental studies of neonatal hypoxic-ischemic encephalopathy[1] however, sex-linked differences in pathophysiological mechanisms of hypoxic-ischemia (HI) brain injury have not been established. Mitochondrial bioenergetic and apoptotic dysfunction contributes to cell death following HI[2] and evidence indicates that there are sex differences in the mitochondrial metabolism of adult mammals[3]. This study tested the hypothesis that brain mitochondrial respiratory impairment and associated oxidative stress is more severe in males than females following HI.

Methods: HI was performed using the Rice-Vannucci model[4]. Male and female postnatal day 7 rat pups were randomly assigned to sham or HI groups. Anesthesia was induced with 3% isoflurane and maintained with 1.5% under constant temperature. The right carotid artery was severed between two ligatures. Pups were then placed in a chamber and exposed to 8% O2 for 75 min. Brain homogenates and isolated brain mitochondria were obtained from the ipsilateral hemisphere (hypoxic/ischemic) and the contralateral hemisphere (hypoxic) 20 hr after HI. Mitochondrial respiration was measured with an oxygen electrode apparatus. Glutathione and antioxidant enzymes were measured in homogenates and isolated mitochondria. Additional rats were perfusion-fixed at 24 hr and used for immunohistochemical measurements of protein oxidation (carbonyl groups).

Results: Maximal respiration by ipsilateral brain mitochondria was two-fold more impaired in males compared to females following HI. Contralateral brain mitochondria were also impaired in males but not in females. The endogenous antioxidant glutathione was 30% higher in the brain of sham females compared to males. Females also exhibited increased glutathione peroxidase (GPx) activity following HI injury. Conversely, males displayed a reduction in mitochondrial GPx4 protein levels and mitochondrial GPx activity. Moreover, a 3 to 4-fold increase in oxidative protein carbonylation was observed in the cortex and hippocampus of injured males, but not females.

Conclusions: These data provide the first evidence for sex differences in mitochondrial respiratory dysfunction and oxidative damage following HI in neonates. This example of sexually dimorphic ischemic brain injury mechanisms is not a consequence of differences in circulating sex hormones as they are not different between male and female rats at this age. Such sex-dependent differences in the pathophysiology of brain injury at any age should be considered during the development and testing of potential neuroprotective interventions.

References

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3. Demarest TG and McCarthy MM, J Bioenerg Biomembr 47:173-88 (2015).
4. Rice JE III et al., Ann Neurol 9:131-141 (1981).

Basic Neuro/AA/NN 65 (102)
Novel Neuro-Restorative Strategy to Improve Memory Function after Global Cerebral Ischemia

Paco S. Herson, PhD; Robert M. Dietz, MD, PhD; James E. Orfila, PhD; Guiring Deng, MD; Nidia Quilinan, PhD; Richard J. Traystman, PhD

University of Colorado School of Medicine, Aurora, Colorado

Introduction: Cardiac arrest (CA) occurs in approximately 600,000 people each year in the United States alone and is a major cause of mortality and morbidity. Cardiac arrest results in global cerebral ischemia and hypoxic-ischemic injury, and the consequent neuronal damage results in long-term cognitive impairments. The neuropsychological consequences of CA-induced ischemic damage frequently include memory disturbances and more general executive disorders. The memory disorders commonly observed following CA are readily explained by the selective vulnerability and dysfunction of CA1 pyramidal cells of the hippocampus. Indeed, our recent study indicates that surviving neurons in the hippocampus exhibit physiological changes that likely contribute to cognitive deficits. Therefore, the current study investigated the role of synaptic signaling downstream of the oxidative-stress activation ion channel TRPM2 and its role on ischemia-induced synaptic dysfunction.

Methods: Male and female C57Bl/6 mice (20-25g) were subjected to 8 min cardiac arrest and cardiopulmonary resuscitation (CA/CPR). Hippocampal CA1 function and synaptic plasticity were evaluated using acute brain slices 7 days after CA/CPR or sham controls. Synaptic plasticity was measured by long term potentiation (LTP) of synaptic signals following theta-burst stimulation (TBS). Increase in field excitatory post-synaptic potential (fEPSP) slope 60 min after TBS was analyzed as a measure LTP. Slices or mice were treated with our newly developed peptide inhibitor of TRPM2, termed tatM2NX at times indicated below.

Results: Consistent with our previous reports, recordings obtained in brain slices from male mice 7 days after CA/CPR exhibited a near complete loss of LTP when cells were exposed to the same TBS stimulation that stimulates robust LTP in sham control mice (161±9%, n=6 in sham compared to 105±9%, n=8 on day 7 after CA/CPR). Remarkably, bath application of the TRPM2 channel inhibitor tatM2NX (1μM) for 2 hours reversed the CA/CPR-induced loss of LTP, recovering to 149.8±26% (n=3; $P<0.05$ compared to paired 7 day CA/CPR slices recorded from the same animal on the same day). Similar to our ex-vivo observation, in vivo administration of tatM2NX (20 mg/kg administered ip on day 6 after CA/CPR) reverses CA/CPR-induced impairments in hippocampal LTP, recovering to 171±11% (n=6 recordings from 4 mice treated with peptide; $P<0.05$ compared to 7 day CA/CPR slices). Similar data was observed in female mice (data not shown). Finally, delayed administration of tatM2NX improves memory function in post-ischemic male mice, measured using the well-established hippocampal-specific memory task, contextual fear conditioning (CFC). CA/CPR causes a significant reduction in freezing behavior, indicative of lack of memory, which was reversed in CA/CPR mice administered tatM2NX (20 mg/kg, single ip injection 24 hr before testing) on day 7 post-CPR compared to vehicle injected mice.

Conclusions: These data indicate that following global cerebral ischemia synaptic TRPM2 channels are chronically activated, contributing to long-lasting impairments of the remaining hippocampal network. Therefore, inhibition of TRPM2 channels at chronic timepoints following ischemia may represent a novel strategy to improve functional recovery following cerebral ischemia.

Basic Neuro/AA/NN 66 (45)

Elevated Serum TNF-alpha Levels Lead to Abnormal Cortical Synaptic Dynamics in a Mouse Model for Neuroinflammation: Could Cytokines Play a Similar Role in Postoperative Cognitive Dysfunction?

Scott M. Hayes, MD; Guang Yang, PhD; Christopher Parkhurst, PhD; Wenbiao Gan, PhD

New York University, New York, New York

Background: Pro-inflammatory cytokines including TNF-alpha are known to modulate synaptic plasticity in-vitro, but the effect of cytokines on neuronal structure and function in the cerebral cortex remains unclear [i,ii,iii]. We utilized a mouse model for experimental autoimmune encephalomyelitis (EAE), a model commonly used to study neuroinflammatory disease [iv], to examine the effect of inflammation on the structure of synaptic connections in the somatosensory cortex.

Method: Dendritic spines and axonal boutons in the mouse somatosensory cortex were imaged in-vivo with two-photon microscopy through a thinned-skull window to visualize changes in synaptic structure over time [v]. Mice expressing yellow florescent protein (YFP) in layer V pyramidal neurons allowed for visualization of synaptic structures. For EAE induction, mice were injected s.c. with MOG35-55 peptide. NIH ImageJ software was used to track the same dendritic and axonal segments at 7, 14, and 28 days after EAE induction. We used RT-PCR to measure TNF-alpha expression in the periphery and CNS. To study the effect of TNF-alpha inhibition, mice received daily i.p. injections of dominant negative TNF inhibitor [vi] (dn-TNF) immediately after EAE induction and for 7 consecutive days.

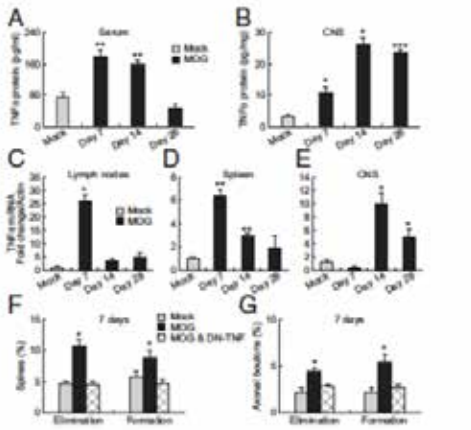

Fig. 5. Peripheral TNF-α production contributes to early synaptic instability in the cortex. (*A* and *B*) TNF-α protein levels in serum and CNS of Mock- and MOG-immunized animals. TNF-α protein level was significantly increased in both serum and CNS tissues at days 7 and 14 post-MOG immunization, but only in CNS tissues at day 28 post-MOG immunization. (*C*–*E*) TNF-α mRNA levels in lymph nodes, spleen, and CNS of Mock- and MOG-immunized animals. At day 7 postimmunization, a significant increase of TNF-α mRNA levels was observed in lymph nodes and spleen, but not in CNS of MOG-immunized animals compared with the Mock-immunized control. (*F*) Spine elimination and formation over 7 d after MOG immunization were significantly reduced in animals treated with DN-TNF. (*G*) Elimination and formation rates of axonal boutons over 7 d after MOG immunization were significantly reduced in animals treated with DN-TNF. Data are presented as mean ± SEM. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

Results: Peripheral elevation of TNF had a destabilizing effect on cortical dynamics, resulting in increased turnover of synaptic networks at both presynaptic axonal buttons and postsynaptic dendritic spines. The elimination and formation rates of dendritic spines and axonal boutons increased within 7 days of EAE induction. Synaptic instability was associated with peripheral expression of TNF-alpha. Administration of TNF inhibitor prevented abnormal turnover of dendritic spines and axonal boutons in pre-symptomatic EAE mice.

Conclusion: Peripheral inflammation can cause changes to the structure of cortical synapses, and TNF-alpha is likely a key mediator. Increased turnover of cortical synapses is thought to represent instability of cortical networks and cortical dysfunction[vii]. The effect of inflammation on cortical synapse structure may have wider implications beyond autoimmune disease. Recent literature has hypothesized that surgical inflammation including TNF-alpha, may play a role in cognitive changes in post-operative cognitive dysfunction[viii]. Further studies are needed to utilize in vivo imaging to provide insight into many disease states relevant to anesthesiology.

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Basic Neuro/AA/NN 67 (149)

Isoflurane Inhibits Excitatory Neurotransmission in the Anesthetic Hypersensitive Mouse Mutant, NDUFS4(KO)

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Introduction: Mitochondrial complex I dysfunction is linked to volatile anesthetic sensitivity in nematodes, mice and children[1-3]. Mice with loss of a mitochondrial complex I subunit, NDUFS4, are very hypersensitive to volatile anesthetics (VAs).1 Limiting NDUFS4 loss to a subset of glutamatergic neurons recapitulated the total knock-out (KO) VA hypersensitivity phenotype. Exposure to 0.6% isoflurane, which anesthetizes KOs but not controls, selectively depressed spontaneous excitatory neurotransmission in KO CA1 neurons (submitted for publication). Here we investigated excitatory neurotransmission under conditions of high energetic demand caused by high frequency stimulation (HFS).

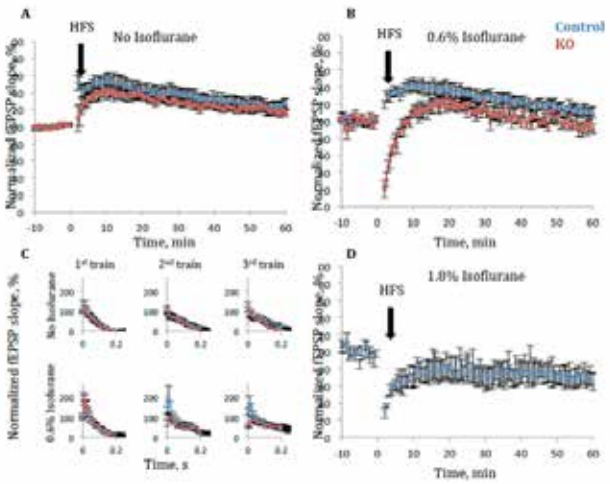

Figure 1. Mitochondrial complex I dysfunction inhibits recovery from HFS-induced fEPSP depression. **A.** Effect of HFS on control and KO fEPSP slopes without isoflurane exposure. **B.** Effect of HFS on control and KO fEPSP slopes in the presence of 0.6% isoflurane. **C.** Control and KO fEPSP potentiation and depression recorded during HFS. **D.** Effect of HFS on control fEPSP slopes in the presence of 1.8% isoflurane. In all panels each fEPSP slope was normalized to the average fEPSP slope recorded 10 min prior to HFS and expressed as per cent.

Methods: All studies were approved by our IACUC. Coronal brain slices were prepared from 23-30 days old mice. Bipolar platinum electrodes were placed on Schaffer collateral fibers and evoked field excitatory postsynaptic potentials (fEPSPs) were recorded with a microelectrode placed in the stratum radiatum of CA1. Fibers were stimulated every 30s for baseline activity and for at least 60min following HFS, which consisted of 3 trains of 100Hz delivered at 20s intervals. In some experiments isoflurane-containing solution was superfused for 40min prior to HFS, and for the duration of the experiment.

Results: HFS failed to induce potentiation in KO slices within 2min, while control slices showed potentiation to ~150%. By ~10min, KO and control slopes of fEPSPs displayed very similar potentiation, of ~140%, which gradually decreased to ~120% at 60min (Fig. 1A). 0.6% isoflurane exposure initially decreased slopes of fEPSPs in the KO to only 20% of baseline, gradually increasing to match potentiation in control slices of about 120% over 20min (Fig. 1B). There were no differences between KO and control in the slopes of fEPSPs during HFS in room air. In 0.6% isoflurane the KO preparations displayed much lower slopes in the first 50msec in the second and third train of HFS (Fig. 1C). 0.6% isoflurane corresponds to ~1.5 MAC for the KO. We tested 1.5 MAC isoflurane (1.8%) in controls. Isoflurane reduced fEPSPs to ~25% of baseline at 30s post-HFS, recovering to ~80% by 15min, without further changes (Fig. 1D).

Conclusion: Under energetically demanding conditions, isoflurane markedly inhibited the ability of a mitochondrial mutant to recover excitatory synaptic transmission. HFS in our model uncovered selective differences in Ndufs4(KO) neuronal function that are consistent with whole animal data for both the global KO and cell specific loss of this protein. Depression of excitatory synaptic function by isoflurane may limit the frequency of effective neurotransmission in key circuits responsible for normal response to VAs.

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Basic Neuro/AA/NN 68 (159)
Isoflurane Differentially Inhibits Firing Correlations Among Parvalbumin Interneurons Versus Pyramidal Neurons in Mouse Frontal Cortex

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Introduction: During volatile anesthesia, large amplitude slow oscillations dominate brain electrical activity, reflecting increased synchronization among cortical pyramidal cells.[1] One possible source of this phenomenon is the loss of coordinated inhibitory activity in parvalbumin (PV) expressing interneuron networks. We used the fluorescent calcium indicator GCAMP-6 to compare effects of isoflurane on PV neurons to non-PV neurons in layers 2/3 of adult mouse prefrontal cortex in vivo. Our results suggest that changes in synchronization of the cortical pyramidal population may be mediated by shifts in firing statistics of PV neurons.

Methods: All procedures were approved by the UCLA animal care and use committee. Adult PV-cre Ai9 mice that selectively express the red fluorescent protein TdTomato in PV neurons were used for this experiment. We injected GCCAMP6 AAV vector in layer 2-3. Images were acquired from head fixed mice spontaneously breathing isoflurane with a resonant scanning 2 photon microscope after 2-3 weeks of viral protein expression. Radiant warming maintained temperature. Recording began after equilibration to 2% isoflurane, sufficient for burst suppression. Isoflurane concentration then decreased to 1.5% and further decreased in 0.25% increments until return of coordinated movement. Frames were aligned and neurons identified using shape and correlation behavior amongst pixels. PV neurons were identified by high red fluorescence. Green fluorescent signals from GCAMP6 were extracted frame-by-frame by averaging pixels within each neuron. Calcium influx was approximated from fluorescence F as $\Delta F/F$.[2]

Results: In both PV and non-PV neurons, $\Delta F/F$ was highest at 2% isoflurane, consistent with profound depolarization during bursts from burst suppression. $\Delta F/F$ in non-PV neurons was higher at 2% isoflurane than in PV neurons, though median PV $\Delta F/F$ was higher for all other anesthetic concentrations. Variance of $\Delta F/F$ paralleled changes in median $\Delta F/F$. Rightward skew in the distribution of zero-lag correlation coefficients among neurons reflects simultaneous calcium influx. PV-PV correlation coefficients demonstrate significantly more rightward skew than nonPV-nonPV correlations at intermediate concentrations of anesthetics (0.75-1.25% isoflurane), though there is no difference at 1.5% or 2% isoflurane.

Discussion: These data demonstrate a differential modulation by isoflurane of PV neurons firing statistics in the intact cortical microcircuit, most prominently a loss of coordinated activity among PV cells that occurs approximately at 1.25-1.5% isoflurane. Mouse cortical PV neurons are coupled by gap junctions that, together with GABA-ergic synaptic transmission, allows the entrainment of gamma-frequency oscillations in layer 2/3.[3] Gap junctions have been shown in vitro and in slice to be inhibited by multiple anesthetics, and connexin 36 knockout mice are more sensitive to isoflurane.[4] Hence we hypothesize that the observed differential effect of isoflurane on synchronization in PV cells is at least part due to inhibition of gap junctions in the PV cell network.

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Basic Neuro/Inj 106 (77)
Lidocaine Inhibited Glioma Cell Proliferation via TRPM7 Channels

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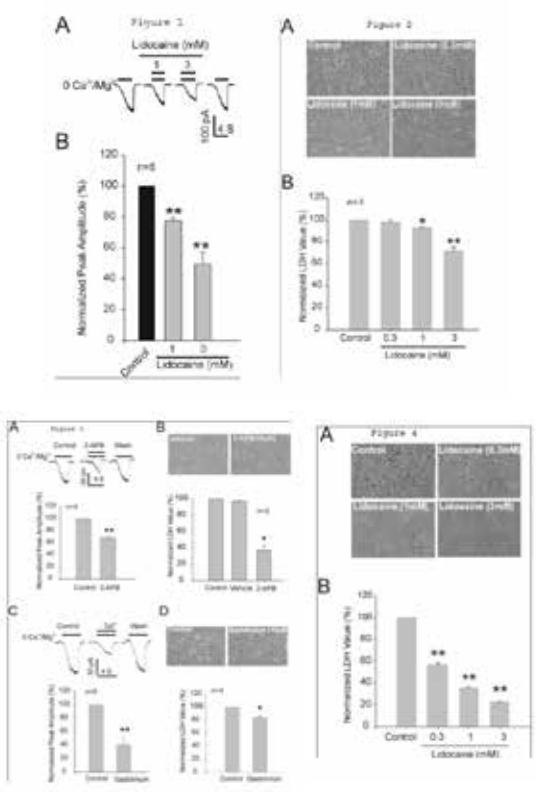
Introduction: Inhibition of glioma cell proliferation may reduce the potential of recurrence of malignant glioma following surgery. Melastatin-like transient receptor potential 7 (TRPM7) mediates the entry of Ca2+ and Mg2+ in cancer cells regulating the cell function and cycle (1). Our previous studies have demonstrated that TRPM7 play an important role in the proliferation, migration and invasion of human malignant glioma cells (2), suggesting that TRPM7 might serve as a target for intervention. We have also found that lidocaine inhibits TRPM7 currents in HEK293 cells and cultured neurons (3). Therefore, we hypothesized that lidocaine inhibits the proliferation of malignant glioma cells by inhibiting TRPM7 channels.



Methods: TRPM7 currents were recorded in rat C6 glioma cells using the whole cell patch clamp technique. Cell growth and proliferation were assessed under microscopic examination and LDH assays. Data are expressed as mean ± S.E.

Results: Lidocaine inhibits TRPM 7-like currents in a dose-dependent and reversible manner. Around 20% and 50% of TRPM7 currents were inhibited by 1 and 3 mM lidocaine, respectively (Figure 1). At these concentrations, it is effective in inhibiting the proliferation of C6 cells. The inhibition of proliferation was supported by LDH assays (Figure 2). TRPM7 inhibitors gadolinium and 2-Aminoethoxydiphenyl borate inhibited TRPM7 currents and proliferation of C6 cells (Figure 3). Similar to its effect on C6 cells, lidocaine inhibits the proliferation of A172 cells, a human glioblastoma cell line (Figure 4).

Discussion: TRPM7 has been shown to be overexpressed in a number of human cancer cells. Inhibition of TRPM7 currents or knockdown of TRPM7 expression by siRNA was able to suppress their malignant biological behaviors. In this study, we show that lidocaine inhibited the TRPM7 currents and caused significant reduction in the proliferation of C6 cells. The role of TRPM7 in mediating the effect of lidocaine was supported by TRPM7 inhibitors exhibiting similar inhibitory effects. The suppressing effect of lidocaine was also demonstrated in A172 human glioma cells. The effective concentration of lidocaine may be reachable locally during surgery depending on the route and speed of administration. Application of a well-known local anesthetic with known profile during surgical resection of glioma might be beneficial with little risk. Further study is needed to disclose the mechanism of lidocaine to develop local anesthetics with higher potency and efficacy targeting TRPM7.

Conclusion: Lidocaine significantly reduced the proliferation of glioma cells, which is mediated, at least in part, by inhibiting currents of TRPM7 channels.

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Basic Neuro/Inj 107 (94)
The Underlying Mechanism of Sevoflurane-Induced Cognitive Impairment

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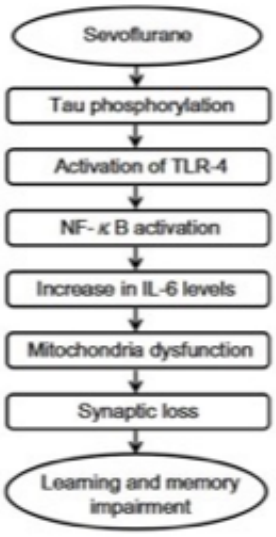
Introduction: Children who have multiple exposures to anesthesia and surgery may have a higher risk of developing a learning disability[(1)]. Tau protein phosphorylation plays an important role in Alzheimer's disease dementia and cognitive dysfunctio[n (2)]. Our previous studies have shown that anesthesia with 3% sevoflurane for two hours daily for three days can induce cognitive impairment and Tau phosphorylation in young mice[(3)]. However, the underlying mechanisms remain largely to be determined.

Methods: Six-day-old wild-type (WT), Tau knockout (KO), interleukin-6 KO, cyclophilin D KO and TLR-4 receptor KO mice were treated with 3% sevoflurane for two hours daily for three days. The effects of the sevoflurane anesthesia on Tau phosphorylation, neuroinflammation, synapse number and cognitive function were determined by Western blot analysis, ELISA, electron microscopy, and Morris Water Maze. The effects of sevoflurane on the NF-βB signaling pathway were also investigated using immunostaining. Finally, effects of naltrexone, a TLR-4 receptor antagonist[(4)], on the sevoflurane-induced cognitive impairment were determined.



Results: The sevoflurane anesthesia induced Tau phosphorylation, enhanced activation of glycogen synthase kinase 3β (GSK3β) (the kinase related to Tau phosphorylation), caused mitochondrial dysfunction (ROS elevation, reduction in mitochondrial membrane potential and ATP levels), decreased levels of postsynaptic density protein-95 (PSD-95) and synapse number in the hippocampus, and induced cognitive impairment in the WT mice. The GSK3β inhibitor lithium mitigated the sevoflurane-induced adverse effects. The sevoflurane anesthesia did not induce significant changes in interleukin-6 levels, mitochondrial dysfunction, reduction in PSD-95 levels and synapse number in the hippocampus, or cognitive impairment in Tau KO mice. The sevoflurane anesthesia only induced GSK3β activation and Tau phosphorylation in the interleukin-6 KO mice. In the cyclophilin D KO mice, the sevoflurane anesthesia caused GSK3β activation, Tau phosphorylation, and interleukin-6 elevation, but no other effects. Sevoflurane induced activation of the NF-βB signaling pathway in neurons. However, sevoflurane anesthesia did not induce cognitive impairment in TLR-4 KO mice. Finally, naltrexone attenuated the sevoflurane-induced cognitive impairment in WT mice.

Conclusion: These data suggest that sevoflurane activates GSK3β, which induces Tau phosphorylation. The phosphorylated Tau then acts on TLR-4 receptor to increase interleukin-6 production via NF-βB signaling pathway. Finally, interleukin-6 prompts mitochondrial dysfunction and synaptic loss, causing cognitive impairment in the mice as demonstrated in the Figure.

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Basic Neuro/Inj 108 (96)
Olfactory Impairment and Postoperative Cognitive Dysfunction

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Introduction: Postoperative cognitive dysfunction (POCD), one of the most common post-operative complications in senior patients [(1)], is associated with increased cost, morbidity, and mortality [(2, 3)]. However, its pathogenesis remains largely unknown, which has become a barrier that impedes further studies of POCD, leading to no treatment or prevention. Olfactory impairment is associated with Alzheimer's disease dementia; we therefore set out to assess whether surgery under general anesthesia can induce olfactory impairment, leading to POCD in mice.

Methods: Four- and 18-month-old WT (C57BL/6) mice received abdominal surgery under isoflurane anesthesia. Buried pellet test, olfactory habituation/dishabituation test and block test were used to measure the olfactory function in mice. The three behavior tests were performed the day before, 6 hours, and 1, 2, and 3 days after the surgery under isoflurane. Note that the buried pellet test measures the food motivation aspect of olfaction; the olfactory habituation/dishabituation test measures the ability of the mouse to discriminate between familiar and novel, innocuous scents; and the block test measures more of the social aspect of olfactory function, testing the ability of mice to discriminate between their own scent and that of a conspecific one. We also used Barnes maze test to measure the cognitive function in the mice after the surgery under isoflurane. Finally, we measured ATP levels in the hippocampus after the anesthesia and surgery in mice.

Results: Here we showed that olfactory discrimination between familiar and novel scents decreased after surgery with isoflurane in both 4- and 18-month-old mice. The ability to discriminate between their own scent and that of a conspecific one only decreased the second day after the surgery under isoflurane in 4-month-old mice, while it decreased 6 hours and 1 and 3 days after the surgery under isoflurane in the 18-month-old mice. Locomotor activity test showed that the changes in olfactory function did not result from the difference in locomotor activity. The surgery under anesthesia induced cognitive impairment, represented as an increase in the latency to find the correct hole in Barnes maze. Enhancement of olfactory function attenuated the anesthesia/surgery-induced cognitive impairment in mice. Finally, the anesthesia and surgery reduced ATP levels in the hippocampus of the mice.

Conclusion: These data suggest that surgery under general anesthesia may impair the olfactory function in mice, which then induces cognitive impairment in the mice. Reduction in brain ATP levels would contribute, at least partially, to these behavioral changes in the mice. These findings would illustrate the potential causes and cellular mechanism of POCD, which might lead to the development of treatment and prevention for POCD.

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Basic Neuro/Inj 109 (147)
Selective Alkylphenol Anesthetic Binding to Gabaa Subunits in Native Neuronal Tissue

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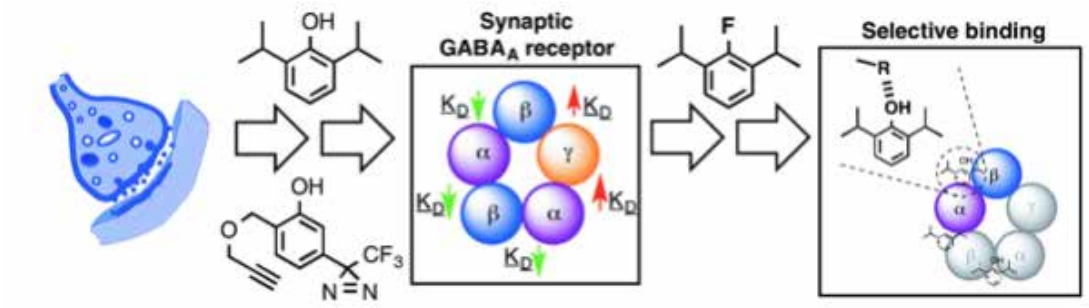
University of Pennsylvania

Propofol is a positive modulator of the GABAA receptor, but the mechanistic details, including the relevant binding sites, remain disputed. Here, we designed and synthesized a photoaffinity tandem bioorthogonal propofol ligand, ortho-alkynyl-meta-azipropofol (AziPm-click), for the unbiased identification of propofol-binding proteins in their native milieu within mouse synaptosomes. After confirmation of retained GABAergic and in vivo anesthetic character by our probe, our affinity-based protein profiling strategy combined with quantitative mass spectrometry identified ~4% of the synaptosomal proteome as potential propofol-specific protein targets, including five α or β GABAA receptor subunits. γ subunits were not identified, a finding that was not due to low abundance. Molecular dynamics simulations allowed the hypothesis that the higher affinity interactions for propofol at α/β relative to γ -containing interfaces were due to differential hydrogen-bonding. Application of a hydrogen-bond null propofol analogue supported this hypothesis. This investigation provided the first experimental evidence for direct propofol interaction with specific GABAA receptor subunits within native tissue. Further, these results expand the list of potential alkylphenol molecular targets.



Basic Neuro/Inj 110 (158)

Protecting Mitochondrial Function by Reducing miRNA-210 Facilitates Immature Neuron Survival after Injury

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Introduction: Post-stroke treatments aimed at salvaging neurons have been extensively investigated without success. Facilitating functional recovery by targeting endogenous neurogenesis remains an appealing target. Ischemia increases neurogenesis, but this fails to provide significant repair after stroke [(1)]. Most newborn neurons die, in part due to exposure to the inflammatory milieu. We previously demonstrated that mitochondrial protection ameliorates this deficit [(2)]. In this study we tested a new strategy, reducing microRNA-210 (miR-210) levels to protect mitochondrial function and tested the ability of this manipulation to rescue the impairment of neurogenesis caused by microglia inflammation in vitro. MicroRNAs (miRNAs) are a large class of endogenous short RNAs that control gene expression at the post-transcriptional level. The ability of miRNA-210 (miR-210) to downregulate mitochondrial function and mediate the metabolic switch to glycolysis is well established (3). This study tested whether reduction of miR-210 levels could improve mitochondrial function and survival of young neurons under inflammatory conditions.

Methods: We use neurosphere-derived mouse neural progenitor cells (NPC) to study mitochondrial function and survival during in vitro inflammatory injury. Lipopolysaccharide (LPS) treated microglial BV-2 cells were used to produce proinflammatory medium. We investigated mitochondrial function using the mitochondrial membrane potential sensitive dye TMRE, assayed activity of mitochondrial enzymes cytochrome c oxidase and aconitase, and assessed glucose consumption and lactate production. Effects on inflammation induced death of immature doublecortin (Dcx)-positive neurons was quantitated by staining and counting in differentiating cultures. Inhibitor of miR-210 or control was transfected into NPC and differentiating cells, and levels of miR-210 assessed by RT-qPCR.

Results: We demonstrated that Dcx+ cells are particularly sensitive to mitochondrial impairment, as evidenced by early loss of mitochondrial membrane potential and preferential loss of Dcx+ cells from differentiating NPC cultures. Unexpectedly we found that reducing miR-210 reduces proliferation of NPC cells, by blocking the switch to glycolytic metabolism. However, protection of mitochondrial function by reducing miR-210 levels did prevent the inflammation induced death of Dcx+ neuroblasts, and markedly reduced levels of apoptosis. Aconitase activity and cytochrome c oxidase activity were higher with reduced levels of miR-210, and mitochondrial membrane potential was increased.

Conclusions: Our findings identify the immature Dcx+ neurons as exquisitely vulnerable to mitochondrial impairment and demonstrate that mitochondrial protection provides a novel strategy to prevent death of new neurons under conditions of inflammation. These results suggest that reducing miR-210 levels is a potential new protective strategy to improve survival of young neurons during inflammation, such as seen after ischemic brain injury. Overall, altering miR levels may enhance successful neurogenesis and attenuate inflammation injury during post-stroke injury.

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Basic Neuro/Inj 111 (106)
Targeting α5GABAA Receptors to Treat Memory Impairment after Traumatic Brain Injury

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Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Concussion or mild TBI (mTBI) accounts for more than 75% of all TBI, and has an estimated cost of over $17 billion per year in the United States alone. Cognitive impairments, particularly deficits in memory and executive function, are common after mTBI and strongly predict poor long-term functional recovery and loss of independence. The mechanisms underlying these cognitive deficits remain elusive and there are no effective treatments. Previous studies identified γ-aminobutyric acid type A receptors (GABAARs) that contain the ±5 subunit (α5GABAARs) as key mediators of inflammation-induced memory deficits. TBI triggers an intense inflammatory response in the brain that can persist for years after the initial insult. Here, we test the hypothesis that post-traumatic cognitive deficits are caused by increased α5GABAAR activity and that inhibiting α5GABAARs will improve cognitive impairment after mTBI.

Methods: Approval from the local Ethics Committee was obtained and investigators were blinded to the treatment groups. Under anesthesia, a modified free weight drop method was used to produce mTBI in the mice. Cognitive performance was tested in TBI and sham mice (anesthesia only) 1 week after the injury. Memory was assessed by measuring the discrimination ratio in a Novel Object Recognition (NOR) and an Object Place Recognition (OPR) assay (i.e. the ratio of time spent exploring the novel or the displaced object to the time spent exploring both objects). Executive function was assessed with a puzzle box (PB) assay. The role of α5GABAARs was tested by treating mice with a drug that selectively inhibits α5GABAAR function (L-655,708 0.5 mg/kg i.p.). Statistical analyses were conducted using GraphPad Prism 5.0. All values are expressed as mean ± SEM.

Results: After a single brief concussive injury, mice recovered their righting reflex spontaneously and showed no overt impairment of behavior. One week after mTBI, mice exhibited impaired performance in both NOR (Sham: 0.67 ± 0.03; TBI: 0.48 ± 0.02, n = 12-23; $p<0.0001$) and OPR (Sham: 0.54 ± 0.04; TBI: 0.41 ± 0.02, n = 7-17; $p<0.001$) assays. In addition, mTBI mice demonstrated impaired executive function ($F(3, 100)=2.78$, $p<0.05$), short-term memory ($F(2,75)=4.37$, $p<0.05$) and long-term memory ($F(1,45)=7.47$, $p<0.05$) compared to sham animals. Mice treated with L-655,708 showed improved memory performance in both NOR (Vehicle: 0.48 ± 0.02; L6: 0.54 ± 0.03, n = 20-23; $p<0.05$) and OPR (Vehicle: 0.41 ± 0.02; L6: 0.52 ± 0.03, n = 14-17; $p<0.05$) assays. Inhibiting Ð5GABAARs also improved short term memory ($F(2,91)=4.13$, $p<0.05$) but did not reverse executive function or long term memory impairment in the PB assay.

Conclusions: One week after mTBI, mice exhibited impaired memory and executive function performance. Inhibiting α5GABAARs with L-655,708 reversed the memory impairment but not the executive dysfunction. These results suggest that α5GABAARs are novel targets for treatments that aim to improve memory performance after mTBI. The results also support the notion that radio-labelled α5GABAARs (e.g. with [11C] Ro15-4513) may serve as biomarkers in imaging studies for post-concussive memory deficits.

Basic Neuro/Inj 113 (71)
Carbon Monoxide and Isoflurane-induced Neurodegeneration in the Developing Brain

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Background: The majority of commonly used general anesthetics activate the mitochondrial apoptosis pathway in the developing mammalian brain, resulting in widespread neurodegeneration and impaired cognition and behavioral disorders later in life. Carbon monoxide (CO), as a potential neuroprotectant, is of interest because infants and children are routinely exposed to CO during low-flow anesthesia. We have recently demonstrated that low concentrations of CO prevent isoflurane-induced lipid peroxidation and apoptosis in the forebrain of newborn mice in a dose-dependent manner. However, the effect of CO on anesthesia-induced neurodegeneration is unknown. We hypothesize that CO will prevent isoflurane-mediated effects on gross brain size and volume and will preserve neuronal content following a postnatal exposure.

Methods: 7 day old C57Bl/6 mice underwent 1-hour exposure to 0 ppm (air), 5 ppm, or 100 ppm CO in air with or without isoflurane. A separate cohort of 7 day old mice served as unexposed controls. One week or 8 weeks after exposure, we measured body weight and brain weight and determined brain volume via Archimedes' principle. Neuronal content was then estimated in each cohort by performing immunoblot analysis for NeuN in forebrain homogenates. Densities were quantified with chemiluminescence. A total of 5 animals per exposure group per time point were evaluated in order to detect a 10% difference in brain weight with a power of 80%. Statistical significance was determined with two-way ANOVA and post-hoc Tukey's test and was set at $P < 0.05$.

Results: Brain weight, brain volume, and body weight increased significantly overtime in each cohort as would be expected with normal development. However, there was no difference between cohorts at any time point with regard to gross brain weight and brain volume or with brain weight and brain volume normalized to body weight. On the other hand, steady-state levels of forebrain NeuN significantly decreased by 15% in animals exposed to isoflurane with air compared to air-exposed controls suggesting loss of neuronal content. In contrast, steady-state levels of NeuN were unchanged from control values in cohorts exposed to either concentration of CO with or without isoflurane.

Conclusions: Isoflurane exposure appears to induce neurodegeneration without affecting gross brain weight or volume. Furthermore, CO potentially limits isoflurane-induced effects on neuronal content. The lack of effect of isoflurane on overall brain size may be due to compensatory increases in other types of cells, an increase in non-cellular volume (such as CSF), or the lack of a gross effect seen with microscopic cellular loss. Future work will evaluate markers of other non-neuronal cell types and quantify region specific volumes in the developing murine brain following exposure. Our preliminary findings support the concept that low dose CO may protect the developing brain from isoflurane-induced neurodegeneration. These CO-mediated effects could have implications for the development of low-flow anesthesia in infants and children in order to prevent anesthesia-induced neurotoxicity.

Basic Neuro/Inj 114 (82)
Ketamine Modulates GSK-3β-Disc1 Interaction in a Rat Model of Anesthetic-Induced Developmental Neuroapoptosis

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Introduction: Disrupted in schizophrenia-1 (DISC1) is a scaffolding protein whose mutated form has been linked with schizophrenia, bipolar affective disorder and recurrent major depression. Blockade of the N-methyl-D-aspartate receptor (NMDA-R) not only causes neuroapoptosis, aberrant dendritic growth and psychotic behavior, but also decreased DISC1 expression. DISC1 is a known upstream regulator of glycogen synthase kinase-3Ð. In the present study, we tested the hypothesis that ketamine modulates DISC1 expression, which leads to increased GSK-3β activity.

Methods: Neuroapoptosis was measured by cleaved caspase-3 by Western blot and immunohistochemistry. Protein levels of GSK-3β and DISC1 were measured in postnatal day 7 rat pups after 1.5, 3, 4.5 and 6-h exposures to ketamine and a cohort of rat pups subjected to a 6-hour exposure to ketamine with and without the nonspecific GSK-3β antagonist, lithium. Interaction of DISC1 and GSK-3β was determined by co-immunoprecipitation.

Results: Ketamine increased cleaved caspase-3 and decreased DISC1 levels. This corresponded with decreases in phosphorylated GSK-3β, which leads to increased GSK-3β activity. Lithium increased DISC1 levels and mitigated this response. Ketamine also decreased co-immunoprecipitation of DISC1 with GSK-3β.

Conclusions: These findings demonstrate that ketamine-induced neuroapoptosis is associated with a temporal decrease in DISC1. This corresponds to a reduction of DISC1-GSK-3β binding, which leads to increased GSK-3β activity. Given the DISC1 essential role in neurogenesis, differentiation and synaptic maintenance, perturbations in its expression should have an impact on neurodevelopment.

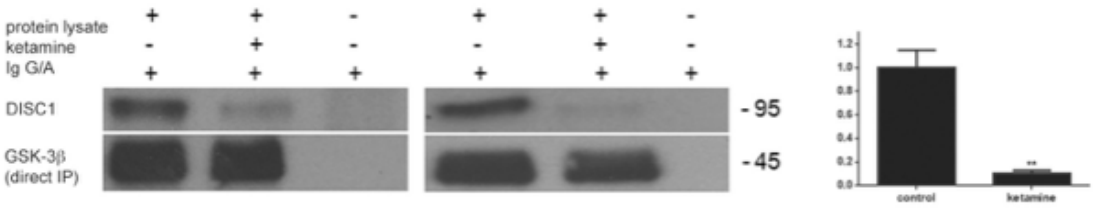

FIGURE: The interaction of DISC1 and GSK-3Ð protein was determined in P7 rat pups treated with ketamine or saline by co-immunoprecipitation (IP). The result showed that Ketamine reduced GSK-3Ð bound to DISC1 protein in the p7 brain. (** $p<0.01$, compared to the negative control).

Basic Neuro/Inj 115 (121)
Genetics of Isoflurane-induced Neurotoxicity

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Introduction: Early developmental exposure to volatile anesthetics leads to anesthetic induced neurotoxicity (AIN) in nematodes, rodents, and primates [1-3]. The precise mechanisms by which anesthetics cause neurotoxicity are unknown. Using an array of genetic mutations, which affect neuronal development, we have taken a genetic approach in C. elegans to identify the molecular mechanisms underlying AIN. We have identified interacting pathways that control AIN and which may be useful to alleviate AIN.

Methods: Chemotaxis. C. elegans L1 larvae were age synchronized and exposed to isoflurane at their EC95s from hours 4-8 after hatching. Larvae were removed from the anesthetic, and grown to adulthood. Chemotaxis on day one of adulthood (day 4 of life) was used as a measure of integrated neuronal function [1]. Preconditioning (PC). Synchronized L1 larvae were exposed to isoflurane at their EC50s for hours 1-2 after hatching, followed by air for 3 hours and then exposure to isoflurane and chemotaxis studies as described above. Rapamycin. Rapamycin (LC laboratories) was dissolved in 100% DMSO at 50 mg/ml and added to plate agar to 100uM with final DMSO concentration of 0.2%. Nematodes were exposed to rapamycin for the first day of life then removed to regular plates and treated as above.

Results: AIN was induced by exposure to the isoflurane at its EC50 for immobilization (6.5%) and a mammalian clinical concentration 2%). Mutations in the insulin-like receptor, DAF-2, induces a stress response and completely attenuates AIN in C. elegans (Figure 1A).

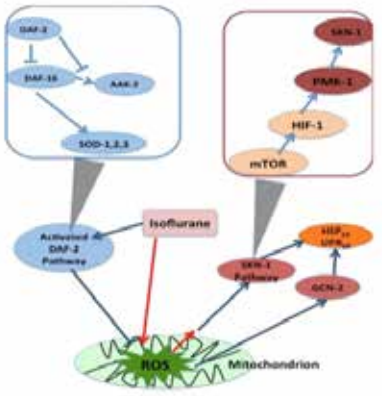

Figure 1. Two intersecting pathways that affect AIN in C. elegans. The grouping on the left of the figure (blue ellipses) represents the DAF-2 pathway which, when induced, is capable of inhibiting AIN. The genes on the right (red ellipses) are activated by ROS, leading to ER-stress, apoptosis and causing AIN. The mitochondrial/ROS isoflurane target is at the bottom in green. The pathways are expanded in the upper inserts.

Studying the downstream targets of DAf-2 identified a pathway (DAF-16, SOD-2, SOD-3, AAK-2) that controls AIN (Figure 1A). In addition, mutations blocking the ER-stress response also eliminated AIN. These included the kinase GCN-2, the heat shock protein HSP-4 and the transcription factors, SKN-1 and HIF-1. Both the target of DAF-2, DAF-16, and HSP-4 were activated by exposure to isoflurane. Preconditioning completely alleviated AIN in the wildtype N2. The DAF-2 pathway and ER-stress interact through the mechanistic target of rapamycin (mTOR). Inhibition of mTOR with rapamycin completely alleviated AIN.

Discussion: The sum of our data earmark two pathways, highly conserved from nematodes to mammals, including mitochondrial dysfunction, ROS generation, and the ER-stress response as key regulators of AIN (Figure). The preconditioning results further indicate that a stress response can be induced by anesthetic pretreatment that protects against AIN. Since isoflurane exposure causes activation of the daf-2 pathway that results in protection from ROS damage, we hypothesize that activation of that pathway leads to protection from AIN. A second pathway, ER-stress, is causative for AIN and inhibition of the pathway completely eliminates AIN. Inhibition of translation with rapamycin eliminates AIN. This suggests several testable mechanisms for potential alleviation of AIN in mammals.

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CS 116 (73)
Cytoskeletal Perturbing Drugs and Their Effect on Cell Elasticity

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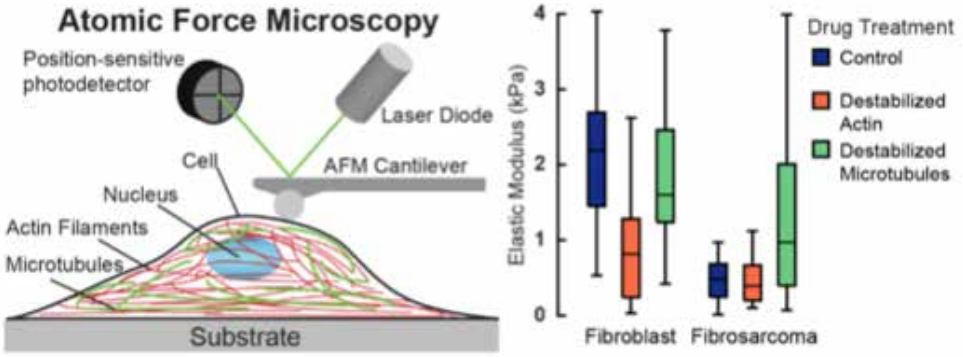
The cytoskeleton is primarily responsible for providing structural support, localization and transport of organelles, and intracellular trafficking. The structural support is supplied by actin filaments, microtubules, and intermediate filaments, which contribute to overall cell elasticity to varying degrees. We evaluate cell elasticity in five different cell types with drug-induced cytoskeletal derangements to probe how actin filaments and microtubules contribute to cell elasticity and whether it is conserved across cell type. Specifically, we measure elastic stiffness in primary chondrocytes, fibroblasts, endothelial cells (HUVEC), hepatocellular carcinoma cells (HUH-7), and fibrosarcoma cells (HT 1080) subjected to two cytoskeletal destabilizers: cytochalasin D and nocodazole, which disrupt actin and microtubule polymerization, respectively. Elastic stiffness is measured by atomic force microscopy (AFM) and the disruption of the cytoskeleton is confirmed using fluorescence microscopy. The two cancer cell lines showed significantly reduced elastic moduli values (~ 0.5 kPa) when compared to the three healthy cell lines (~ 2 kPa). Non-cancer cells whose actin filaments were disrupted using cytochalasin D showed a decrease of 60-80% in moduli values compared to untreated cells of the same origin, whereas the nocodazole-treated cells showed no change in elasticity. Overall, we demonstrate actin filaments contribute more to elastic stiffness than microtubules but this result is cell type dependent. Cancer cells behaved differently, exhibiting increased stiffness as well as stiffness variability when subjected to nocodazole. We show that disruption of microtubule dynamics affects cancer cell elasticity, suggesting therapeutic drugs targeting microtubules be monitored for significant elastic changes.



CS 120 (54)

Modulation of Human Myometrial Anoctamin-1 Attenuates Aontractile Agonist-Induced F-Actin Formation

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Introduction: We previously described that pharmacological antagonism of the calcium-activated chloride channel anoctamin 1 (ANO-1) leads to significant attenuation of human uterine smooth muscle (USM) contractility in vitro and completely abolishes intracellular calcium elevations in human myometrial cells. At a cellular level, USM contractions mechanistically result from actin-myosin cytoskeletal effects including increases in thin filamentous actin (f-actin) formation.1 Inthis study, we questioned if ANO1 antagonism modulates oxytocin-induced f-actin formation.

Methods: Primary human myometrial cells (HuUSM) were grown to 70% confluence on sterile coated coverslips and transfected with a red fluorescent indicator (pCMVLifeAct-TagRFP) of f-actin formation according to manufacturer's recommendations (Ibidi®). Subsequent live cell imaging utilizing confocal microscopy (Nikon Eclipse Ti) allowed for real-time quantitative measurement of changes in f-actin (555/584 nm (Exmax/Emmax)) evoked by contractile agonist (oxytocin 1uM) in the presence or absence (vehicle controls) of the ANO1 antagonist benzbromarone (100uM). Data was compiled and analyzed by student t-test, and $p<0.05$ was taken as significant.

Results: The ANO-1 antagonist benzbromarone (100uM) suppressed oxytocin mediated elevations in f-actin fluorescence [TRITC] by 95.1% + 6.3% ($p < 0.001$, N=7) compared to vehicle controls (N=5).

Conclusions: ANO1 channel modulation exerts positive pro-relaxant effects on thin filamentous actin formation of the contractile apparatus in human myometrial cells. Our results provide exciting evidence that ANO-1 antagonism exerts a pro-relaxant effect at the level of cellular actin-cytoskeletal regulatory mechanisms.

CS 121 (51)
Opposite Effects of Dexmedetomidine and Midazolam on Lung Cancer Cell Biology In Vitro

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Introduction and General Purpose of the Study: There is increasing evidence that inhalational anaesthetics may affect cancer cell biology of renal, prostate and ovarian cell cultures via cell signal pathways including hypoxia inducible factor system [1-3] which may shorten cancer patient long term survival due to cancer recurrence and metastasis reported very recently [4]. Sedatives, e.g. dexmedetomidine, an alpha2-adrenergic receptor (alpha2-AR) agonist, and midazolam, a Benzodiazepines (BZDs) receptor agonist, are often used during surgery for cancer patients. However, their effects on cancer cell biology remain elusive. In this study, non-small cell lung cancer (NSCLC) cultures were used to compare the possible cancer cell biological properties of dexmedetomidine and midazolam.

Methods: Cultured lung adenocarcinoma (A549) cells was treated with dexmedetomidine (from 0.001 to 10 nM) with or without cisplatin (6.0 μg/ml) or midazolam (from 25 to 400 mM). Cell viability, proliferation, migration capability were measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl-2H-tetrazolium bromide (MTT), scratch assay, flow cytometry with Propidium Iodide (PI) staining or in situ immunofluorescence staining.

Results and Major Findings: Dexmedetomidine treatment with the tested doses for 24 hours significantly increased lung cancer proliferation and migration of cells. Dexmedetomidine also increased cisplatin resistance in cells after incubation for 48 hours. Cells treated with both dexmedetomidine and cisplatin had significantly reduced apoptosis compared to those treated with cisplatin alone. Conversely, midazolam decreased cell viability in a dose-dependent manner. Migration capability was also inhibited by 35% at the highest concentration of midazolam ($p < 0.05$). Cleaved caspase 3 was significantly increased by midazolam at 400mM.

Conclusions: Unlike dexmedetomidine, midazolam decreases lung cancer cell proliferation and migration. These opposite effects of both sedatives seen in vitro need to be confirmed in in vivo settings urgently.

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CS 122 (146)
Opsin 3 and 4 Mediate Blue Light-Dependent Pulmonary Vasorelaxation

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Introduction: Pulmonary hypertension is a progressive disease characterized by increase in pulmonary vascular resistance due to both sustained contraction and structural remodeling of the pulmonary arteries, eventually leading to right heart failure. Despite improvements in treatment over the last two decades, mortality rates remain high. In the pediatric population, especially neonates, pulmonary hypertension occurs in the context of cyanotic congenital heart disease and respiratory compromise with failure to transition from the fetal to adult circulation. Drug therapy remains incompletely effective and is limited by side effects, spurring research to discover and characterize novel and effective therapies. We have recently characterized a non-visual opsin (opsin 4 or melanopsin) mediated blue-light induced vasorelaxation in the systemic circulation. In this study, we report the discovery of opsin receptors in the pulmonary vasculature, their signal transduction system, and mechanism of regulation.

Methods and Results: PCR demonstrates the expression of Opsin3/4 in the pulmonary artery (PA) of rats and mice. PA vasoreactivity was examined in vitro by wire myography. Blue light induces vasorelaxation in pre-constricted pulmonary arteries in vitro. Inhibition of G-protein coupled receptor kinase 2 (GRK2) not only amplifies the light-respone, but also prevents desensitization due to repeated exposure to light. Both eNOS inhibition with L-NAME and scavenging of NO with cPTIO did not affect light-mediated vasorelaxation. Inhibition of PDE5 with T1056 did not affect vasorelaxation; however inhibition of both PDE5 and 6 with Zaprinast signifincantly attenuated light-responsiveness. Importantly, in an ex vivo isolated, perfused lung model, blue light mediated photorelaxation of hypoxia-induced pulmonary vasoconstriction.

Conclusions: We demonstrate the presence of opsin3/4 mediated photorelaxation in the pulmonary vasculature. This process is GRK2 and PDE6 dependent and NO independent. Photorelaxation is present in intact, perfused lungs with hypoxia-induced pulmonary vasoconstriction. Together, these findings have profound implications for the use of phototherapy in conjunction with GRK2 inhibition for the treatment of PH.

CS 123 (50)
Contribution of Mitochondrial Oxidative Stress in the Formation of Endothelial-Derived Microvesicles

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Endothelial-derived microvesicles (eMVs), small membrane-bound particles released from the vascular endothelium in response to various stimuli, are known to be elevated and actively involved in many pathological processes including atherosclerosis, acute kidney disease, and sepsis.[1] Our laboratory has recently shown that ceramide, a sphingolipid formed during cellular stress[2], is a potent stimulus for eMV formation when administered to human cardiac microvascular endothelial cells (HMVECs). Further, these ceramide-derived eMVs have detrimental effects on the human microvasculature. When administered intraluminally to human adipose arterioles, they initiate a switch in the mediator of flow-induced dilation (FID) from anti-inflammatory nitric oxide (NO) to pro-inflammatory, pro-thrombotic, hydrogen peroxide (H2O2), the same transition that occurs between health and disease. We have also shown that eMVs generated from plasminogen-activator inhibitor 1 (PAI-1), a known eMV stimulus, are capable of initiating this same switch in vasoactive mediator. Tandem mass spectrometry (MS/MS) analysis revealed that despite protein composition differences, proteins identified in ceramide- and PAI-derived eMVs exhibited strong correlations to mitochondrial dysfunction and oxidative stress. To determine if reactive oxygen species are necessary for the development of ceramide- and PAI-1-generated eMVs, we hypothesized that suppression of cellular and mitochondrial-derived ROS during PAI-1 or ceramide treatment would impair eMV formation. HMVEC-Cs were treated with vehicle (DMSO), C2 Ceramide (15 ?M), PAI-1 (20 ng/mL), or a mitochondrial pro-oxidant (antimycin A; 10?M) for 3hrs in the presence or absence of the cytosolic antioxidant L-phenylalanine-4'-boronic acid (FBA; 10 μM), or the mitochondria-targeted phenylboronic acid (mitoPBA; 100 μM). To quantify eMV formation, flow cytometry was utilized to count CD31/Annexin V+ vesicles. All data is presented as fold change ± SEM versus vehicle. eMV formation was significantly increased in all three treatment groups (3.4±0.7, 2.7±0.6, and 3.7±0.9 in ceramide, PAI-1, and antimycin A, respectively, n=4 all groups, $p<0.05$, one-way ANOVA). In FBA-treated cells, eMV generation was only decreased in cells treated with antimycin A (1.3±0.1 vs. 3.7±0.9, n=3 and 4, respectively), whereas mitoPBA significantly decreased the number of eMVs produced in all treatment groups (0.45±0.1, 0.44±0.1, and 0.55±0.1, in ceramide, PAI-1, and antimycin A, respectively, n=3 all groups). These data suggest that mitochondrial-derived ROS play a critical role in the formation of eMVs generated by ceramide and PAI-1. We conclude that suppression of mitochondrial ROS and subsequent formation of eMVs may mitigate endothelial dysfunction observed in acute and chronic disease.

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Clin Manag 15 (55)

Raman Spectroscopy Differentiates Each Neuraxial Tissue: A Novel Method for Epidural Needle Placement?

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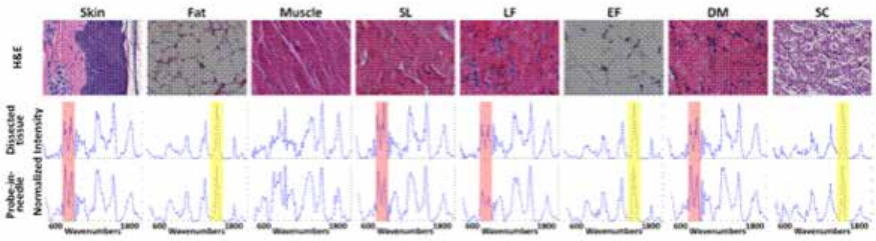
Background: Many medical procedures, including neuraxial anesthesia and epidural steroid injection, use a blind, or semi-blind, approach for needle tip placement. These techniques require precise anatomical targeting to ensure successful and safe analgesia.

Generally regarded as safe, minor complications including wrong tissue injection and dural puncture do occur. The accidental dural puncture rate has been reported to be as high as 6%, and the failure rate for epidural catheter analgesia as high as 22%. Over half of the failures associated with this technique may be due to an inability to accurately locate the epidural space. Fortunately, serious side effects including stroke and spinal cord injury are much less common, but are catastrophic when they take place. As a result of the rare, but serious, complications during epidural corticosteroid injection (ESI), the U.S. Food and Drug Administration convened a panel of experts to determine techniques to decrease their incidence. The loss of resistance (LOR) technique is the most common method of locating the epidural space, but suffers from a lack of specificity.

The combination of diffuse reflectance (DRS), fluorescence (FS), and Raman (RS) spectroscopies, multi-modal spectroscopy (MMS), provides complementary tissue data and has previously been shown to aid tissue identification for various clinical purposes. We hypothesized that MMS may aid neuraxial procedures, and tested the ability of these spectroscopic methods to differentiate individual porcine neuraxial and paravertebral tissues.

Methods: Porcine tissue of the posterior thorax was dissected from skin to spinal cord, and the spectra of individual tissues were obtained using DRS, FS, and RS. Raman spectra were collected during passage of a probe-in-needle through intact paravertebral and neuraxial porcine tissue to test real-time needle tip tissue differentiation. The individual tissues underwent H & E staining and examination by a qualified pathologist. DRS, FS, and RS data collected from dissected tissue were divided into two data sets, one for spectrum analysis and one for tissue identification accuracy, and then analyzed for the ability of each spectroscopy to differentiate the relevant tissues. A machine learning model, using Raman spectra collected during probe-in-needle insertion into tissue, was developed for real-time tissue classification.



Results: Raman spectroscopy shows unique spectra for each tissue type from skin to spinal cord (Figure 1). The epidural space can also be located using RS as epidural fat has a unique RS spectrum compared to the surrounding tissues. Results after examination of the same tissues with diffuse reflectance spectroscopy and intrinsic fluorescence spectroscopy did not show as clear differentiation of tissue types. Tissue type assignments were confirmed by a neuropathologist after H & E staining. Real-time RS spectra of posterior thoracic tissues using a two millimeter (mm) probe-in-needle device were similar to individual tissue results.

Conclusions: This study demonstrates Raman spectroscopy can distinguish all tissues encountered during neuraxial procedures. This technology may prove useful during needle placement by increasing the confidence of its anatomical localization.

Clin Manag 16 (168)
Real Time Compliance Solutions in a Disparate Electronic Medical Record System

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Background: Noncompliant documentation of clinical services can result in improper billing, revenue loss, financial sanctions, and exclusion from government insurance programs. Institutions have addressed billing non-compliance through Information Technology (IT). In many institutions, including ours, a purely IT solution cannot be implemented due to disparate medical record systems and workflow challenges. Therefore, we developed a real-time 100% documentation compliance audit system blending IT solutions with direct staff interaction.

Methods: Real-time interventions were developed and implemented (in collaboration with compliance specialists, clinical staff, and IT professionals) in October 2015 with an initial focus on anesthetic record generation and postoperative evaluation documentation. First, to ensure that staff had appropriate and timely information to intervene, we used institutional IT systems to identify missing postoperative documentation. Further, a software application was developed to identify incomplete anesthetic records. Leveraging these IT systems, two compliance staff members conducted real-time audits during normal business hours and contacted the anesthesia care team directly when non-compliance was identified. Initial contact was to the resident or CRNA. If these team members failed to respond, the attending anesthesiologist of record was contacted. If action was not taken within 2 h, the audit supervising attending anesthesiologist was contacted to maintain compliance. Educational materials were developed for compliance staff, a Ground Rounds presentation and faculty presentation were given regarding these interventions, and constant feedback to providers was given by the supervising attending anesthesiologist. Rates of non-compliance during the intervention period were calculated and presented per 1,000 cases.

Results: Between October 12, 2015 and January 9, 2016 a total of 655 compliance interventions were made on a case volume estimated to be 12,399 cases: 319 (48%) did not transmit properly to the EMR, 255 (39%) related to postoperative evaluation documentation, 48 (7.3%) related to pre/post-operative vital signs documentation, and 8 (1.2%) related to electronic signature. The rate of successful compliance interventions for monitored items ranged from 12.6 to 80.9 per 1,000 cases. A greater number of interventions were noted at study initiation and again as monitoring was expanded beyond postoperative notes (Figure 1). A similar trend was identified for missed non-compliant cases (range: 1.0 to 21.9 per 1,000 cases). Of missed non-compliant cases, 49% occurred outside normal hours, bypassing our intervention system.

Conclusion: Compliance initiatives must include buy-in and education of clinical staff, and requires empowerment and collaboration with compliance staff members and IT experts to monitor compliance to take real-time action. Real-time notification of non-compliance successfully yielded a 0.7% failure rate on these elements. A limitation to the system described includes lack of staffing coverage beyond normal hours. Additional compliance elements can be integrated into this real-time compliance system in the future to improve compliance with documentation of all seven measures of anesthetic care.

Clin Manag 17 (172)
Proposed Anesthetic Management for Embolization of an Antenatal Hepatocellular Adenoma

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Introduction: Hepatocellular adenomas, are also known as hepatic adenomas or liver cell adenomas, are uncommon benign tumors of the liver that occurs particularly in women during their reproductive years. Histologically, they are of presumable epithelial origin and occur in less than 0.004% of the population at risk [1]. The majority of neoplastic liver masses in non-pregnant patients are malignant [1]. In contrast, masses identified during pregnancy are more commonly benign. In United States, hepatocellular adenomas are extremely rare. The annual incidence is 1 to 1.3 cases per 1 million persons per year [1]. There are numerous papers describing when to manage these subset of patient medically as well as when to intervene surgically. However, in our literature review, there is little data that offers suggestions regarding the intraoperative anesthesia management. We would like to propose the use of a Neuraxial anesthesia for a patient with multiple hepatocellular adenomas's presenting during the 2nd trimester of pregnancy for embolization of multiple enlarging hepatocellular adenomas.

Case Presentation: Details in PDF saved version

Discussion: Hepatocellular adenomas occur mostly in women of childbearing age and are strongly associated with the use of oral contraceptive pills (OCPs) and other estrogens. This is reflected by a dramatic increase in the incidence of this disease since OCPs were introduced in the 1960s [1]. However, in women using OCPs, adenomas were more common in patients taking OCPs containing higher doses of estrogen and with prolonged use (73.4 m) when compared with matched controls (36.2 mo) ($P < 0.001$) [2]. A 5-fold increased risk exists with 5-7 years of OCP exposure, and a 25-fold increased risk exists with longer than 9 years of OCP exposure [1].

In a case series of 3 patients, Baum et al suggested an association between hepatic adenomas and OCPs [3] Klatskin [4] and Rooks et al [5] reported that the greatest risk occurs in women older than age 30 years taking OCPs for longer than 5 years, but in 10% of patients, exposure may be as short as 6-12 months. Cherqui et al also reported that adenomas are occasionally diagnosed after discontinuation of OCPs [6].

Liver masses in pregnancy are rare. A precise incidence is difficult to define as many are asymptomatic and symptoms may be attributed to gestation. Etiologies range from infectious to neoplastic, presenting a unique diagnostic challenge to the clinician and creating a number of difficult decisions regarding management [5]. Certain masses can behave more aggressively in gestation. Pregnancy itself limits the diagnostic modalities and interventions may be associated with greater risk [7]. While there is an abundant literature addressing benign hepatic masses, the scarcity of case series regarding anesthetic management of hepatocellular adenomas during gestation has left the anesthesiologists with little data to develop an evidence-based algorithm for their evaluation and management of such patients [6].

Pregnancy has been associated with hepatic adenoma, and rupture of the adenoma during pregnancy has been associated with high rates of maternal and fetal mortality [8]. In the literature, the maternal and fetal mortality risks of ruptured hepatocellular adenomas during pregnancy have been reported to be 44 and 38% respectively [7]. However, all these cases were published in the 1970s or 1980s, in which there might have been a delay in diagnosis as the entity of ruptured HCA was not well known and less advanced imaging methods were used[9].

In the recent years the widespread use of highly advanced image modalities has probably decreased the delay in the diagnosis of hepatocellular adenomas and the associated maternal and fetal mortality significantly[10]. The hormone-induced growth and risk of rupture seemed to be highest during the third trimester of pregnancy, most probably because of the cumulating level of estrogens and an increase in the hyperdynamic

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Proposed Anesthetic Management for Embolization of an Antenatal Hepatocellular Adenoma

circulation combined with an increase in vascularity of the liver [11,12].

Nearly 20-25% of cases have right upper quadrant pain, and 30-40% experience hemorrhage (one third within the mass, two thirds into the abdomen)[13,14]. In a systematic review including a total of 1176 patients, the overall frequency of hemorrhage was 27.2% among patients. Hemorrhage occurred in 15.8% of all hepatocellular adenoma lesions. Rupture and intraperitoneal bleeding were reported in 17.5% of patients [15].

Although a tumor size of 5 cm is the standard for resection owing to the increased risk of hemorrhage and malignant transformation, multiple case series have reported hemorrhage in sizes less than 5 cm, even as small as 1 cm [15,16]. The risk, though, appears to be minimal. The risk of hemorrhage appears to be related to size and not related to the number of lesions.

The mortality rate associated with an acute hemorrhage into the peritoneum may be as high as 25-30% in patients with large tumors [16].

The risk of malignant transformation is not completely known and may be as high as 13% based on small studies [15]. A recent systematic review incorporating all reports on malignant degeneration of hepatocellular adenoma into hepatocellular carcinoma showed an overall risk of 4.2%, with only 4.4% of these malignant transformations occurring in lesions less than 5 cm in diameter [17].

If a woman has large tumors or has experienced complications of hepatocellular adenomas in previous pregnancies, an intervention (surgery, RFA, embolization) should be recommended before or during pregnancy [9]. Intervention during pregnancy may be associated with greater risk for both mother and child. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) provided guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy [18,19]. These guidelines suggest that the laparoscopic approach should be preferred instead of laparotomy in most abdominal operations [12]. Timing of surgical intervention must be based on balancing better fetal outcomes in the second and third trimester with the perceived maternal risk [20]. However, no suggested guidelines for anesthetic evaluation and management of HCAs patients have been documented in any of the reviewed articles.

Careful intra-partum follow-up is crucial and resection needs to be considered for rapid tumor enlargement[13]. Therefore, close guidance of and monitoring of the hepatic adenoma by liver ultrasound every 6 weeks during pregnancy are strongly advocated [14].

Conclusion: Based on our literature investigation on hepatic masses during pregnancy and with our own current experience in developing a multidisciplinary anesthetic approach to the management of our patient with hepatocellular adenomas, has allowed us to get a basic understanding of managing such patients peri-operatively. Hepatic masses during pregnancy can present with serious diagnostic and management predicaments. Gestation can alter the natural history of these lesions and may increase the risk of any interventions. During the process, we had to weigh the risks and benefits of general anesthesia versus regional anesthesia; where in this case, it was decided to proceed with neuraxial anesthesia with sedation, in order to avoid any harmful effects of the general anesthesia to the patient and the fetus. Despite our patient showing small hepatocellular adenomas, less than 5cm, it was recommended that patient undergo IR embolization given the increased growth during a short time frame and possible rupture at the time of delivery. In cases where an intervention is indicated, minimally invasive procedures should be considered, especially in smaller lesions [5]. An intervention is safest in the 2nd trimester[1,12]. Close monitoring by liver ultrasound every 6 months should offer adequate information for surveillance of the hepatic lesion before and after an intervention [5].

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Clin Manag 17 (172)
Proposed Anesthetic Management for Embolization of an Antenatal Hepatocellular Adenoma

Our recommendation would be to always review the history of the patient including the co-morbidities, weigh in the risks and benefits of different anesthetic modalities, for example, general versus regional anesthesia, when taking care of such patients with hepatocellular adenomas. Thus, providing a multidisciplinary anesthetic approach for the safety of the patient and the fetus. We strongly advocate regional anesthesia for anesthetic management for patients with hepatocellular adenomas presenting during 2nd trimester of pregnancy for embolization of enlarging hepatocellular adenomas. Regional anesthesia is not completely devoid of complications, however, in comparison to general anesthesia, it offers a safer risk profile with slow controlled titration of anesthetic medications with spontaneous ventilation. Here at our institute, after managing this current case, we are in the process of generating a mini case-series to be presented at a future meeting.

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Clin Manag 18 (40)
Intracardiac Thrombosis Associated with Cardiopulmonary Bypass: Index Case and Review of Case Reports

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Introduction: Acute intracardiac thrombosis following cardiopulmonary bypass (CPB) is a life threatening event, but the literature is scarce due to its rarity and underreporting. 34 cases of intracardiac thrombus were identified in 2011 but pathological mechanisms are not yet well understood.(1) We have recently experienced a case of intracardiac thrombosis, which prompted an updated literature review to better understand the factors associated with a post-CPB hypercoagulable state.

A 32-yr-old male presented with type A aortic dissection of the ascending aorta and arch. The patient underwent a hemiarch replacement under CPB (204 min) with deep hypothermic circulatory arrest (33 min). Epsilon aminocaproic acid was infused during CPB at 1 g/hr without a bolus dose. After CPB, platelets (1 U), and cryoprecipitate (90 ml) were transfused, and infusion of PCC was started as heparin was being reversed with protamine. During PCC administration (560 IU), the patient developed profound hypotension and right heart failure. TEE revealed right and left atrial thrombi for which CPB was reinstituted for thrombectomy.

Methods: A search was conducted using PubMed/ SCAHQ archives using the key words: "intracardiac thrombosis", "thrombus", "cardiopulmonary bypass", "embolism", and "cardiac surgery" with publication date after 2011. Pediatric CPB, adult non-CPB, VA/VV ECMO and cases without adequate clinical details were excluded.

Results: There were 11 cases that met inclusion criteria and our institutional case brought the total to 12, which were combined with the previous 33 cases identified for a final tally of 45 cases. The most common presentation was elevated pulmonary artery pressures. A total of 23 patients had a history of heart failure, 22 cases had CPB runs greater than 120 minutes, and 35 cases reported the use of an antifibrinolytic. The majority of patients did not survive the acute event.

Conclusions: Putative risk factors for intracardiac thrombosis includes antifibrinolytic use, bypass > 2 hours, heparin resistance and congestive heart failure(1) CPB induces an inflammatory state resulting in activation of thrombin, a strong procoagulant, with continuing dilution of endogenous anticoagulants.(2,3) Increased thrombin generation is reported in aortic dissections during CPB,(4) and hemostatic intervention after heparin reversal can induce hypercoagulability due to lack of endogenous coagulation inhibitors.(1) PCC-related thrombosis is reported to have an incidence of 1.4%, but the risk may be higher after prolonged CPB with hemodilution.(5)

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Clin Manag 19 (76)

Autonomic Dysreflexia in a Patient with a Recent Cervical Spine Injury Resistant to Conventional Therapy

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A fifty-nine-year-old morbidly obese male, quadriplegic following a motor vehicle accident seventeen days previously, presented for cervical laminectomy and fusion (C2-C7) with neuro-monitoring. He had a history of hypertension, diabetes mellitus 2, and a drug-eluting stent placed eleven months previously. Following beta blockade, a dexmedetomidine infusion was started. Local anesthesia was injected prior to arterial line cannulation. Hypertension to 200/80 occurred immediately, and proved to be resistant to fentanyl, midazolam, sevoflurane, and multiple doses of nifedipine and captopril over four hours. At that point, the blood pressure acutely decreased to 80/50, responsive to phenylephrine boluses. The remainder of his perioperative course was unremarkable. We discuss the anesthetic considerations of spinal cord injury, management of autonomic dysreflexia, and importance of educating patients and their families.

Clin Manag 20 (119)
Neonatal Intensive Care to Operating Room Handovers: What We Have Learned from Observation

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Introduction: Failures of communication are a major contributor to perioperative adverse events. Transitions of care may be particularly vulnerable, particularly for complex ICU patients. The demands of system-level support by multiple providers, complex medical regimens and rapidly changing physiologic conditions increase the risk of communication errors and adverse events [(1)]. Neonatal patients are especially susceptible to medical errors and events due to their limited physiologic reserve, fluctuating body weight, and inability to communicate [(2)]. While there has been appreciable research on improving the care transition from the OR to the ICU, the ICU-to-OR handover has been understudied.

Methods: We observed 60 NICU-to-OR handovers to ascertain current handover practices, including the participants involved, handover content, as well as barriers and facilitators of effective handovers. We rated these handovers based on several factors including length of handover, completeness of content, providers present, handover tools utilized and an overall global effectiveness score. We also observed for near misses and non-routine events. A non-routine event is any deviation from a patient's optimal care path, which, if uncorrected, may lead to an adverse event [(3)].

Results: The observations identified numerous barriers and facilitators to effective NICU-to-OR handovers notably including infrequent prior notification, infrequent structured verbal handovers, unclear roles and responsibilities, lack of a hard stop, frequent interruptions and distractions, lack of necessary transport equipment and absence of attending physicians. On average, handovers lasted 17.25 minutes with many critical items being missed during the handover (weight, consent, allergies, NPO status, past medical history, 24 hour events, medications due, disposition plan, post-operative respiratory support plan and whether there were any questions). In only 9/60 observations (15%) were all critical items discussed. The average score of handovers was 2.9 on a 5-category Likert-type scale. Forty-one cases (68.3%) experienced non-routine events or near misses. Memory was used exclusively in 32/60 (53.3%) handovers.

Conclusions: This study identified issues with NICU-to-OR care transitions that have not been documented previously. These findings highlight the current deficiencies, key areas for future research, and potential interventions to improve the preoperative handovers of neonates.

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Clin Manag 27 (124)
Surveying ICU Nurses Regarding Perspectives on Patient Communication

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Introduction: ICU patients have a concerning incidence of depression, anxiety, and post-traumatic stress disorder.[1] For mechanically ventilated (MV) patients, these issues may be compounded by the inability to speak. Some data suggest that engaging in communication with MV patients is also frustrating for caregivers, particularly ICU nursing staff.[2] As part of a project to develop advanced communication technology for these patients, we delivered a survey to ICU nurses across several settings about provider needs and perceptions.[3] The results of this survey will contribute to the final design of a proposed communication system.

Methods: After IRB approval and an introduction to the project through a brief presentation, a total of 334 bedside nurses in 6 ICU settings (2 Neuro ICUs, 1 Medical/Surgical ICU, 1 Surgical ICU, 1 Medical ICU, and 1 Respiratory Acute Care Unit) at 2 tertiary care academic medical centers are being administered a 10-12 minute anonymous online survey (REDCap [4]). The survey remains open for two weeks. The questions in the survey include whether nurses could understand MV patients (and have sufficient time to do so); whether these patients and their family members are satisfied with existing communication methods; and whether nurses experience avoidance or frustration when engaging with these patients. Future potential design features of a novel communication system are also a focus of the survey.

Results: Analysis from the first surveyed hospital (n=204 nurses in 4 settings) is presented here. Thirty percent of nurses overall started the survey, and 25.5% of nurses completed it. The nurses were highly experienced (17.3 +/- 12.2 years of experience), with the majority of work experience in critical care (14.0 +/- 11.3 years on average).

Nurses were dissatisfied with their ability to communicate with and understand MV ICU patients. Eighty percent of nurses disagreed with the idea that communication methods in use for intubated ICU patients were sufficient. Forty-two percent of nurses disagreed with the statement "I can understand most ICU patients who are unable to speak", while only 2.0% strongly agreed. Eighty percent of nurses agreed with the statement: "Most ICU patients have difficulty communicating their needs when unable to speak", and 63% disagreed with the statement that "Most non-speaking ICU patients are satisfied with the methods of communication used in the ICU" (with another 31% not sure).

Fewer than 40% of nurses agreed that they were completely comfortable communicating with a non-speaking patient, and more than half noted that they avoided some contact with patients who were difficult to understand.

Conclusions: There is an urgent need to improve the ability for patients on mechanical ventilation to communicate with their ICU caregivers. Future research should be directed at the development of assistive communication technology, including how this technology might improve patient outcomes.

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Clin Manag 28 (126)
Designing a Novel Manual Communication System for Mechanically Ventilated ICU Patients

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Introduction: Current research shows that the existing methods for mechanically ventilated (MV) ICU patients to communicate are insufficient. While a number of basic communication methods are often tried with these patients (such as writing on whiteboards/ clipboards, use of letter boards, and mouthing words), patients and caregivers consistently report dissatisfaction with available methods and limited success in their use.[1] Furthermore, patients consider the lack of successful communication strategies to be extremely stressful.[2] The ICU setting is more complicated for assistive communication technology use than other settings due to patient population heterogeneity; variation in individuals' physical/cognitive capabilities over time; robustness and hygiene concerns for communication tools; and a lack of available training time prior to patients' need for communication assistance.

Methods: We are developing a communication system that is easily accessible by MV patients who lack sufficient dexterity to write clearly due to complications of critical illness. Using this novel system, a patient will manually operate a hand-held component that communicates in real time with a tablet computer, producing audiovisual content specific to ICU patient needs. Three sets of system requirements have guided the design of this technology: features required by the ICU setting, by the patient, and by the nurses/care team. Features required by the ICU setting include the presence of ICU-specific topics and cost-effective design that is appropriately hygienic. The patient-related system requirements involve a short learning curve; hardware and software that is adaptable to individual patients; and inclusion of non-medical topics of value to patients and their families. Synthesized speech output and some form of tactile feedback are also planned for the final system version to meet patient needs. In considering the requirements of the nurses and care team, the system should be accessible despite physical restraints and should demonstrate a patient's level of responsiveness, allowing for a clearer assessment of a patient's cognitive state.

Results: This system has been demonstrated in its prototype form to physicians, nurses, researchers, and engineers. Based on their feedback, we have prepared more than a dozen improved versions of the device in preparation for deployment with MV ICU patients. Figure 1 shows the design of the communication device in its current version. The system will undergo proof-of-concept testing in a pilot trial in MV patients.

Conclusions: Existing communication methods for MV ICU patients do not meet the emotional and logistical needs of these patients. We are designing and testing a new communication system with the goal of allowing MV ICU patients to communicate despite a variety of physical impairments.

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Neuro Clin 32 (104)
Cerebral Hyperemia Following Circulatory Arrest in Humans

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Introduction: Deep hypothermic circulatory arrest (DHCA) is commonly employed to facilitate surgery on the aorta and great vessels. Although cooling dramatically reduces the cerebral metabolic rate, it does not prevent the occurrence of ischemia, which can be documented by electrophysiologic and metabolic markers after as little as 15 minutes.[1] The availability of non-invasive qualitative measures of relative changes in cerebral flow (cerebral flow index-CFI) allow the assessment of the hemodynamic effects of this ischemia.

Methods: Eight patients undergoing DHCA were monitored for cerebral flow index (CFI) using c-FLOW monitors (Ornim, Inc.). CFI was recorded continuously and averaged in1 minute epochs throughout cardiopulmonary bypass (CPB) and DHCA. The pre-arrest baseline CFI was determined after cooling was complete and before beginning DHCA. The duration of DHCA was measured, and the time and value of the peak CFI after beginning reperfusion were recorded. Duration of hyperemia was measured from the beginning of reperfusion until CFI returned to pre-arrest baseline or began to increase due to rewarming. Duration of cooling prior to arrest and other aspects of case management were based on routine clinical care practices.

Results: 6 patients had retrograde cerebral perfusion during the arrest period, one had “whole body retrograde”, and one had no form of cerebral perfusion. One patient underwent 2 periods of circulatory arrest. The temperature at the start of DHCA averaged 20.4oC. The duration of DHCA averaged 29 minutes (range 20-56). On average, the peak CFI during reperfusion was 16% greater than the value before arrest (range 7-24), $P<0.01$. The time from the beginning of reperfusion to peak CFI ranged from 2 to 14 minutes, with an average of 6 minutes. The duration of hyperemia varied from 6 to 22 minutes with an average of 12.9 minutes.

Conclusions: These results demonstrate the occurrence of cerebral hyperperfusion following DHCA, even when retrograde perfusion is utilized. Hyperperfusion following ischemia has been associated with poor outcomes in both carotid endarterectomy and cardiac arrest[2,3], suggesting that this phenomenon should be avoided. Thus optimal management may require modifying perfusion parameters during the early stage of reperfusion in order to limit hyperperfusion.

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Neuro Clin 33 (173)

Tissue Damage Induced Perioperative Inflammation is Associated with a Greater Risk of Postoperative Delirium in Elderly Patients Undergoing Spine Surgery: A Prospective Observational Study

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Introduction and General Purpose: Postoperative delirium (POD) is a common and severe complication in elderly surgical patients. Although perioperative inflammation appears to play a significant role[1], there is an urgent need to further clarify the pathophysiology of POD. We hypothesized that greater surgical tissue damage is associated with a greater incidence of POD within 3 days after spine surgery in elderly patients. We also hypothesized that perioperative inflammation mediates this association.

Cytokine	Threshold [pg/mL]	Baseline [pg/mL] Q50(IQR)		Intraoperative [pg/mL] Q50(IQR)		Postoperative [pg/mL] Q50(IQR)	
IL-1β	0.98	1.66 (1.22-1.91)	1.17 (1.11-1.74)	1.27 (1.21-1.72)	1.42 (1.18-2.04)	1.38 (1.17-2.38)	1.46 (1.11-2.05)
IL-2	0.98	2.35 (1.24-2.81)	1.99 (1.50-3.72)	2.12 (1.51-3.38)	1.85 (1.33-2.92)	1.82 (1.203.14)	2.22 (1.52-4.38)
IL-5	0.98	1.62 (1.07-2.23)	1.70 (1.26-2.71)	1.37 (1.17-2.32)	2.17 (1.52-3.10)	1.70 (1.26-2.43)	2.13 (1.31-2.92)
IL-6	0.36	0.90 (0.71-2.10)	0.97 (0.65-1.95)	1.33 (0.59-1.66)	0.96 (0.71-1.69)	39.68 (23.71-112.63)	13.53 (2.50-27.10)
IL-8	0.98	3.66 (1.99-5.06)	3.35 (2.28-4.87)	4.25 (2.44-8.03)	2.97 (2.13-4.76)	8.99 (5.17-18.72)	4.66 (3.06-6.18)
IL-10	2.93	6.51 (4.24-7.85)	4.59 (3.76-7.01)	6.00 (4.38-18.43)	12.56 (4.59-17.64)	7.50 (4.27-12.18)	7.19 (4.01-11.27)
IL-12	0.98	1.49 (1.26-1.82)	2.18 (1.52-3.32)	1.85 (1.15-2.66)	1.88 (1.41-3.16)	1.17 (1.05-2.04)	2.24 (1.58-3.97)
IL-13	0.49	1.90 (1.31-4.54)	2.8 (1.40-8.08)	1.96 (0.79-5.91)	2.68 (1.29-6.32)	1.25 (0.78-6.02)	2.92 (1.63-5.79)
IL-17	1.46	2.12 (1.67-6.57)	3.75 (2.95-6.90)	9.09 (1.78-22.83)	2.91 (2.21-5.72)	7.33 (2.95-50.16)	2.92 (2.17-4.67)
IL-23	15.07	48.28 (19.55-156.44)	40.43 (26.82-56.31)	40.75 (28.13-86.52)	47.05 (34.33-82.30)	47.41 (24.54-138.80)	45.10 (28.36-96.72)
TNFα	0.85	2.21 (1.15-3.82)	1.56 (1.15-2.94)	1.50 (1.06-2.48)	2.03 (1.30-3.0)	2.09 (1.43-2.72)	1.56 (1.08-2.75)
IFNγ	1.22	4.08 (3.36-7.16)	3.85 (2.51-7.85)	4.52 (3.18-8.29)	4.98 (2.84-8.43)	5.67 (1.87-8.19)	3.03 (2.12-6.32)
		POD	No POD	POD	No POD	POD	No POD

Table 1
Cytokine plasma concentrations in pg/mL at baseline, intraoperatively (1 hour after incision), and postoperatively (1 day after surgery)

Methods: This is a prospective observational study conducted at Columbia University Medical Center between December 12, 2014, and November 6, 2015. All subjects aged 65 and older scheduled for elective spine surgery during that period were approached. We used the Confusion Assessment Method (CAM) to identify patients with POD within 3 postoperative days (2). The degree of tissue damage was approximated based on the number of intervertebral levels requiring surgical correction. In addition to demographic and medical data, we collected blood samples serially at baseline, one hour after incision, and one day after surgery to measure plasma levels of 12 cytokines (table 1). All samples were sent to an independent laboratory for blinded analyses using multiplex quantitative methods. We summarized the data using standard descriptive statistics. To test our hypothesis, we built explanatory multivariable logistic regression models sequentially introducing potential inflammatory mediators.

Results: 26 out of 81 (32%) patients met CAM criteria for postoperative delirium. Greater surgical tissue damage was significantly associated with POD (Q50: 2.0 vs. 2.5 levels, IQR: 1.0-3.0 vs. 2.0-6.0, p=0.019). This effect remained significant after adjustment for age and baseline cognitive performance (adjusted OR for delirium per additional intervertebral level: 1.51, p=0.007). Defining major spine surgery as any procedure of at least 3 intervertebral levels, greater tissue damage was associated with greater postoperative median concentrations of TNF? (2.29 vs. 1.24 pg/mL, p=0.010), IL-6 (30.84 vs. 13.65 pg/mL, p=0.005), and IL-8 (8.49 vs. 4.25 pg/mL, p=0.003). Comparing patients with and without POD, greater postoperative median concentrations of IL-6 (39.68 vs. 13.53 pg/mL, p=0.001) and IL-8 (8.99 vs. 4.66 pg/mL, p=0.002) were associated with a worse outcome. On the other hand, greater median concentrations of IL-12 at baseline (1.49 vs. 2.18 pg/mL, p=0.015) were also associated with a better outcome. Such effects remained significant after adjustment for age and baseline cognitive performance. Both IL-6 and IL-8, but not IL-12, appeared to at least partially contribute to the observed relationship between the degree of tissue damage and POD.

Conclusions: Greater tissue damage during spine surgery is associated with both a greater increase in pro-inflammatory cytokines and a higher incidence of POD in elderly patients.

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Neuro Clin 34 (174)

Perioperative Anesthetic and Surgical Risk Factors Associated with Postoperative Delirium In Elderly Patients Undergoing Elective Spine Surgery: A Prospective Observational Study

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Introduction and General Purpose: Postoperative delirium (POD) is a common and severe complication in elderly patients following various surgical procedures [1]. Although several demographic and medical risk factors have been associated with delirium following spine surgery [2], we aimed to assess whether anesthetic and surgical management also affect the risk of POD in this population.

Methods: This is a prospective observational study conducted at Columbia University Medical Center between December 12, 2014, and November 6, 2015. All subjects aged 65 and older scheduled for elective spine surgery during that period were approached. We screened for postoperative delirium using the Confusion Assessment Method (CAM) [3]. We used the CAM and CAM-ICU instruments to assess patients daily while in hospital, and the FAM-CAM instrument for those discharged within three days after surgery. All study subjects were assessed by a trained investigator, who reviewed all results with the principal investigator. Before surgery, in addition to acquiring demographic and medical data, we also assessed cognitive performance using the Telephone Interview Cognitive Status (TICS) instrument. We collected intraoperative and postoperative data from electronic medical records (EMRs) and Sedline electroencephalographic (EEG) monitors.

Variable	Patients with POD (N=26)	Patients without POD (N=55)
Age [years], Q50 (IQR)	72.5 (69-77)	71.0 (66-74)
Male gender, N (%)	13 (50.0)	36 (65.5)
BMI [kg/m^2], Q50 (IQR)	27.2 (26.3-31.7)	27.3 (25.4-30.9)
Graduate level of education, N (%)	7 (26.9)	24 (43.6)
Subjective memory loss, N (%)	9 (34.6)	15 (27.3)
TICS score [points/40], Q50 (IQR)	23.5 (20.0-29.0)	28.0 (25.0-32.0)
Independent for ADLs, N (%)	15 (57.7)	16 (29.1)
Preoperative NRS [severity], Q50 (IQR)	6.0 (3.3-7.8)	4.0 (1.0-6.0)
Pain for more than 3 months, N (%)	23 (88.5)	38 (69.1)
Hypertension, N (%)	21 (80.8)	41 (74.5)
Diabetes mellitus, N (%)	6 (23.1)	14 (25.5)
Obstructive sleep apnea, N (%)	4 (15.4)	9 (16.4)
History of cancer, N (%)	3 (11.5)	15 (27.3)
History of coronary disease, N (%)	5 (19.2)	10 (18.2)
History of stroke or TIA, N (%)	5 (19.2)	3 (5.5)
Taking aspirin, N (%)	12 (46.1)	23 (41.8)
Taking steroids, N (%)	1 (3.9)	7 (12.7)
Taking statin, N (%)	18 (69.2)	36 (65.5)
Taking fish oil, N (%)	12 (46.1)	16 (29.1)
Taking vitamin D, N (%)	16 (61.5)	33 (61.1)
Major surgery, N (%)	16 (61.5)	18 (32.7)
Min. SBP [% baseline], Q50 (IQR)	63.7 (56.5-70.2)	67.8 (60.9-75.2)
Min. DBP [% baseline], Q50 (IQR)	62.13 (53.6-72.6)	69.5 (62.5-77.6)
Min. MAP [mmHg], Q50 (IQR)	62 (56-67)	65 (61-70)
Min. Hemoglobin [g/dL], Q50 (IQR)	10.4 (8.6-11.0)	11.4 (9.5-12.4)
Min. Hematocrit [%], Q50 (IQR)	31.7 (26.8-33.0)	34.7 (27.8-38.2)
Estimated blood loss [mL], Q50 (IQR)	725 (450-1275)	250 (100-600)
Intraoperative transfusion, N (%)	5 (19.2)	5 (9.1)
Admitted to the ICU, N (%)	8 (30.8)	3 (5.5)
Min. SBP on POD1 [% baseline], Q50 (IQR)	73.7 (63.5-82.2)	81.1 (73.5-91.7)
Min. DBP on POD1 [% baseline], Q50 (IQR)	67.2 (57.6-83.6)	79.9 (69.3-88.4)
Min. Hemoglobin [g/dL], Q50 (IQR)	10.4 (8.9-11.0)	11.7 (9.9-12.7)
Min. Hematocrit [%], Q50 (IQR)	30.9 (26.9-33.2)	34.5 (29.4-36.6)
Max. NRS on POD1 [severity], Q50 (IQR)	5 (4-8)	3 (1-5)
Hydromorphone on POD1 [mg], Q50 (IQR)	4.7 (3.2-8.5)	4.8 (2.2-8.4)

Table 2
Preoperative, intraoperative, and postoperative characteristics of the cohort

Results: 26 out of 81 (32%) patients met CAM criteria for postoperative delirium. As summarized in table 1, patients with POD had worse cognitive performance and needed more help at home at baseline. Overall, although they underwent more extensive spine surgery lasting longer and causing greater estimated blood losses, they were not more likely to receive blood products during surgery. In patients with POD, both intraoperatively and during follow up, several variables associated with oxygen carrying capacity such as blood pressure or hematocrit/hemoglobin measurements appeared not only to decline more sharply, but also to remain low longer. Interestingly, intraoperative EEG burst suppression was more commonly observed in patients with POD. Finally, despite reporting greater postoperative pain scores, patients with POD did not receive more analgesics except when admitted intubated and sedated in the ICU.

Conclusions: We identified 10 risk factors associated with POD in elderly patients undergoing elective spine surgery. In the future, such clinical markers may be combined with biological markers. These markers may be used to design a predictive scale identifying subjects at risk for developing POD, who may benefit from prophylactic measures.

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Neuro Clin 35 (175)
EEG Slowing and the Recovery from Postoperative Delirium

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Introduction: Delirium in the postoperative period is common, underdiagnosed, and linked with a greater risk of morbidity and mortality. Electroencephalography (EEG) may allow objective measures for predicting the incidence and course of delirium. In small case-control studies, slowing in the frontal-occipital EEG distinguishes delirious and non-delirious surgical patients [1]. It is not known whether this EEG slowing evolves as surgical patients recover from delirium. For this pilot study, we hypothesized that delirious patients would show EEG slowing compared to non-delirious patients, with a shift of power toward higher frequency bands during resolution of symptoms, as seen with metabolic encephalopathies[2].

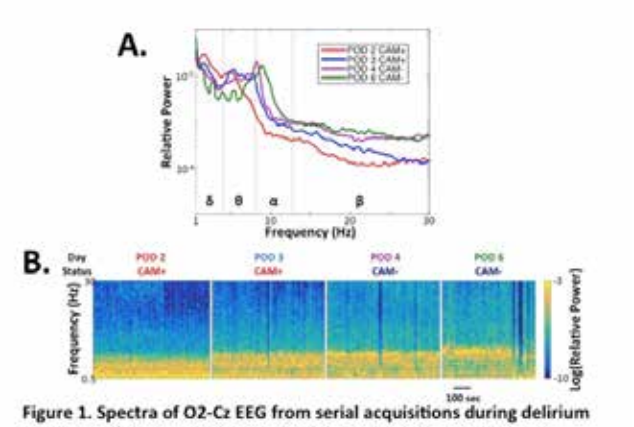

Figure 1. Spectra of O2-Cz EEG from serial acquisitions during delirium resolution. (A) Eyes Closed Spectra. (B) Eyes Closed Spectrogram.

Methods: After HRPO approval, variants of the Confusion Assessment Method were used to assess the presence [3,4] of delirium. Two-channel EEG (F8 and O2, referenced to Cz) were recorded over 10 minute epochs of eyes open and eyes closed. Following multitaper spectral estimation, we calculated the proportion of power in the delta (1-4 Hz), theta (4-8 Hz), and alpha (8-13 Hz) frequency bands. Repeated measures analysis was implemented using a linear mixed model through SAS 9.3 Proc Mixed.

Results: Forty-four recordings were obtained from 27 patients, 13 of whom were followed during delirium recovery. Recordings associated with CAM+ assessments showed greater delta and theta power and lower alpha power (all $p < 10\text{-}4$). While the robustness of delta band power augmentation was similar in frontal and occipital EEG channels, modulation of theta and alpha band power was strongest in the O2-Cz channel. Delirium was also associated with a return of visual reactivity in the alpha band ($p<0.01$). In patients with loss of theta and alpha power, recovery of delirium is associated with the progressive return of posterior dominant rhythm in theta and alpha bands (Figure 1).

Conclusions: A pragmatic sparse EEG montage is feasible for distinguishing recordings for delirious and non-delirious states. Consistent with other studies, lower frequency EEG power predominates during delirious states with occipital channels (delta and theta). These data suggest a shift of EEG power from delta, through theta, and alpha bands during the recovery from delirium, an evolution that may potentially be exploited for detection and tracking of delirium severity.

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Neuro Clin 39 (41)
Differential Synaptic Actions of Isoflurane on Hippocampal and Cortical Connections

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Background/Introduction: Anesthetics are known to depress synaptic transmission, and this effect is thought to underlie the uncoupling of brain regions seen with cortical EEG recordings. We tested the hypothesis that anesthetic-induced depression of synapses leads to uncoupling of electrical activity between frontal cortex and hippocampus.

Methods: The present study used electrophysiologically-guided electrode implants to record Schaffer-collateral to CA1 neuron mono-synaptic responses, as well as frontal cortical micro-EEG signals, using a IRB approved protocol. Rats were allowed to recover from surgery and then isoflurane effects were characterized after several days (>7) to several months (<7) later. Simultaneous recordings of cortical and hippocampal micro-EEG signals, evoked synaptic responses, anesthetic concentration, vital signs and behavior were made.

Results: Loss of consciousness, measured as righting reflex, was consistently associated with increased synchronized delta activity, in hippocampus and cortex, as well as a novel ~15 Hz rhythmic oscillation produced by isoflurane in hippocampal micro-EEG recordings. Surgical anesthesia, measured as loss of tail-clamp reflex, was observed on the transition to burst-suppression activity in both hippocampal and cortical micro-EEG signals. Isoflurane produced a concentration-dependent depression of mono-synaptic responses: at surgical anesthetic depths, excitatory postsynaptic potentials were depressed by 26.6 ± 4.2 % (n=5; $p<0.001$) of control amplitudes, but surprisingly, coupling between cortex and hippocampus was further enhanced.

Conclusion: Clearly, our hypothesis was wrong, since increased coupling between brain regions was observed at the same time that mono-synaptic responses were depressed. We demonstrate for the first time that cortical-hippocampal coupling is increased at both low (loss of consciousness) and at high surgical concentrations of isoflurane.

Support

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Neuro Clin 40 (42)
Chaos Analysis Provides a More Sensitive and Accurate Measure for Loss of Consciousness Compared to Frequency Domain Measures of EEG Signals

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Background: Electroencephalogram (EEG) signals have long been known to be altered by general anesthetics, and provide a basis for brain monitors that can measure depth of anesthesia. Comparisons of commercially available monitors have demonstrated an accuracy of ~ 90%, far below what is needed to prevent awareness in surgically anesthetized patients. We tested whether chaos analysis could provide better sensitivity and accuracy for determining loss of consciousness following propofol administration in surgical patients.

Methods: The time point for loss of response to verbal command (loss of consciousness; LOC) was carefully determined in six randomly chosen patients following a slow anesthetic induction with intravenous propofol. The LOC time point was synchronized to ongoing frontal (F7) EEG signals obtained using a SedLine monitor. Two minute segments of EEG recordings before and after LOC were analyzed for effects on SedLine patient sedation index (PSI), EEG spectral content, frequency domain fast Fourier transform (FFT) changes, wavelet analysis, as well as for changes in chaotic attractor plot shape. Changes in EEG signals for LOC were also compared to changes seen before and after recovery of consciousness (ROC).

Results: No significant nor consistent changes in PSI, spectral content, FFT, nor wavelet analysis of EEG signals were evident in 2 minute EEG segments before and after propofol-induced LOC. In fact, a wide variability in EEG frequency domain measures was seen across patients, both before and following propofol-induced LOC. In contrast, chaos analysis of only 20 seconds of pre- and post-LOC EEG segments revealed a consistent and statistically significant change in attractor plot areas for each patient ($p < 0.002$; ANOVA-Tukey; n=6). Hysteresis (brain inertia) was clearly evident in both chaotic and frequency domain measures when comparing EEG signals for LOC and ROC.

Conclusion: Chaos analysis of EEG signals provides a sensitive and consistent measure of both LOC and ROC in surgical patients, and should be explored as an improved alternative to frequency domain measures of anesthetic depth for new monitor development.

Neuro Clin 41 (160)
Dexmedetomidine Sedation Disrupts Local and Global Communication in Large-Scale Brain Networks

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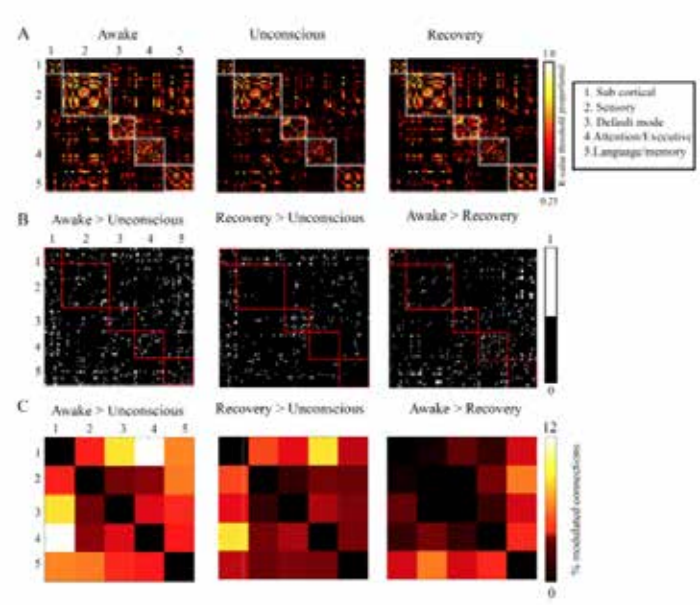
Introduction: Large-scale networks formed by synchronized fluctuations in functional MRI (fMRI) signals show a distinct architecture when observed from the vantage point of complex network analysis and graph theory. Local networks can be represented by clusters of connected brain regions formed by spatial correlations in fMRI signal. These local networks are in turn connected to each other to form a global network primarily though connections between hubs that have both intercluster and intracluster connections. The configuration of these networks is a putative mechanism to explain information dissemination in the brain. Here we studied the effects of dexmedetomidine on the capacity for efficient information transfer within local and global networks.



Methods: Using resting state fMRI (rsfMRI), we imaged the brain of 14 healthy subjects during baseline (awake), dexmedetomidine-induced sedation, and recovery from dexmedetomidine. Using a whole brain network approach, networks were constructed at 6 different network density thresholds from a 131 parcellated brain regions. We used the Brain Connectivity Toolbox and custom codes written in MATLAB. Graph metrics were compared with paired t-tests and results were corrected for multiple comparison using FDR ($p<0.05$).

Results: We found significantly reduced capacity for efficient information transfer within the brain at both a local and a global level in weighted networks during the sedated state. The topological changes were associated with reduced strength of connections at a global mean level during the sedated state ($p<0.05$ for all network density thresholds). Importantly, we did not find significant changes in number of connections at a nodal level (degree distribution). As previously reported, we found reduced connectivity between the thalamus and the default mode network during the sedated state. However, our global network approach also showed reduced functional connectivity within and between all resting state networks. The most robust changes were observed for subcortical connections with multimodal networks, and for sensory connections with language/memory processing networks.

Conclusion: Our findings demonstrate that dexmedetomidine significantly disrupts the capacity for efficient information transfer at a local and a global scale. We found that the effects of dexmedetomidine were not specific to particular brain networks. Rather, connectivity was reduced both within and between several of the resting state networks.

Neuro Clin 42 (90)
Anterior Insula Suppression at Loss of Volitional Behavioural Response

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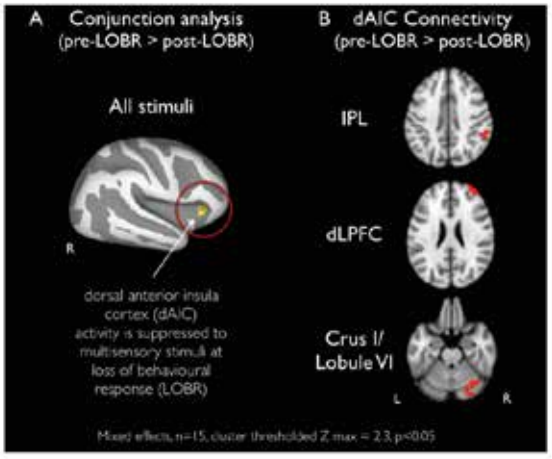
Introduction: Loss of behavioural responsiveness (LOBR) is often used to define anesthesia-induced loss of consciousness both clinically and experimentally [1]. It has been postulated that a small cortical region could underpin LOBR under anesthesia [1,2]. However, no study has yet explicitly shown what brain regions govern LOBR. Identifying the brain regions responsible for LOBR is crucial to understanding the network disruption observed at higher levels of anesthesia [3]. We hypothesised that any brain region demonstrating reduced activation to multisensory stimuli around LOBR represents a key cortical gate underlying this transition. Furthermore, we hypothesised that localised suppression within this region is associated with the breakdown in frontoparietal connectivity observed in previous studies [4].



Methods: During both simultaneous electroencephalography and functional magnetic resonance imaging (EEG-FMRI) and EEG data acquisition, 15 healthy volunteers experienced an ultraslow induction with propofol anesthesia while multisensory stimululi (i.e. auditory tones, words, and noxious pain stimuli) were presented. We performed separate analyses to identify changes in 1) FMRI stimulus-evoked activity, 2) functional FMRI connectivity and 3) frontoparietal EEG synchrony associated with LOBR.

Results: Using an FMRI conjunction analysis, we demonstrated that stimulus-evoked activity was suppressed in the right dorsal anterior insula cortex (dAIC) to all sensory modalities around LOBR (see Figure 1A). Furthermore, we found that after LOBR the dAIC had reduced functional connectivity with frontoparietal and cerebellar regions, specifically the dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule (IPL) and Crus I/ Lobule VI cerebellar regions (see Figure 1B). Finally, EEG power synchrony reductions between electrodes located in these frontoparietal regions was observed in the same subjects after LOBR in a separate session (not shown).

Conclusion: We have identified the dAIC as a potential cortical gate responsible for LOBR. This finding is supported by a body of work postulating the dAIC to be the site of the "sentient self" and a critical hub of a salience/threat detection network [6]. The observed dAIC suppression around LOBR was associated with reduced functional connectivity of the dAIC with frontoparietal brain regions that was measurable using both EEG and FMRI. Furthermore, the brain regions demonstrating altered functional connectivity form part of the executive control network and are highly implicated in decision-making. Although our methods cannot reliably infer directionality or causality, the observed loss of synchrony between these frontoparietal regions potentially indicates failed information transfer caused by the increasing concentrations of propofol. We conclude that pharmacologic lesioning of the right dAIC by propofol anesthesia is (either directly or indirectly) responsible for the measurable loss of volitional behavioral response seen in clinical practice.

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Edu 1 (133)
ReMind: Reducing Delirium and Improving Patient Satisfaction with a Perioperative Mindfulness Intervention

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Introduction: Postoperative (post-op) delirium has an estimated incidence up to 82%(1). Pharmacologic prevention/treatment are not fully effective, but delirium is preventable with non-pharmacologic care, such as the Hospital Elder Life Program(2,3). To date, mindfulness has not been incorporated into delirium prevention programs, though it may help patients adapt to hospitalization or illness. Specifically, "Langerian mindfulness" involves being aware of novelty in experiences and can impact surgical stress and perception of aging(4,5).

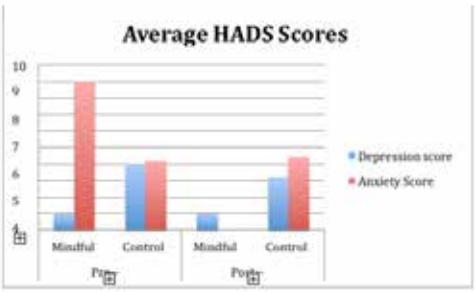

Figure 1. Average HADS scores by group. 0--7 = normal; 8--10 = borderline abnormal; 11--21 abnormal. On average, depression and anxiety scores trend towards improving after surgery. Control group n = 5; Mindful group n = 1. Post--op anxiety score for mindful group patient is 0.

To reduce post-op delirium incidence and increase perioperative patient satisfaction, this randomized, controlled, prospective pilot study employs a preoperative (pre-op) and in-hospital program of thought exercises based on Langerian mindfulness.

Methods: Subjects are provided with a mindfulness audio or preparatory information audio (describing the perioperative experience) to listen to within the week before surgery. Subjects in the mindfulness group perform 3 mindfulness exercises in a pre-op meeting.

After surgery, mindfulness subjects are visited twice daily for mindfulness exercises. Control patients are visited for involvement in relatively neutral conversation.

For all patients, delirium screening (Confusion Assessment Method-Intensive Care Unit, CAM-ICU) is performed twice daily; Post-operative Quality of Recovery Scale (PQRS) is administered on pre-op (to obtain baseline) and on post-op days 1, 3, and 5.

Before discharge, all patients are assessed regarding their affective status (Hospital Anxiety and Depression Scale, HADS) and satisfaction with their hospital stay (Hospital Consumer Assessment of Healthcare Providers and Systems, HCAHPS).

Results: Data collection for 6 patients is complete (goal n = 30); 5 of 6 are controls. Overall trends include 1) post-op HADS scores are improved compared to pre-op (Fig. 1); 2) functional status decreases from pre-op baseline to post-op day 1, then rises towards baseline; 3) all patients thus far rated overall hospital experience as a 9 or 10 of 10, and many shared positive comments regarding the audio files.

Conclusion: Recruitment is ongoing. Patients' reactions to the audio files thus far suggest the audio is associated with patient satisfaction. These audio files have the potential to improve the perioperative experience in a large scale, non-labor-intensive manner.

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Edu 2 (157)
Seeing Through the Eyes of the Intubating Anesthesiologist: Google Glass to Improve Patient Safety during Airway Training

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Purpose: To assess the feasibility of new wearable technology, Google Glass, to effectively supervise endotracheal intubation by anesthesia novices.

Background: Anesthesia trainees can cause significant harm to patients during intubation attempts. The supervising attending is often unable to monitor progress and assistance is limited by the inability to share the view of the deeper airway structures with standard laryngoscope blades.

Fig 1. Direct Laryngoscopy with MAC 3

Fig 2. Intubating the airway with MAC 3

With the advent of wearable technology, we wished to explore ways to utilize these tools to improve the teaching process. Proof-of-concept projects in Anesthesiology include combining Google Glass and Philips IntelliVue Solutions to provide Anesthesiologists with streaming patient case information [(1)]. Utility in medical education has also been demonstrated, as students at UC Irvine SoM are integrating Glass into their curriculum [(2)].

We focus on the feasibility of using Google Glass to share the view of the vocal cords during supervised intubation attempts by anesthesia trainees using standard laryngoscope blades.

Methods: An anesthesia trainee intubated an airway mannequin while wearing the Google Glass unit with a standard laryngoscope blade. Meanwhile, the supervising attending monitored the trainee's intubation attempts on a smartphone and assisted as required.

We utilized one Glass unit paired with an Apple iPhone 6 (iOS 8) via secure personal Wi-Fi and Bluetooth connections. Glass was set to video capture mode and the paired smartphone streamed Glass' camera view via the Glass smartphone app (ver. XE22).

Results: While the images we acquired were of excellent resolution, we faced challenges with acquiring appropriately directed images. The primary challenge is that Glass' camera is mounted on the upper right edge of the lens frame and is only able to move in a horizontal plane causing Glass' line of view to be misaligned with the trainee's. Additionally, live-streaming of Glass' video to the linked smartphone was inconsistent eventually leading to complete shutdown from overheating, making it difficult for the attending to appropriately monitor the trainee's progress.

Though camera movement limitations and hardware overheating are issues that could easily be improved, other factors to consider include the steep learning curve of a new technology like Glass, network security / HIPAA compliance issues, and image whiteout that was notable with even the relatively dim light of the laryngoscope blade.

Conclusions: Wearable technology is promising in Anesthesiology and may improve patient safety during airway training; however, Google Glass, in its current state, is a difficult device to use for this purpose. Nonetheless, the idea of the attending monitoring the trainee's airway management is appealing. We are comparing other new wearable technologies (GoPro, Microsoft HoloLens) to assess which may be the better tool.

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Edu 3 (75)

Faculty and Resident Perceptions of Anesthesiology Milestones: Do We Share A Similar Mental Model of Milestones Achievement?

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Introduction: Anesthesiology residency programs are required by the Accreditation Council for Graduate Medical Education (ACGME) to assess the performance of residents in 25 developmental milestones distributed across all of the ACGME general competencies. Since this assessment method is new, there are no data on whether faculty and residents view the milestones levels of performance with the same mental model. This survey study sought to determine if, 1) residents (R) and faculty (F) would assess milestones achievement similarly when presented with scenarios describing a resident's performance; 2) the level of experience of the evaluator would have any effect on their assessment; and 3)assessors would rate milestones achievement differently if they were provided with the descriptors for level of performance for the milestone compared to those assessors who were only informed of the milestone being assessed with no descriptors provided.

Methods: This anonymous, multi-institutional study was granted exempt status by the IRB. All residents and faculty from 8 Anesthesiology residency programs were invited via email to participate in a survey consisting of demographic questions and scenarios describing resident performance within 12 Anesthesiology milestones. Participants were provided the explanation of Level 1 - 5 performance as defined in the ACGME Anesthesiology Milestones document. At each participating institution residents and faculty were separately randomized to receive 1 of 2 surveys. Survey 1 (R1, F1) only provided the name of the milestone being assessed while Survey 2 (R2, F2) included the descriptors of expected behavior at each performance level provided in the ACGME Milestones document. Participants rated the performance level for each milestone based on the behavior described in the scenario. Data were analyzed using the two sample t-test and the F-test. $P < 0.05$ was considered significant.

Results: A total of 195 faculty and 131 residents from 8 institutions completed the survey. The overall response rate was 36% for faculty and 34% for residents. When provided performance descriptors, residents (R2) and faculty (F2) assigned similar milestones levels for 10 of the 12 scenarios. When assessing performance without descriptors, residents (R1) and faculty (F1) assigned similar levels for 7 of the 12 scenarios. Assessment scores overall differed significantly between those who evaluated with and without descriptors (R2 vs R1, F2 vs F1). Significantly different performance levels were assigned for 12 of 12 scenarios by residents and for 10 of 12 scenarios for faculty. Mean performance levels were higher when assessing without descriptors. Among faculty, years of experience evaluating residents and membership on the Clinical Competence Committee did not affect assessment scoring.

Conclusions: Residents and faculty do share a similar mental model of milestones achievement. However, evaluation of performance is significantly affected by whether evaluators have descriptors of expected behavior at each level of achievement available to them when assessing performance. We recommend that faculty be provided the descriptors from the ACGME Milestones document when evaluating resident performance.

Edu 4 (69)
Addition of Focused Critical Care Transthoracic Echocardiography (FoTE) Learning into an Existing Anesthesiology Residency Training Program: a Prospective Study

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Introduction: Blended or mixed-mode class learning incorporates a portion of educational processes from Web Based sources into an educational initiative. We sought to discover whether competency in acquisition and interpretation of Focused critical care Transthoracic Echocardiography (FoTE) could be achieved by the addition of blended learning to an existing anesthesiology-residency training program. Bedside FoTE starts with a specific question, which requires immediate interpretation and clinical decision-making in the rapidly deteriorating patient [(1)]. Repeated bedside FoTE can be performed to assess the changing status and to modulate treatment accordingly [(2,3)]. The principal goal of this study is to quantify the improvement that anesthesiology residents can achieve in a standardized FoTE exam after a one-day training course.

Methods: A prospective analysis of educational data at a large academic medical center was undertaken. Our methodology is an adapted version from a study previously described [(4)]. A total of 22 anesthesia residents took a standardized pre-test created by the Society of Critical Care Medicine (SCCM) for their basic FoTE course. The test included identification and acquisition of standard transthoracic views, recognition of cardiac structures and interpretation of images from presented clinical cases. All participants completed a one-day training course (four hours web based FoTE video lectures). This was followed by four hours of hands-on FoTE training, moderated by a critical care certified anesthesiologist with expertise in advanced Critical Care Echo.

At the end of the course, all participants repeated the test. The pretest and posttest scores for each participant were compared for improvement. The difference of the scores after training was calculated using the t-test with significance defined as $p<0.05$.

Results: Twenty-two anesthesia residents completed the one-day FoTE course. All of them performed the SCCM standardized pre and post-test and showed improvement of mean scores of 14.5±2.8 (48%) to 18.3±3.2 (61%), ($p=0.000002$).

Conclusion: FoTE training can be a critical and useful modality in diagnosis of shock and acute respiratory insufficiency in the perioperative and critical care setting and should be incorporated as a core competency of anesthesia providers. Although a one-day training course improved resident knowledge in FoTE, it was not enough to achieve competency (defined as score of 80%). We are currently testing if CA-2 residents can achieve competency by 1-week intensive training. A portion of this educational initiative is the SCCM web based FoTE video lectures (total of 8 hours) which has decreased the number of faculty involved in training. The hands-on portion includes practice with Heartworks® simulator followed by at least 30 supervised FoTE studies performed in patients in PACU, POCU and SICU under direct supervision of an advanced FoTE-trained Critical Care Anesthesiologist.

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Edu 5 (120)
Critical Errors in Rarely Performed Procedures up to 5 Years after Training among 105 Surgeons

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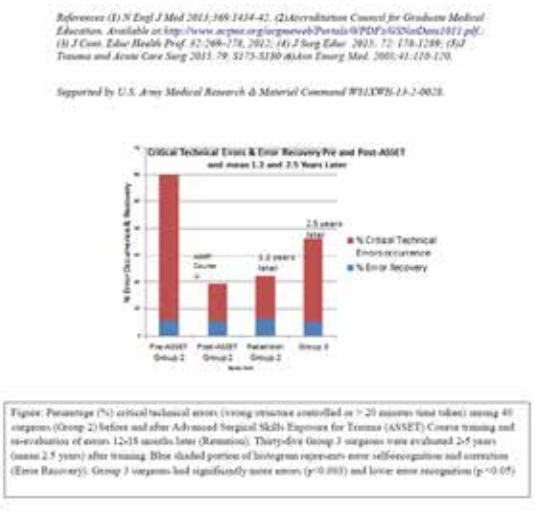
Background: Technical failures in individual clinical skills occur during surgery and are known to increase post-operative morbidity and mortality (1). Graduating general surgery residents have little experience with many procedures needed for trauma, e.g., brachial artery exposures or lower extremity fasciotomy (2). The Advanced Surgical Skills for Exposure in Trauma (ASSET) course was developed to correct this deficit. We hypothesized that the occurrence of critical technical errors (e.g., vessel loop encircled wrong structure) and critical management errors (e.g., life-threatening delays) decrease with training and subsequently increase with post-training interval skill decay. Skill decay in complex procedures occurs widely, including for anesthesiologist's procedural skills (3).



Methods: Surgeons up to 5 years after ASSET training were video recorded performing axillary, brachial, and femoral artery exposure and control (encircle with double vessel loop), and a 4 compartment lower extremity fasciotomy (FAS) on unpreserved cadavers. Skills were evaluated by two trained, co-located evaluators with a standardized script and a validated individual procedure score (IPS) metric (4). Linear mixed modelling included: anatomy skills, years and operative experience since training, and cadaver body habitus.

Results: All 4 procedures were performed on cadavers by 105 surgeons, Group 1: ten trauma surgeons and ten untrained residents were used to develop IPS and script (5). Group 2: forty 2nd - 6th year residents were evaluated before and after training up to 1.5 years later, Group 3: thirty-five practicing surgeons mean 2.5 years after training, and Group 4: a different set of ten expert practicing [mean 16 years] trauma attending surgeons than Group 1. For vascular procedures, among Group 2 surgeons, 60% critical error rate decreased to 19% (P< 0.001) immediately after training, a rate comparable to Group 4 experts (15%). There was no difference in error rates (22%) up to 1-1.5 years post-training. However, Group 3 surgeons error rates increased to 36,5% (P<0.003) and error recovery was lower compared to all other surgeons after training (Figure). A similar pattern was observed for FAS. Only 10% of Group 2 surgeons decompressed all four compartments before ASSET, which improved (p< 0.02) to 50% post-training comparable to 60% four compartment decompression among Group 4 experts. However, only 35% of Group 3 surgeons decompressed all four compartments, fewer (p <0.03) than all other surgeons after training. Among Group 3 surgeons, error recovery was lowest (p<0.05) for the 3 vascular procedures and less FAS compartments were decompressed mean 2.5 years after training (p < 0.03). Four Group 4 experts failed to decompress at least one compartment. Critical errors correlated with IPS measured lack of correct anatomic landmarks and procedural steps, suggesting mitigation efforts may be amenable to focused training interventions (6).

Conclusion: Occurrence of critical errors improved with training, but skills decay was detectable mean 2.5 years later. Refresher strategies, concentrating on anatomy, are required to minimize skills decay in rarely used procedural skills, even among experts.

Edu 6 (166)
Is Pediatric Dental Surgery Under General Anesthesia a Teachable Moment?

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Introduction: Surgical intervention does not effectively resolve pediatric dental caries. Parents may not be aware of the high rate of post-operative disease recurrence. Prevention is dependent upon behavioral change. The phrase teachable moment has been applied to health events that may "motivate individuals to spontaneously adopt risk-reducing health behaviors."[1] Surgical episodes represent such teachable moments and have successfully been targeted by public health interventions to promote post-operative smoking cessation.[2-4] In interviews of parents whose child require surgery, parents indicated an interest in modifying their behavior in order to improve their child's health.[5] Pediatric dental surgery may represent a teachable moment with the potential to improve post-operative oral health outcomes. The objective of this study was to elicit the parental perspective on barriers to behavior change and surgical expectations.

Methods: Nine key informant interviews were conducted with parents whose children were undergoing dental surgery under general anesthesia. Interviews probed the following domains: access/ dental home; disease etiology; surgical expectations; oral health behavior; family history; and community influences. Transcript analysis was guided by modified Grounded Theory principles: data were coded and then organized into domains by multiple coders, and final themes extracted.

Results: Parents reported fears and anxiety about surgery and anesthesia (n=4) more than guilt (n=3) about their child's oral health at the time of surgery. While many subjects expected no disease recurrence (n=4), several subjects did not have a clear understanding of why their child had developed severe disease.

Conclusions: Interventions directed at the pediatric dental surgery population may be effective when implemented in the acute peri-operative period. Parents may be motivated and receptive to behavioral change in an effort to avoid exposing their children to another procedure as well as anesthesia. Incomplete understanding of disease etiology at the time of surgery may contribute to poor oral health outcomes. Future studies will correlate these peri-operative findings with long-term outcomes.

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Edu 7 (165)
Practice Patterns and Outcomes of Older Anesthesiologists

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Introduction: Anesthesiology is a demanding medical specialty, but there are no data that provide a comprehensive picture of whether older anesthesiologists' practice patterns and reported adverse outcome rates may differ from younger anesthesiologists'. We hypothesize that anesthesiologists 65 and older will have systematically different patterns of clinical practice, but no significantly different rate of adverse outcomes compared with younger anesthesiologists.

Methods: Cases performed between 1/1/2010 and 6/30/2015 and reported to the National Anesthesia Clinical Outcomes Registry (NACOR) were included. We excluded organ donors, pain procedures, nonprocedural billing codes, cases without a listed physician (MD or DO) anesthesiologist or where the anesthesiologist had an unknown year of birth, and cases with >1 listed physician anesthesiologist. Practice measures included work shifts (day/night, weekend, and holiday shifts), anesthetic technique, types of procedures, and patient characteristics. Prespecified outcome measures were death or cardiac arrest, severe respiratory events (respiratory failure, arrest, or reintubation), postoperative nausea/vomiting (PONV), and process measures (case cancellation, unplanned admission, and unplanned ICU admission). The primary predictor for practice patterns was anesthesiologist age at the time of the case (<65 and 65+). For the association with outcomes we used a more granular measure of provider age: <40, 40-50, 51-64, and 65+ years old.

Results: We analyzed 18,903,360 cases (3,012,428 with outcome collection) from 21,076 providers, 575 (2.7%) of whom were >65. After adjustment with logistic regression clustered by provider, older anesthesiologists were significantly more likely to be university-affiliated, less likely to perform cases overnight or during the weekend, less likely to perform anesthesia on patients under 18 years, and less likely to perform emergency cases. Older providers were significantly more likely to provide care for patients undergoing endoscopy, eye surgery, and non-OR anesthesia care, compared with younger anesthesiologists (Table 1). Four separate clustered logistic regression models were developed to evaluate adjusted associations between provider age and perioperative adverse outcomes. After adjustment, there was no significant association between provider age and report of death/cardiac arrest, severe respiratory events, severe PONV, or case cancellation or unplanned hospital/ICU admission.

Conclusions: There are systematic differences in the cases older providers report to NACOR, including fewer cases performed on weekends and overnight, fewer emergency cases, and more non-operating room anesthetic cases. We found no evidence for increased rates of adverse outcomes in older providers. This may reflect differential reporting practices, preference for a more predictable or flexible schedule and reduced case complexity near retirement, and/or effective self-compensation for the physiologic changes of aging.

Edu 8 (44)

Work Habits are Valid Component of Anesthesia Resident Evaluations Based on Faculty Anesthesiologists' Daily Written Comments

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Introduction and Objectives: When US employers "were asked" "which abilities influence hiring selections the most", "the trait that most directly rivaled occupational skills (i.e., the ability to do the job) was 'work habits'"[(1)]. "Work habits and attitude (trying hard, enthusiasm, punctuality)" were ranked as the 1st or 2nd most important trait by 65%[(1)]. "Occupational [and] job skills" was ranked 1st or 2nd by 54%. Traits associated with productivity were "ability to learn new occupational and job skills" and "work habits"[(1)].

Our department's faculty anesthesiologists routinely evaluate resident physicians with whom they worked in an operative setting the day before, providing numerical scores to questions and (optional) written comments. Because work habits are important to employers[(1)] and to anesthesia program directors[(2)], and improve with feedback[(3)], we hypothesized that faculty comments would include the theme.

Work habits scale adapted from Dannefer et al. 2005 (4)

Lowest Performance = 1
Consistently seemed unprepared for case(s)
Overlooked important data and failed to identify or solve problems correctly
Did not communicate clearly his or her reasoning process with regard to solving problem(s)
Lacked initiative or leadership qualities
Only assumed responsibility when forced to, and failed to follow through consistently
Dependent upon others for direction with regard to his or her care

Highest Performance = 5
Consistently well prepared for cases(s)
Identified and solved problems using intelligent interpretation of data
Clearly communicated his or her reasoning process with regard to solving problem(s)
Took initiative and provided leadership
Consistently identified tasks and completed them efficiently and thoroughly
Thought and worked independently

Item [1] "for sessions" was changed to "for case(s)." Item [2] "overlooks" was changed to "overlooked." Item [3] "unable to explain clearly" was changed to "did not communicate clearly." Item [4] "lacks initiative" was changed to "lacked initiative." Item [5] "only assumes responsibility" was changed to "only assumed responsibility." Item [6] "learning agenda" was changed to "care."

Methods: We analyzed all 6692 faculty comments from January 2011 through June 2015 by quantifying usage of words and phrases in Dannefer et al.'s work habit scale (Table), and synonyms of the words[(4)].

Results: Approximately half (51%, lower 99.99% confidence limit 48%) of faculty comments contained the "work habits" theme. Multiple sensitivity analyses were performed to exclude individual faculty, residents, and words. All lower confidence limits were >43%.

There may have been a tiny change over time in the count of comments related to work habits (Kendall's tau = 0.024, P = 0.018). We reviewed 9 years of departmental e mail and faculty meeting minutes/ presentations. The phrase "work habit," singular or plural, never appeared. Furthermore, over the past 2 years, faculty have been evaluated daily on their quality of supervision, using a valid and dependable (in a psychometric sense) scale[(5-14)]. Quality of supervision is an independent measure of anesthesiologists' contribution to patient care[(13)]. Text analysis showed essentially no overlap of the 9 items with work habits. Thus, comments about work habits were unlikely cued from information unique to our department (i.e., findings are likely generalizable).

Conclusions: Although faculty anesthesiologists completed numerical questions based on the ACGME competencies to evaluate residents, many written comments included the "work habits" theme. This is important, because there has been little consideration of work habits in anesthesiology since the ABA 1994 study[(2)]. Work habits should be a component of routine resident evaluations.

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Clin Studies/OC 49 (60)

Evaluation of the Vios Medical Wireless Monitoring System - Initial Report of a Clinical Pilot Study

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Introduction: Continuous monitoring of vital signs with stand-alone bedside monitors is standard practice in ICUs and operating rooms; however, these systems are expensive and constrained to certain environments. The Vios System (VMS, Vios Medical, Inc. St. Paul, MN, USA) is the first FDA-cleared platform to utilize commercially available hardware for wireless monitoring of patients in low, mid, or high acuity hospital settings. The VMS system allows for flexible and low-cost monitoring capabilities through a wireless (Bluetooth) sensor placed on a patient's chest. VMS has capability for real-time analysis and display on a bedside or central station monitor, and synchronized for remote viewing from any global location. In this pilot study we evaluated the accuracy of VMS as compared to gold-standard bedside monitoring systems.

Table: Correlation and Bland-Altman plot results

Parameter	*Heart Rate	*Respiratory Rate	SPO_2 (%)	*Pulse Rate	Posture	ECG morphology & artifacting
*Relationship between the two systems (95% confidence)	r^2= 0.99	r^2= 0.81	r^2= 0.71	r^2= 0.98	100%	Equivalent (qualitative analysis)
†Bland-Altman agreement (95% confidence)	±1.1%	±4.2%	±2.8%	±1.4%	N/A	N/A

*beats or breaths per minute; †p <0.00 for heart rate, respiratory rate, pulse oximetry and pulse rate (for pulse rate n=17)

FIGURE: The Vios Monitoring System

Methods: After IRB approval and informed consent 1 physician and 8 nurses were trained on the VITALS1 protocol. 55 adult patients clinically indicated for monitoring within the cardiac step-down unit following cardiac catheterization were enrolled into the study.

Vital sign data was acquired simultaneously by the VMS (figure 1) and the existing bedside monitor. Specifically, ECG (lead I and II morphology/artifacting), heart rate, respiratory rate, oxygen saturation, pulse rate, axillary temperature, and patient posture were captured by each system.

Each patient was monitored for a minimum of 10 minutes, during which 5 comparative data points were captured for each vital sign. For patient posture, the nurse recorded a visual assessment of the patient. After the monitoring episode, the nurses and patients each completed a questionnaire about the VMS system. The data was analyzed using regression analysis and Bland-Altman plots with a 95% confidence considered significant ($p<0.05$).

Results: The patients had a mean age of 55 years (range 19-82), mean weight 65kg (range 48-90), and mean BMI 26.2 kg/m2 (range 20-67). None were unstable following their cardiac catheterization. The comparative data was highly correlated ($p<0.00$) for ECG, heart rate, respiratory rate, pulse rate and oxygen saturation with significant agreement between the traditional and VMS System readings (Table). Patient posture was accurately reflected 100% of the time. The nurses and patients were favorably impressed and preferred the VMS to the existing system.

Disscussion and Conclusions: This pilot study confirmed the successful transmission, analysis, and accuracy of the VMS. The patient and nurses accepted the VMS without issues. Several studies are being planned to evaluate its role in standard clinical practice and its capability to extend vigilance into environments beyond the hospital allowing remote patient management services. Monitoring of patient orientation and activity are additional value points of the VMS system. Benefits of this new clinical metric are: 1) ability to monitor neurological status, 2) potential to decrease pressure ulcers and deep vein thrombosis, and 3) be used as a readiness for discharge tool. The system also provides use of a patient activated distress alarm situated on the chest. The utility of this alarm will be validated in future studies.

Clin Studies/OC 50 (46)

Reduction in Cryoprecipitate Waste in the Pediatric Cardiovascular Operating Room: A Goal-Directed Transfusion Algorithm Based on Rotational Thromboelastometry

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Introduction: Patient blood management (PBM) is a multidisciplinary concept designed to manage anemia, optimize hemostasis, and establish decision thresholds for administration of blood products [1]. The Joint Commission has partnered with the American Association of Blood Banks to develop a hospital certification for PBM [2]. Two of the strategies implemented in PBM are the optimization of hemostasis and the establishment of decision thresholds for the blood therapy [1].

As part of a Quality Improvement (QI) initiative, we implemented a goal-directed transfusion pathway based on rotational thromboelastometry (ROTEM®, TEM Systems, Inc., Durham, NC) in the pediatric cardiovascular operating room to improve blood product utilization. Cryoprecipitate was targeted as the blood product to track due to its consistently high rate of waste.

Methods: This study targeted the use and waste of cryoprecipitate in the cardiovascular operating rooms at Texas Children's Hospital. A ROTEM-guided goal-directed transfusion pathway was developed after review of published evidence, and in collaboration with the Transfusion Medicine Service [3,4]. This pathway (see figure 1) recommends human fibrinogen concentrate (RiaSTAP®, CSL Behring, King of Prussia, PA) as a substitute for cryoprecipitate for bleeding secondary to hypofibrinogenemia in patients weighing more than 5 kg. Educational materials describing the transfusion pathway, ROTEM® ordering and interpretation instructions, and fibrinogen concentrate administration were disseminated in anesthesiology and multidisciplinary conferences, and the study started in April, 2015. Data on cryoprecipitate use and waste, ROTEM® use and fibrinogen concentrate use were collected for 7 months before and after introduction of the transfusion pathway.

Results: The run chart (Figure 2) demonstrates a sustained decrease in cryoprecipitate wastage after education and implementation of the transfusion pathway. The increase in use of ROTEM® and fibrinogen concentrate is shown graphically in Figure 3. The numbers of cases per month for the periods before and after the initiation of the project were 78.7 ± 5.4 and 86.4 ± 8.5 (Mean ± SD).

Conclusions: Patient Blood Management is a concept formulated to optimize patient safety and blood utilization. Implementation of PBM in adult cardiac surgery has been associated with reduced transfusion and improved outcomes [5-7]. We introduced a goal-directed transfusion pathway, improved the ease and efficiency of ROTEM® measurement, and provided education and access to human fibrinogen concentrate, an alternative to cryoprecipitate.

The future of transfusion medicine will involve PBM, point of care testing, pharmacologic coagulation factors, and goal-directed transfusion guidelines. Our study involves all of these strategies in a high volume, high acuity pediatric cardiac surgery program. We plan to study the effect of our transfusion pathway on transfusion of all blood products and other outcome measures such as bleeding and other clinical parameters.

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Clin Studies/OC 50 (46)
Reduction in Cryoprecipitate Waste in the Pediatric Cardiovascular Operating Room: A Goal-Directed Transfusion Algorithm Based on Rotational Thromboelastometry

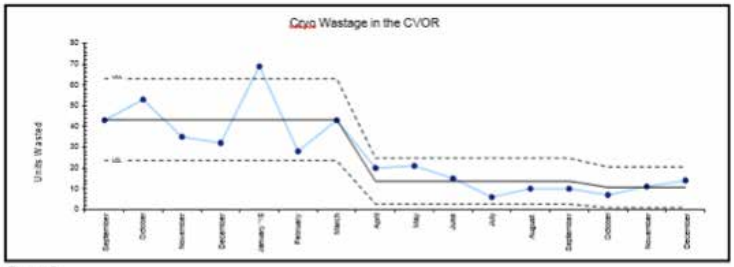
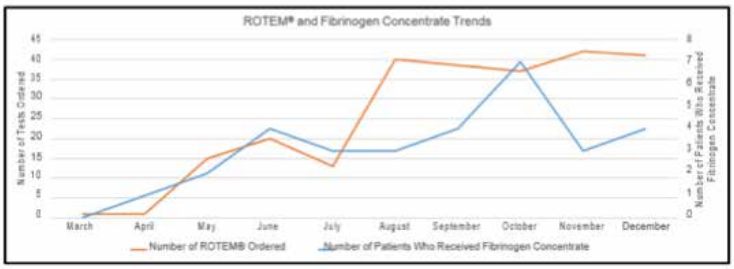


Figure 2



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Clin Studies/OC 51 (65)

A Comparison of the Effectiveness of Two Commonly Used Two-Handed-Mask Ventilation Techniques on Unconscious Apneic Obese Adults: A Non-Inferiority Trial

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Mask ventilation and tracheal intubation are basic techniques for airway management. They are mutually inclusive rescue measures to restore ventilation implying that optimization of mask ventilation is as important as tracheal intubation. The aim of this study was to determine and compare the effectiveness of mask ventilation with two commonly used techniques of two-handed-mask ventilation in obese unconscious apneic adults. Methods Eighty-one adults with a body mass index (BMI) >30 kg/m2 were enrolled in this study. Once apnea occurred following induction, subjects received mask ventilation using C-E clamp and modified V-E clamp techniques for 1-minute each in a randomized and crossover manner. C-E technique was to apply the mask by forming a C shape with each thumb and index finger over each side of the mask while the third, fourth, and fifth fingers of both hands lifting the mandible toward the mask. While modified V-E technique was done with the thumbs and thenar eminence placed over each side of the mask and the second through fifth digits pulling the jaw upward. Mechanical ventilation was provided utilizing a pressure control mode, at a rate of 10 breaths per minute, with an I:E ratio of 1:2, and a preset plateau airway pressure of 20 cmH2O. The primary outcome was expired tidal volume (Vt). Results Mean BMI for the 81 subjects was 36.5 ±4.9 (kg/m2). The failure rates (Vt <50ml) for mask ventilation were 44.4% and 0% for the C-E and V-E techniques respectively ($p<0.05$). Expiratory tidal volumes were 351 ±364 ml utilizing C-E and 720 ±244 ml for V-E ($p<0.001$). The peak airway pressures were 20.9 ±1.5 cm H2O for C-E and 20.6 ±1.3 cm H2O for V-E ($p<0.001$). Conclusion Mask ventilation employing the modified V-E technique is more effective than mask ventilation with the C-E technique in unconscious obese apneic adults. Subjects who failed mask ventilation with the C-E technique can be effectively ventilated with the V-E technique. Further studies are needed to validate this observation in other populations and to determine if improved mask ventilation with V-E technique positively impacts the quality of patient care.

Clin Studies 52 (59)
Barriers to Hepatitis C Virus Epidemiology in Anesthesia Care Workers

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Introduction and General Purpose of the Study: Hepatitis C Virus (HCV) causes life-threatening hepatitis, but may remain asymptomatic and undiagnosed for decades. Despite standardized protocols for HCV diagnosis[1], and therapy with well-tolerated medications that result in high rates of virologic cure, up to 1.5% of Americans are infected[2], with health care workers clearly at increased risk [3]. Although daily use of sharps in the care of infected patients may place anesthesia care workers at heightened risk of infectious exposures, the prevalence of HCV in this professional population is surprisingly unknown as an essential predicate to broaden the benefits of screening and intervention.

Methods: To establish HCV seroprevalence by immunoassay and correlate HCV seropositivity with worker age and years in practice, a multicenter, cross-sectional study comprising 500 enrollees at 1 rural and 4 urban medical centers was designed to ascertain HCV infection rates. The study was powered at an estimated prevalence of 1-3% for covariate testing of age, gender, years in practice, practice mix, and geographic locale.

Results and Major Findings: Several barriers to enrollment were identified during the course of project development and the study was deemed impossible to conduct. These obstacles included 1) variability between medical centers in providing routine, anonymous HCV screening, 2) costs of conducting the protocol (e.g., HCV RNA nucleic-acid testing to confirm positive serologic screens and document active infection, and third-party counseling regarding results), 3) potential enrollment bias (e.g., failure of known HCV-positive participants, and those at risk from earlier-life exposures, to volunteer), and 4) unresolved issues relating to costs conceivably incurred by HCV-positive anesthesia-care workers (e.g., medications, gaps in insurance coverage, loss of confidentiality, stigmatization in the workplace and home, risks to patients, and HCV as a proxy for other exposures).

Conclusions: In view of clear-cut benefits of the proposed investigation-which included identification of persons needing treatment for HCV infection and documentation of baseline seronegativity for professionals entering a high-risk profession-to all anesthesia-care workers, we propose that resources and coordination required for acquisition and analysis of the foundational data best fit a top-down, organization-driven model (e.g., an ASA and AANA initiative). We believe this is preferable to a bottom-up, investigator-driven approach, which must overcome fiscal, logistical, and social obstacles to advance this important work in the interest of clinician, as well as patient health and safety.

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Clin Studies 53 (91)
System-Wide Modulation of Patients Immune Response to Surgery by Pre-Operative Immune-Enhancing Nutrients

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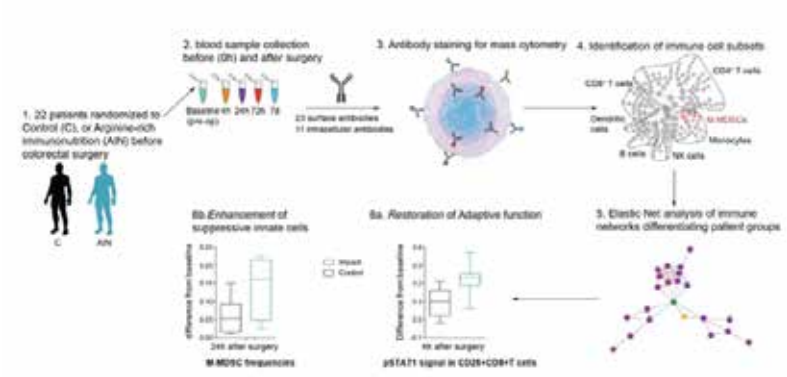
The recent emphasis on enhanced recovery after surgery (ERAS) protocols in perioperative care highlights the significance of efforts towards improving surgical recovery. However the elements of these protocols that may improve recovery are uncertain. A better understanding of the biological mechanisms of ERAS protocols is critically needed.



Arginine-rich Immuno-Nutrition (AIN) is a component of ERAS protocols integral to the perioperative management of patients undergoing colorectal surgery. AIN has been the center of much debate, as AIN consistently decreased post-operative infectious complications after elective surgery, but increased morbidity and mortality in critically ill patients. Thus, a mechanistic understanding of the immune modulatory properties of AIN is essential to unify these apparent discrepancies. In this study, we applied mass cytometry to comprehensively characterize the effects of perioperative AIN on major immune cell subsets and associated intracellular signaling pathways of patients undergoing elective colorectal surgery..

Methods: 22 patients scheduled for elective colorectal surgery were randomized to AIN treatment (IMPACT®, 950mL/day for 5 days prior to surgery) vs. no treatment. Whole blood samples were collected before surgery (Baseline) then 4h, 24h, 72h and 7 days after surgery and submitted to mass cytometry analysis of immune cell subset frequencies and intracellular signaling responses. Plasma cytokine levels were quantified on a Luminex platform. An Elastic Net analysis that integrated immune cell frequencies, intracellular immune responses and plasma cytokine levels was applied to identify groups of correlated immune features that best predicted the effect of AIN on patients' immune response to surgery.

Results: Consistent with speculations that AIN restores adaptive cell function after surgery, a robust but transient increase in STAT1 signaling in memory CD8+ cytotoxic T cells was a prominent feature of the immune network associated with AIN. However, AIN also increased the frequency of CD11b+CD14+HLA-DRlow myeloid derived suppressor cells (MDSCs), a cell type intimately involved in Arginine-dependent suppression of adaptive immune cells in the context of malignancy, sepsis and traumatic injury.

Conclusion: The mass cytometry analysis of peri-operative AIN immune modulation revealed systems-wide alterations in immune cell subsets of patients undergoing colorectal surgery. While aspects of adaptive cell function were transiently restored, AIN also induced a prolonged increase in MDSC frequencies, a cell type associated with immune suppression in sepsis and cancer. These findings have important implications for the selection of patients that may benefit from peri-operative AIN. Future studies will examine the utility of peri-operative immune profiling to tailor AIN (and other pre-habilitation interventions) to patient-specific immune states.

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Clin Studies 54 (80)
Delirium Risk Factors in Critically Ill Children

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Introduction: The recent validation of pediatric delirium monitoring tools, including the preschool Confusion Assessment Method for the Intensive Care Unit (psCAM-ICU) for use in children 6 months to 5 years of age, has demonstrated an alarming delirium prevalence of over 50% in critically ill infants and preschoolers during their ICU stay.[1] We undertook this prospective cohort study to elucidate possible risk factors for delirium in our most vulnerable patients.

Methods: We enrolled critically ill patients aged 6 months to 5 years admitted to the pediatric medical ICU (PICU) and cardiac ICU (PCICU) of a tertiary medical center, and excluded those with hearing/visual impairments, those who were non-English speaking, moribund, or for whom the surrogates refused consent. Patients were evaluated for delirium using the psCAM-ICU for up to 14 daily assessments while in the ICU. Baseline demographic data and daily in-hospital information including medication exposure, presence of mechanical ventilation, and laboratory data were collected. Multivariable negative binomial regression was used to assess the associations of admission severity of illness (PRISM score), admission diagnosis of either sepsis or ARDS, history of cyanotic heart disease, exposure to benzodiazepines and opiates, cardiovascular SOFA score, mechanical ventilation, and hypoxia with delirium duration. Multinomial regression was used to investigate possible in-ICU risk factors for developing delirium on a given day versus having normal mental status or being comatose.

Results: Our cohort of 300 patients had a median age of 20 months (IQR 11, 37), 48% required mechanical ventilation, and 44% had at least one positive delirium assessment. Greater severity of illness [RR 1.04 (CI 1.01, 1.08, p=0.017)] and higher benzodiazepine exposure [RR 2.01 (CI 1.25, 3.24, p=0.002)] were both significantly associated with more days of delirium. In our multinomial models, higher benzodiazepine exposure (p=0.009) was significantly associated with a higher likelihood of being delirious the following day compared to having a normal mental status.

Conclusions: Delirium is prevalent among critically ill children. Higher severity of illness and, more importantly, benzodiazepine exposure are independent risk factors for increased delirium duration. Benzodiazepine administration is also significantly associated with the development of delirium the day following drug exposure. Studies targeting benzodiazepine exposure as a potentially modifiable target to reduce burden of delirium are warranted.

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Clin Studies/OC 78 (63)
The Effect of Vasopressor Infusion During Spine Surgeries in Prone Position on Renal Function

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Introduction and Purpose: To investigate the effects of intraoperative vasopressor infusion on postoperative renal function in patients undergoing complex spine surgery in the prone position. Dogma of prior studies has led to fear of inducing renal injury by use of vasopressor infusion to treat hypotension; we, however, tested the hypothesis that the use of vasopressor infusion to maintain adequate renal perfusion pressure would be associated with smaller changes in renal function postoperatively in this retrospective, propensity-matched case control study.

Methods: Data was obtained on 2,972 adult patients undergoing complex spine surgery at the Cleveland Clinic between January 2005 and September 2014 from the Cleveland Clinic Perioperative Health Documentation System. After excluding patients with preoperative kidney disease, as well as those with < 30 minutes of intraoperative vasopressor infusion or those with incomplete medical records, the primary outcome measure was percent change in eGFR from preoperative baseline to postoperative day 7. Each patient who received vasopressor infusion intraoperatively was matched using a propensity score to a comparable patient who did not receive an intraoperative vasopressor infusion; we successfully 1:1 matched 540 vasopressor infusion patients to controls for a total of 1,080 patients. Secondary outcome measures were acute kidney injury, postsurgical non-absorption and 10-point surgical Apgar score.

Results: Among the matched patients, intraoperative vasopressor infusion was not significantly associated with percent change in eGFR compared to control patients (difference in mean eGFR change 0.9%, 95%CI -0.8 - 2.5%). Nor was intraoperative vasopressor infusion associated with the secondary outcome of AKI; in fact, the patients in the vasopressor infusion group had a trend towards less AKI (OR 0.66; 95% CI 0.26 - 1.67; P = 0.32) and lower postoperative SCr, though these did not reach significance. Intraoperative vasopressor infusion was associated with worse surgical Apgar score (difference in mean score -0.3; 95% CI -0.5 - -0.1; P = 0.001), mostly due to greater blood loss in the vasopressor group; the vasopressor group did have a higher incidence of colloid fluid resuscitation and blood transfusion. There were not enough postoperative non-absorption events recorded for formal analysis.

Conclusion: Vasopressor infusion during complex spine surgery in the prone position had no adverse effect on postoperative renal function, with no significant difference in eGFR percent change in patients who were treated with intraoperative vasopressor infusions versus those who were not; in fact, a trend towards fewer incidences of AKI in the vasopressor infusion group was noted, although it did not reach significance. Further randomized studies are needed to better clarify the effect of vasopressor infusion on renal function in complex spine surgery.

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Clin Studies/OC 79 (85)
Mortality in Hospitalized Non-Traumatic Subarachnoid Hemorrhage Patients

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Introduction: The mortality of patients enrolled in clinical trials focused on treatment of aneurysmal subarachnoid hemorrhage (SAH) is less than 10%[1,2] but due to selection criteria, this underestimates mortality for all patients with SAH. To gain better insights, we reviewed the demographics, treatment decisions and outcomes in all adult patients with nontraumatic SAH admitted to the University of Iowa (UI) over a 5 year period. The UI is the only center which provides comprehensive care for patients with SAH in Iowa (population 3,000,000).

Methods: Since July 2010, the Departments of Anesthesia and Neurosurgery have jointly gathered data on all admitted non-traumatic SAH adult patients as part of a Quality Assurance program. These data were examined to gain an "all admissions" perspective of the clinical course of such patients. Analysis and reporting of these data was approved by the IRB.

Results: 449 patients with non-traumatic SAH were admitted to the UI between July 1, 2010 and June 30, 2015. In 25 (6%), age and/or poor admitting neurologic condition precluded additional diagnostic workup after an initial CT scan. 23 of these patients died, with a mean time to death of 1.2 days. 424 (94%) patients underwent further diagnostic imaging (CT and/or conventional angiography). No aneurysms were identified in 113 patients, 66 of whom were deemed to have perimesencephalic hemorrhages [3]; only 6 (9%) of these patients died during hospitalization. In the remaining 47 patients, 8 died (17%). An intracranial aneurysm was identified in 311 patients (69% of admissions). Patients with demonstrated aneurysms presented with poorer neurologic grades than those without (e.g. World Federation of Neurologic Surgeons Grades I and II in 57% of patients, vs. 75% in others). In 30 patients with aneurysms, no further treatment was offered due to age and/or poor neurologic status; 21 of these (70%) died. 281 underwent coiling/stenting (201) or open clipping (74). Mortality in the two groups was similar, i.e. 15.0% vs 10.8% respectively. Overall mortality (all admissions) was 21.6%. Additional details on patients, treatments and outcomes will be presented.

Conclusion: While most reports of outcome following SAH focus on the effects of various interventional treatments, examining the disorder from the perspective of "all patients admitted" paints a different picture. While mortality in treated patients with identified aneurysms was 13.5%, overall mortality for patients arriving at the UI was 21%, with 61% of deaths occurring in patients deemed ineligible for any definitive treatment; this ignores patients who die before reaching definitive medical care. Limiting our efforts to those with demonstrated aneurysms who undergo treatment ignores a large fraction of patients. Progress in the management of SAH will come only with the development of methods to prevent hemorrhage rather than solely responding to its consequences.

The authors wish to thank Gatana Stoner RN for her data collection efforts.

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Clin Studies/OC 80 (125)
Pathophysiology of Perioperative Acute Coronary Syndromes: A Coronary Angiographic Investigation

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Introduction: Approximately 5% of patients age 45 or older undergoing noncardiac surgery experience a cardiac complication, with perioperative myocardial infarction (PMI) being most prevalent. The pathophysiology of PMI remains poorly understood. Although mismatch in myocardial blood supply-oxygen demand (type 2) has classically been believed to antecede many perioperative MIs, strong evidence to support this hypothesis remains lacking. Other studies have suggested that plaque rupture (type 1) may be an underappreciated etiology of PMI. While a plethora of studies have focused on risk assessment and prevention of myocardial ischemia in the perioperative period, limited evidence exists regarding the etiology of PMI.

Methods: Following IRB approval, we reviewed hospital records and coronary angiograms of adult patients who underwent angiography for acute coronary syndrome (ACS) within 30 days of noncardiac surgery at a major tertiary hospital between 1/2008-12/2015. Angiograms were retrospectively reviewed independently by an interventional cardiologist and an interventional cardiology fellow who were initially blinded to clinical data and outcomes, and when interpretation was discordant, electrocardiogram, procedure note and/or echocardiogram findings were reviewed to reach consensus. Based on the findings, the etiology was classified as type 1 (plaque rupture), type 2 (supply/demand mismatch), or type 4b (stent thrombosis).

Results: 145 patients were identified. More than half of patients (51%) had pre-existing CAD and 44% were on beta-blockers at the time of surgery. The distribution of MI types 1 (plaque rupture), 2 (supply/demand mismatch), and 4b (stent thrombosis) was 26.9% (39/145), 71% (103/145), and 2.1% (3/145), respectively. Thirty-day mortality was 3.4% (5/145); one patient died following type I MI, and four patients following type II. Median peak post-operative troponin I was 3.2 ng/ml (IQR 0.9-8.2), and median time to peak troponin was 1.8 days (IQR 0.8-2.9). The median hospital length of stay was 9.3 days (IQR 6.3-14.3).

Conclusion: In this single center cohort, nearly 3 out of 4 patients who underwent coronary angiography for ACS following noncardiac surgery had supply/demand mismatch compared to a primary coronary event as the etiology. To date this is the largest angiographic series of patients with perioperative ACS.

Clin Studies/OC 81 (127)
Anomalous Billing by Health Care Providers: Evidence from Anesthesia

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Introduction: As part of their practice, most physicians must exercise discretion in choosing billing details that determine payment for their services. Understanding the degree to which physicians inappropriately use this discretion has important implications for setting payment policies. However, separating higher case complexity from inappropriate billing has made this a challenging issue to study. Anesthesia offers a useful test case because practitioners are partly compensated by self-reported length of time ("anesthesia time") spent on a case. Therefore, the truthfulness of an anesthesia practitioner's times can be objectively evaluated by evaluating the presence of statistical anomalies such as an excess number of anesthesia times ending in a multiple of 5. In this study, we characterized the incidence and consequences of inappropriate discretion among anesthesia providers, as measured by anomalous patterns of anesthesia times.

Methods: Using data from the National Anesthesia Clinical Outcomes Registry, we created a sample consisting of 4,221 anesthesia practitioners who performed 6,261,955 cases across 931 facilities between January 1, 2010 and Mar 31, 2015. As a first step, we identified providers with anomalous patterns as those reporting an unusually high number of anesthesia times ending in a multiple of five (e.g., 65 minutes). We then examined the degree to which these providers reported longer anesthesia times.

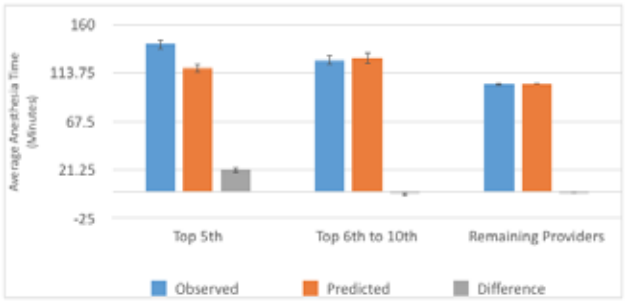

Figure 1: Reported and Expected Anesthesia Times

Anesthesia practitioners were classified into one of three groups based on the extent to which their reported anesthesia times ended in a multiple of 5 minutes (top 5th percentile, top 6th to 10th percentile, and remaining practitioners). **Figure 1** reports the mean observed anesthesia times, mean expected anesthesia times, and the mean difference between the observed and expected time for each group. Error bars with

95% CI are shown and are corrected for clustering within practitioners.

Results: The incidence of anomalous billing patterns (specifically, an excess number of cases ending in a multiple of 5) was high among our sample. For 20% of anesthesia practitioners, the percentage of cases ending in a multiple of 5 was significantly (at the $p<0.00001$ level) higher than the expected value of 20%. For anesthesia practitioners in the top 5th percentile (n=212), the proportion of cases ending in a multiple of 5 ranged from 36.8% to 96.1% of cases. Moreover, practitioners in the top 5th percentile submitted anesthesia times that exceeded the expected time (adjusted for facility, case mix, and patient comorbidities) by 22.3 minutes (95%CI 16.7-27.8) on average (Figure 1).

Conclusions: A small minority of anesthesia practitioners report a higher-than-expected proportion of anesthesia times ending in a multiple of 5 minutes, which reflects anomalous billing. On average, these practitioners also sought reimbursement for longer than expected anesthesia times.

Clin Studies/OC 82 (131)
High-Sensitivity Cardiac Troponin for the Diagnosis of Perioperative Myocardial Injury and Infarction: A Comparison of Different Approaches

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Introduction: A particularly notable feature of recently introduced high-sensitivity cardiac troponin (hscTn) assays is the ability to detect preoperative baseline values, which allows the comparison with postoperative values and the quantification of relative and absolute change. Change metrics for hscTn have been advocated by experts for the diagnosis of acute MI. However, for the diagnosis of perioperative myocardial injury or infarction (MI) no evidence exists as to which metrics may be optimal.

Methods: In an ancillary study to the Vitamins in Nitrous Oxide Trial, we compared several approaches to diagnose perioperative MI according to the Third Universal Definition of MI. Myocardial injury was defined as cardiac troponin elevation without ischemic ECG changes. Patient had serial 12-lead ECGs and standard cTnI as well as hscTnT obtained preoperatively and on the first 3 postoperative days. To diagnose MI, two conditions had to be met: (1) ECG changes indicative of myocardial ischemia and (2) cTn elevation >99th percentile URL.

Table 1: Patients who meet Diagnosis of MI by Day

Standard cardiac- Troponin I	EOS	POD 1	PO D2	POD 3	Total Number of MI
New Postop is >=99th %tile (>=0.07 ug/L)	4	13	17	11	35 (5.8%)
New Postop is >=99th %tile and baseline cTnI is <99th	1	9	15	10	29 (4.8%)
cTnI increase >=50% from baseline and baseline is <99th %tile, or cTnI increase >=20% from baseline and baseline is >99th %tile (ACCF	3	15	18	11	37 (6.1%)
High sensitivity- cardiac Troponin T (hs-cTnT)	**EOS**	**POD 1**	**PO D2**	**POD 3**	**Total Number of MI**
Postop hs-cTnT >=99th %tile	17	37	26	12	63 (10.4%)
Postop hs-cTnT >=99th %tile if baseline <99th	2	10	6	5	18 (3.0%)
Postop hs-cTnT increased >=50% from baseline	5	19	16	9	39 (6.4%)
Postop hs-cTnT increased >=50% from th	2	9	7	5	16 (2.6%)
Postop hs-cTnT increased >=100% from baseline	4	12	13	9	33 (5.4%)
Postop hs-cTnT increased >=100% from baseline and	2	6	6	5	15 (2.5%)
Postop hs-cTnT increased by >=100% if baseline <99th%.	5	17	15	9	39 (6.4%)
Postop increased by 5µg/L or more compared to baseline hscTnT	7	23	19	10	44 (7.2%)
Postop increased by 10 µg/L or more compared to	7	18	16	9	37 (6.1%)

Results: Out of 607 study patients, 70 patients developed ischemic changes on postoperative ECGs (11.5%). 82 patients (13.5%) developed new postoperative cTnI elevation using a standard assay. 351 patients (57.8%) developed a new hscTnT elevation >99th percentile; 177 patients (29.2%) had a >50% hscTnT increase, and 89 patients a >100% increase (14.7%). Using standard cTnI plus ischemic ECG signs as criteria, 35 patients (5.8%) met the criteria for postoperative MI. Using hscTnT plus ischemic ECG signs as criteria, up to twice as many patients met the criteria for acute MI (max: n=63, 10.4%; Table 1). Based on the hscTnT metric, the incidence rate of postoperative myocardial injury was between 7.9% (n=48) and 52.6% (n=319).

Conclusions: The adoption of novel hscTn assays has the potential to substantially increase the number of patients who meet the criteria for postoperative MI and myocardial injury compared to standard cardiac troponin assays. The choice of hscTn metric will have a substantial influence on incidence rates.

Clin Studies/OC 83 (145)

The Relationship between Intraoperative Hypotension, Defined by Reduction from Baseline or Absolute Thresholds, and Myocardial Injury after Non-Cardiac Surgery: A Retrospective Cohort Analysis

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Introduction and General Purpose of the Study: Intraoperative hypotension is associated with postoperative morbidity and mortality. Classical anesthesia teaching suggests keeping blood pressure within 20% of preoperative values. Several recent studies report associations between blood pressure below various absolute thresholds and organ injury.[1-5] But how best to characterize intraoperative hypotension, and whether it is important to use preoperative pressures as a reference remain unclear. We thus assessed the relationship between myocardial injury, and intraoperative absolute (intraoperative MAP) and relative (reduction from preoperative pressure) mean arterial pressure thresholds.

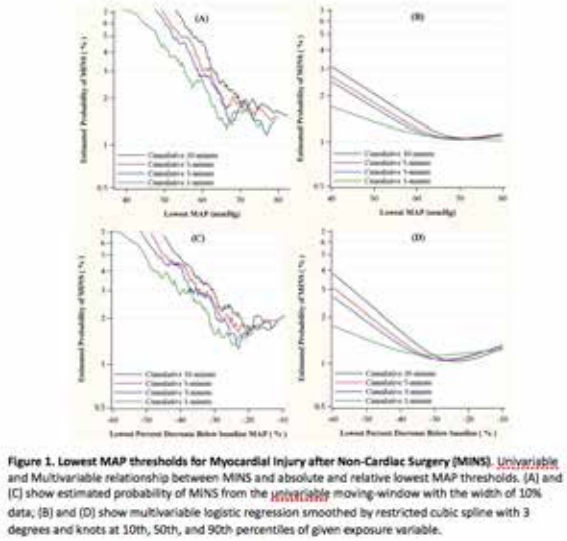

Figure 1. Lowest MAP thresholds for Myocardial Injury after Non-Cardiac Surgery (MINS). Univariable and Multivariable relationship between MINS and absolute and relative lowest MAP thresholds. (A) and (C) show estimated probability of MINS from the univariable moving-window with the width of 10% data; (B) and (D) show multivariable logistic regression smoothed by restricted cubic spline with 3 degrees and knots at 10th, 50th, and 90th percentiles of given exposure variable.

Methods: We assessed the relationship between absolute MAP thresholds or the percentage reduction in MAP from baseline, and myocardial injury after noncardiac surgery (MINS). We characterized hypotension by lowest MAP below various absolute and relative thresholds for cumulative 1, 3, 5, or 10 minutes. We also measured time weighed average MAP below various absolute and relative thresholds to assess total hypotensive exposure. We modeled relationships using logistic regression, using restricted cubic splines to estimate trends. We then evaluated the interaction between preoperative MAP and the relationships between intraoperative hypotension and MINS. Finally, we assessed the strength of associations between absolute and relative thresholds, and MINS using C statistics.

Results and Major Findings: MAPs below an absolute threshold of 65 mmHg or a relative threshold of 20% below baseline were progressively related to myocardial injury. At any given threshold, prolonged exposure increased odds (Figure 1). Increased time weighted average MAP below all absolute thresholds increased odds of MINS. A similar but less prominent relationship was present for relative thresholds. There were no clinically important interactions between preoperative blood pressures and relationship between hypotension and MINS at intraoperative mean arterial blood pressures below 65 mmHg. Absolute and relative thresholds were comparably predictive of MINS (univariable C statistics ~ 0.60-0.66).

Conclusion: Pressures that until recently were considered clinically acceptable, for instance a mean arterial pressure of 65 mmHg, were associated with myocardial injury. At lower pressures, association was stronger and only brief exposures were required. While we cannot assess causality, our results suggest that maintaining MAP>65 mmHg may reduce the risk of myocardial injury - the leading cause of 30-day postoperative mortality. Associations based on relative thresholds were no stronger than those based on absolute thresholds. Furthermore, there was no clinically important interaction with preoperative pressure. Anesthetic management can thus be based on intraoperative pressures without regard to preoperative pressure. This result is fortuitous because absolute thresholds are easier to use in that they do not require a reliable baseline pressure, and can thus more easily be incorporated into decision support systems.

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Clin Studies/OC 85 (163)

Low Health Literacy is a Predictor of Hospital Admission, Length of Stay and Other Hospital Quality Outcomes

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Importance: Prior studies have shown that health literacy can impact patient outcomes, but the role of health literacy in perioperative care and its impact on postoperative outcomes is not well understood.

Objective: To determine the effect of health literacy on likelihood of hospital admission, hospital length of stay, days to discharge, postoperative days to readmission or death, and risk of 30-day readmission.

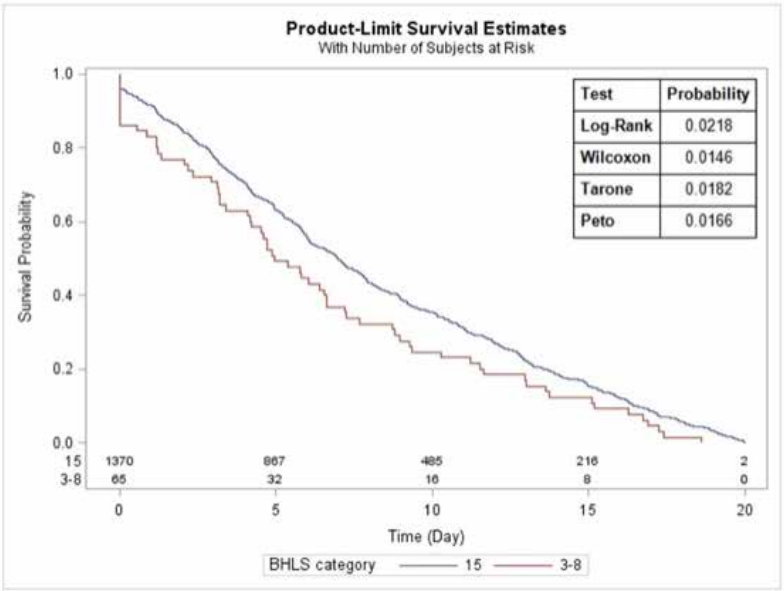
Design, Setting, and Participants: Retrospective observational study of patients over 18 years of age who completed a brief health literacy screen between 2010 and 2014 and subsequently underwent a non-emergent surgical procedure at a tertiary care academic medical center.

Exposure: The brief health literacy screen was used to assign patients a score from 3-15, with lower scores indicating potential health literacy limitations.

Main Outcome Measures: Risk of hospital admission after surgery, postoperative hospital length of stay, days to discharge, days to readmission or death, and risk of 30-day readmission.

Result: Of the total 66,106 patients analyzed, 79%, 12%, 6%, and 3% had brief health literacy screen scores of 15, 12 to 14, 9 to 11, and less than 9, respectively. Patients with a low level of health literacy as measured by health literacy scores were more likely to be older, male, less healthy, less educated, and covered by Medicare. Lower scores were associated with an increased risk of hospitalization and readmission, as well as longer postoperative lengths of stay.

Kaplan Meier curves for readmission or death



Conclusions and Relevance: Recovery after surgery often requires knowledge, self-care, and medication adherence. Since low health literacy is a modifiable predictor postoperative outcomes, interventions aimed at reducing hospitalization, postoperative length of stay, and postoperative readmissions should consider the role of health literacy.

Clin Studies/OC 86 (164)

Ace Inhibitors and Angiotensin Antagonists Were Not Associated With Decrease in Incidence of Postoperative Delirium in Surgical ICU Patients

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Introduction: The incidence of Postoperative delirium varies between 1-52% and is associated with significant morbidity and mortality. It was associated with poor functional and cognitive outcomes, longer hospital stay and higher health care costs. The etiology of postoperative delirium is not clear and preoperative medications are known to be the most common cause of post-operative delirium. Statins had been associated with decreased incidence and beta blockers with increased incidence of delirium. The positive effects of ACE inhibitors on cognitive function has been explored in non-operative settings. However there is paucity of data whether ACE inhibitors had this protective effect during perioperative settings and hence we sought to find association between ACE inhibitors and postoperative delirium.

Methods: We included adult patients who were admitted to surgical intensive care unit (SICU) after non-cardiac surgery between 2011 and 2014. We excluded patients with preoperative diagnosis of dementia, preoperative altered level of consciousness and patients undergoing carotid endarterectomy. After approval from the Institutional Review Board and waiver of individual patient consent, demographic and perioperative clinical information of patients were obtained from the Institute's Patient Registry. Delirium was assessed using the Confusion Assessment Method. We considered patients to have experienced postoperative delirium when CAM testing was positive at any assessment during SICU stay. CAM evaluates four features: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and, 4) altered consciousness. A positive CAM test was defined by the presence of features 1 and 2, and either 3 or 4.

Statistical Analysis: We used propensity-score matching to control for the potential confounders. A greedy distance matching algorithm (using a maximum allowable propensity score difference of 0.1 units) was used. Then, we compared the two matched groups on the incidence of delirium during SICU stay, using a multivariable logistic regression model with a backward model selection procedure (alpha-to-stay criterion was 0.1).

Results: We utilized data from 1,733 patients including 121 patients who were treated with ACEIs or ARBs in the preoperative period and 1,612 patients who were not. All patients had at least one CAM assessment during SICU stay; the median number of CAM assessments was 10 for patients treated with ACEIs or ARBs and 9 for patients who were not (Figure 1). The incidence of delirium was 42.2% for patients who were treated with ACEIs or ARBs and 45.5% for patients who were not (unadjusted P-value = 0.48). The estimated odds ratio of experiencing delirium during SICU stay was 0.87 for ACEI / ARBs patients versus control patients (P = 0.53). There were no differences between the two groups in mortality as well. Patients who were treated with ACEIs or ARBs were older in age, more likely to have higher body mass index, hypertension, a longer surgery, and higher dose of opioid as compared to the patients who were not treated with ACEIs or ARBs.

Conclusion: Treatment of ACEIs or ARBs in the preoperative period is not associated with reduction of incidence of postoperative delirium in SICU patients. The false negative results could be due to low statistical power.

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Clin Studies/OC 86 (164)

Ace Inhibitors and Angiotensin Antagonists Were Not Associated With Decrease in Incidence of Postoperative Delirium in Surgical ICU Patients

Table 1. Patient characteristics

Variable	ACEI / ARB (N = 121)	Control (N = 1,612)	ASD
Demographic & baseline variables			
Age, years	67 ± 11	62 ± 14	0.39
Gender (male), No. (%)	65 (54)	848 (53)	0.02
Caucasian, No. (%) Body	98 (81)	1318 (82)	0.02
mass index, kg/m^2 Co-	32.6 ± 8.1[1]	29.9 ± 9.2[52]	0.31
morbidity, No. (%)			0.05
History of stroke or TIA	3 (2)	29 (2)	0.14
Vascular disease Diabetes	26 (21)	259 (16)	0.12
Hypertension Psychiatric	49 (41)	556 (34)	0.77
disease	118 (98)	1156 (72)	0.17
Preoperative creatinine level, mg/dl ASA	34 (28)	577 (36)	0.02
physical status, No. (%)	1.4 ± 1.7[8]	1.4 ± 1.5[68]	0.24
I			
II			
III	0 (0)	1 (<1)	
IV	3 (2)	102 (6)	
Intraoperative variables Emergent	80 (66)	918 (57)	
surgery, No. (%) Type of	38 (31)	591 (37)	
procedure†, No. (%)			0.25
Exploratory laparotomy	8 (7)	230 (14)	
Colorectal resection			
Other organ transplantation	6 (5)	186 (12)	
Other hernia repair	9 (7)	143 (9)	
Hip replacement, total and partial	0 (0)	114 (7)	
Duration of surgery, hours	10 (8)	61 (4)	
General anesthesia, No. (%)	6 (5)	61 (4)	0.38
Estimated blood loss, L Blood	6.0 [4.1, 8.4]	4.7 [2.9, 7.3]	0.001
transfusion, No. (%)	119 (98)	1585 (98)	0.17
Hypotension, No. (%)	0.25 [0.1, 0.5]	0.2 [0.05, 0.6]	0.09
Total opioid dose (IV morphine	38 (31)	575 (36)	0.10
equivalent), mg	79 (65)	978 (61)	0.23
	28.3 [20.0, 37.5]	25.0 [15.0, 38.3]	

ASA = American Society of Anesthesiologist; TIA = transient ischemic attack

*

ASD (absolute standardized difference): Absolute difference in means or proportions divided by the pooled standard deviation.

† Type of surgery was characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. The most frequency 5 categories are listed due to limited space.

Appendix 1. Sensitivity analysis - Patient characteristics before and after propensity score matching

	Before matching			After matching		
Variable	ACEI / ARB (N = 121)	Control (N = 1,612)	ASD*	ACEI / ARB (N = 115)	Control (N = 511)	ASD*

ASA = American Society of Anesthesiologist; TIA = transient ischemic attack

* ASD (absolute standardized difference): Absolute difference in means or proportions divided by the pooled standard deviation.

† Type of surgery was characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. The most frequency 5 categories are listed due to limited space.

Appendix 1. Sensitivity analysis - Patient characteristics before and after propensity score matching

	Before matching			After matching		
Variable	ACEI / ARB (N = 121)	Control (N = 1,612)	ASD*	ACEI / ARB (N = 115)	Control (N = 511)	ASD*
Demographic & baseline variables						
Age, years	67 ± 11	62 ± 14	0.39	66 ± 11	65 ± 12	0.09
Gender (male), No. (%)	65 (54)	848 (53)	0.02	59 (51)	285 (56)	0.09
Caucasian, No. (%)	98 (81)	1318 (82)	0.02	94 (82)	426 (83)	0.04
Body mass index, kg/m^2	32.6 ± 8.1[1]	29.9 ± 9.2[52]	0.31	32.8 ± 8.2	31.1 ± 8.4	0.20
Co-morbidity, No. (%)						
History of stroke or TIA	3 (2)	29 (2)	0.05	3 (3)	8 (2)	0.07
Vascular disease	26 (21)	259 (16)	0.14	24 (21)	99 (19)	0.04
Diabetes	49 (41)	556 (34)	0.12	47 (41)	217 (42)	0.03
Hypertension	118 (98)	1156 (72)	0.77	112 (97)	485 (95)	0.13
Psychiatric disease	34 (28)	577 (36)	0.17	34 (30)	155 (30)	0.02
Preoperative creatinine level, mg/dl	1.4 ± 1.7[8]	1.4 ± 1.5[68]	0.02	1.4 ± 1.7	1.5 ± 1.8	0.08
ASA physical status, No. (%)			0.24			0.04
I	0 (0)	1 (<1)				
II	3 (2)	102 (6)		3 (3)	14 (3)	
III	80 (66)	918 (57)		76 (66)	329 (64)	
IV	38 (31)	591 (37)		36 (31)	168 (33)	
Intraoperative variables						
Emergent surgery, No. (%)	8 (7)	230 (14)	0.25	8 (7)	32 (6)	0.03
Type of procedure †, No. (%)			0.97			0.28
Exploratory laparotomy	6 (5)	186 (12)		6 (5)	30 (6)	
Colorectal resection	9 (7)	143 (9)		9 (8)	45 (9)	
Other organ transplantation	0 (0)	114 (7)		0 (0)	0 (0)	
Other hernia repair	10 (8)	61 (4)		10 (9)	45 (9)	
Hip replacement, total and partial	6 (5)	61 (4)		5 (4)	25 (5)	
Duration of surgery, hours	6.0 [4.1, 8.4]	4.7 [2.9, 7.3]	0.38	6.2 ± 2.9	5.7 ± 3.0	0.16
General anesthesia, No. (%)	119 (98)	1585 (98)	0.001	113 (98)	502 (98)	0.001
Estimated blood loss, L	0.25 [0.1, 0.5]	0.2 [0.05, 0.6]	0.17	0.25 [0.1, 0.5]	0.2 [0.05, 0.6]	0.13
Blood transfusion, No. (%)	38 (31)	575 (36)	0.09	36 (31)	154 (30)	0.03
Hypotension, No. (%)	79 (65)	978 (61)	0.10	73 (63)	307 (60)	0.07
Total opioid dose (IV morphine equivalent), mg	28.3 [20.0, 37.5]	25.0 [15.0, 38.3]	0.23	28.2 [20.0, 36.7]	26.5 [17.5, 38.3]	0.07

Clin Studies/OC 88 (167)

Frequency, Severity and Location of Perioperative Hypoxemia in Patients with No Respiratory Disease

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Background: The frequency of postoperative hypoxemia after discharge from PACU, when respiratory monitoring is significantly reduced, is not well known. A recent study (Sun et al., Anesth&Analg 2015:121(3):709-715) suggests that postoperative hypoxemia is common and persistent. This study found that 21% of adult patients presented ≥10min/h of SpO2<90% during the first 48h after non-cardiac surgery, but included patients with a variety of respiratory comorbidities and type of anesthesia (general, regional). The frequency, severity and location of postoperative hypoxemia in surgical patients with no respiratory disease in our hospital system (located at ~1,600m above sea level) are unknown. We hypothesized that hypoxemic events occurring in surgical patients without any respiratory disease would be more frequent on the postoperative floor after general anesthesia, compared to those not receiving general anesthesia.

Methods: The Epic Clarity database was queried for all procedure encounters performed in adults under anesthesia care at the University of Colorado Health System (2 community and 1 academic hospital) from 1/1/2012 to 12/31/2014. Emergencies, ICU transfers and subsequent encounters for each patient were excluded. Patients with asthma, COPD, any respiratory disease or at risk for OSA were excluded. General anesthesia was identified by the presence of any reported airway intervention. We analyzed the presence of ≥1 episode of hypoxemia, defined as a SpO2<90% reading by continuous pulse oxymetry for a minimum of 3 contiguous measurements and/or ≥3 minutes (OR/PACU) or of any duration if validated and/or manually entered in the medical chart by the patient's nurse (floor). Hypoxemic events were classified as mild (lowest SpO2 85-89%) or moderate/severe (SpO2 ≤85%). Demographics, comorbidities, postoperative respiratory therapies, and hospital length of stay were also collected. Chi Square tests were used to compare the frequency of hypoxemic events in patients with and without general anesthesia at different perioperative locations. Statistical significance was accepted at p<0.010 to adjust for the large sample size.

Table 1. Frequency, severity and location of perioperative hypoxemia in surgical adult patients with no respiratory disease.

Variables	Total (n=16,473)	General Anesthesia (n=9,548)	No General / Unknown (n=6,925)	P-value
OR				
SpO_2 86-89%	1,916 (11.6)	982 (10.3)	934 (13.5)	<0.001
SpO_2 ≤85%	967 (5.9)	507 (5.3)	460 (6.6)	<0.001
PACU				
SpO_2 86-89%	912 (5.5)	570 (6.0)	342 (4.9)	0.007
SpO_2 ≤85%	411 (2.5)	266 (2.8)	145 (2.1)	0.007
FLOOR				
SpO_2 86-89%	1,881 (11.4)	1,086 (11.4)	795 (11.5)	0.692
SpO_2 ≤85%	3,517 (21.4)	2,225 (23.3)	1,292 (18.7)	<0.001

Results: The Epic Clarity database was queried for all procedure encounters performed in adults under anesthesia care at the University of Colorado Health System (2 community and 1 academic hospital) from 1/1/2012 to 12/31/2014. Emergencies, ICU transfers and subsequent encounters for each patient were excluded. Patients with asthma, COPD, any respiratory disease or at risk for OSA were excluded. General anesthesia was identified by the presence of any reported airway intervention. We analyzed the presence of ≥1 episode of hypoxemia, defined as a SpO2<90% reading by continuous pulse oxymetry for a minimum of 3 contiguous measurements and/or ≥3 minutes (OR/PACU) or of any duration if validated and/or manually entered in the medical chart by the patient's nurse (floor). Hypoxemic events were classified as mild (lowest SpO2 85-89%) or moderate/severe (SpO2 ≤85%). Demographics, comorbidities, postoperative respiratory therapies, and hospital length of stay were also collected. Chi Square tests were used to compare the frequency of hypoxemic events in patients with and without general anesthesia at different perioperative locations. Statistical significance was accepted at p<0.010 to adjust for the large sample size.

Conclusions: Postoperative hypoxemia in patients with no respiratory disease is common. The highest frequency observed was for moderate/severe hypoxemia on the postoperative floor after general anesthesia. Further analysis of our findings and the involved risk factors is needed to identify those patients at risk. Increased awareness, monitoring and interventions may be beneficial for these patients at a priori low risk for postoperative hypoxemia.

Pain 92 (110)

Adeno-associated Viral (AAV) Vectors Expressing the Wild Type Mouse Carbonic Anhydrase-8 (Car8) Gene Inhibits Chronic Inflammatory Nociception and Regulates Calcium Signaling

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Introduction: Carbonic Anhydrase-8 (Car8) is a protein that is an allosteric regulator of inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) calcium release channel, altering affinity for the inositol 1,4,5-trisphosphate (IP3) ligands and associated excitatory calcium signaling. We generated adeno-associated viral (AAV) vectors expressing mouse wild type or mutant Car8 with a V5 tag and sought to determine their role on inflammatory pain and ITPR1 signaling.

Methods: In accordance with the guidelines of the animal care and use committee of the University of Miami, we tested mechanical and thermal sensitivity in naïve C57BLKS wildtype mice (n=12)(WT) and C57BLKS mutant mice homozygous for the 19-base pair (BP) deletion in exon 8 (Car8 wdl-/-)(MT) (n=12). We developed vectors containing the full-length wild type mouse Car8 (AAV2-V5-Car8WT) gene and the full-length mutant mouse Car8 (AAV2-V5-Car8MT) gene. Both WT and MT mouse Car8 vectors were attached to a V5 tag. The mutant Car8 gene had an inactivating exon 8 deletion mutation. We tested the in vitro effects of these vectors in N2A and HEK293 cells to study ITPR1 phosphorylation and calcium release. To study the in vivo effects of these vectors in a model of complete Freund's adjuvant CFA-induced inflammatory pain, we delivered AAV2-V5-Car8WT and AAV2-V5-Car8MT constructs to lumbar sensory neurons via direct sciatic nerve injection in Car8 deficient mutant C57BLKS/J mice.

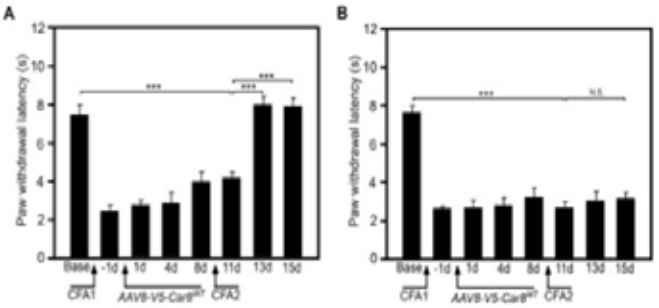

Figure 1. Gene transfer of V5-Car8^{WT} produces thermal anti-hyperalgesia in a complete Freund's adjuvant (CFA) chronic inflammatory pain model. Chronic inflammatory pain produced by injection of 30 µl 1% CFA in the left hind palm on minus day 2, and day 9. CFA induces thermal hyperalgesia starting on minus D1. Sciatic nerve injections of *AAV2-V5-Car8^{WT}* virus (1.5µl, 1.29E+14 genome copies / mL) on day zero increased basal latencies (Fig. 2A) by day 13. In contrast, sciatic nerve injections of *AAV2-V5-Car8^{MT}* virus (1.5µl, 1.61E+14 genome copies /mL) failed to alter basal thermal latencies (Fig. 2B) at any time. (N = 8. *** P<0.001 by one-way ANOVA.)

Results: In vitro analysis showed that Car8 wildtype protein overexpression down regulates ITPR1 phosphorylation and inhibits ATP-induced free calcium release in cell cultures. Both mechanical withdrawal threshold and thermal withdrawal latency are significantly decreased in Car8 deficient mutant mice as compared to wild type mice. Our neurobehavioral data demonstrate that Car8 deficiency causes both mechanical allodynia and thermal hyperalgesia at baseline. We also found that V5-Car8WT expressing constructs, but not the V5-Car8MT expressing constructs, significantly inhibited CFA-induced thermal hyperalgesia (Fig. 1 A and B) in Car8 deficient mice, suggesting an important role in inflammatory pain.

Discussion: We report the utilization of an adenovirus vector containing the wild type mouse Car8 gene as a viral vector approach to reduce inflammatory nociception and alter ITPR1 phosphorylation and calcium signaling. Our data imply that Car8 may constitute a reasonable biological target for future, novel therapies employing gene transfer in cases of intractable and persistent pain.

Pain 99 (95)

Physicians Dispense More Opioid Than Needed To Treat Same Day Surgery Pain: A Prospective Pediatric Cohort Study

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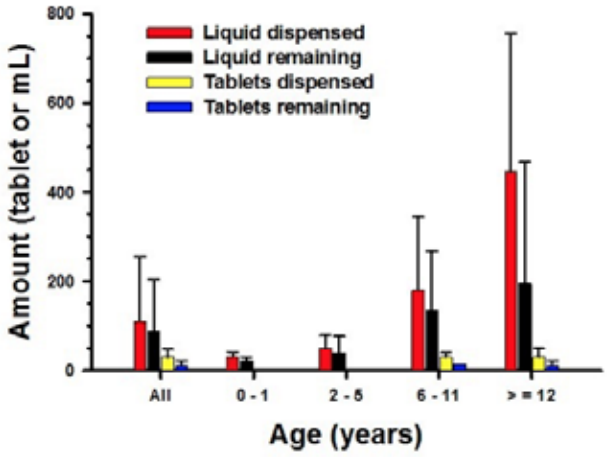
Introduction: The treatment of pain has become a national and institutional priority and has led to increases in both the number of opioid prescriptions written and the amount of drug dispensed. When over-dispensed, unused opioids can be diverted and abused, leading to an epidemic of non-medical use of prescription opioids (NMUPO). In adolescents this has become the primary source of drug addiction. The purpose of this study is to determine the amount and formulation of opioids prescribed to pediatric same day surgery patients on discharge, the amount of unused medication at the conclusion of therapy, and the disposition of this medication in order to better define the scope of this problem.

Methods: After receiving IRB approval and consent, we recruited 152 English-speaking outpatients who were given opioid prescriptions on discharge from a pediatric same day surgical suite in a university children's hospital. All prescriptions were generated with the hospital's computerized narcotic prescription writer and were analyzed by the investigators following discharge for drug, formulation, and quantity dispensed. Parents were interviewed by phone within 2 days of discharge and again 10-14 days after discharge to determine if prescriptions were filled, if pain was controlled (with a 4-point Likert scale), how long opioids were used, the amount of medication left at completion of therapy, if patients were given instructions regarding disposal of leftover drugs, and if remaining drugs were actually discarded. Additionally, the number and age of all individuals residing in the household were collected. Data are presented as means ± standard deviation.



Results: Parents of 118 (78%) enrolled patients completed the 2 day and/or 10-14 day interviews. The patients (M:F: 101:17) averaged 6.0 ± 5.0 years of age (range, 1-19 years) and 27 ± 19 kg (range, 6.0-96 kg). Oxycodone was prescribed to 85% of the patients while 15% received Hydrocodone and Acetaminophen (Lortab); 88% received the drugs in a liquid formulation, 12% received tablets. Patients took opioids for 4 ± 3 days (range, 0-11 days). Pain control was rated as excellent (51%), good (31%), fair (7%), poor (1%), and no response (10%). At 14 days, 12 ± 9 tablets (range, 3-25 tablets), 86 ± 118 mL (range, 0-505 mL), and overall 22 ± 14 doses (range, 0-60) of medication remained unused. On average, patients used only 34% of their prescribed amount. Patients averaged 1 ± 1 siblings (range, 0-6), and a quarter (26%) had a sibling aged 12 or older. Most parents (63%) were not told what to do with leftover medicine, and only 7% of parents disposed of leftover medication at the conclusion of therapy.

Conclusion: In our zeal to provide opioids to patients in moderate to severe pain, pediatric providers are dispensing far more medicine than is needed (or used) to treat pain. This excess of "left over" medication may be contributing to the epidemic of NMUPO. This is a particular concern because a quarter of our pediatric patients live in homes with adolescent siblings, for whom NMUPO is the gateway to opioid addiction. Finally, our results support the need for an improved method of opioid destruction or "take back" programs to help eliminate left over medications from entering the public domain.

Pain 100 (87)
Remotely Triggered On-Demand Adjustable Local Anesthesia

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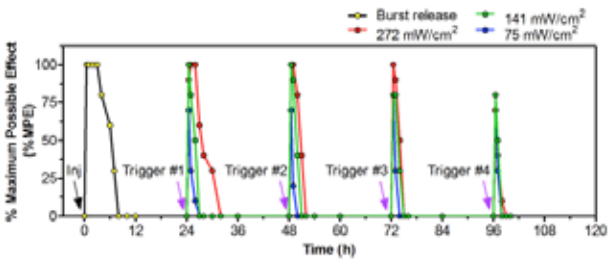
Introduction and General Purpose of the Study: Investigators have developed many drug delivery systems to provide prolonged duration local anesthesia (PDLA) for management of perioperative or chronic pain[1]. Some can provide PDLA for days from a single injection. Such systems have the have the limitation that nerve blockade lasts until the drug content of the device is depleted. The timing and intensity of nerve blockade cannot be modulated to account for changes in daily activity or level of pain. This may be particularly burdensome given that local anesthetics also cause motor nerve blockade. Devices that can produce PDLA that can be modulated in real time by the patient would be highly desirable.



We have developed two injectable liposomal formulations[2,3] that can provide on-demand adjustable local anesthesia, modulated by near infrared (NIR) light)[4-8]. One (Lip-GNR) is a liposome containing tetrodotoxin and dexmedetomidine[9], with gold nanorods attached to the lipid surfaces. Upon irradiation with NIR light, the gold nanorods heat up, increasing the permeability of the liposomes, releasing drug. In the second (Lip-PS), liposomes are composed of unsaturated lipids and contain tetrodotoxin and a NIR-absorbing photosensitizer (PdPC(OBu)8). Upon irradiation with NIR light, the photosensitizers release reactive oxygen species, which cause lipid peroxidation in the liposomes, increasing drug efflux.

Tetrodotoxin has ultrapotent local anesthetic properties. Its effects on peripheral nerve can be enhanced by co-delivery with a variety of molecules[10-12], including dexmedetomidine 9. Related compounds have been encapsulated to provide PDLA[2,3,13-16].

Methods: Lip-GNR and Lip-PS were formulated as described, and drug loading and efflux were characterized[2,3].

Lip-GNR were infiltrated in the rat footpad, and local anesthesia was assessed with a Touch Test® Sensory Evaluator. For four days after injection, the injection site was irradiated with a 808 nm laser at 141 mW/cm2 for 10 minutes, and local anesthesia was monitored.

Lip-PS were injected at the rat sciatic nerve, rats then underwent footpad hotplate testing [16,17]. At predetermined intervals, the site of injection was irradiated with a 730 nm laser, and local anesthesia was monitored.

Results and Major Findings: Injection of Lip-GNR and Lip-PS produced transient local anesthesia. Subsequent irradiation produced on-demand and repeated anesthesia (e.g. Fig. 1 for Lip-GNR). The timing, intensity, and duration of nerve blockade could be controlled by adjusting the timing, irradiance, and duration of irradiation (e.g. Fig. 2 for Lip-PS). Tissue toxicity was minimal.

Conclusion: Triggerable sustained release systems provide the possibility of on-demand adjustable local anesthesia.

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Pain 101 (177)

Acute and Subacute Postoperative Pain after Partial and Total Mastectomy: Association with Prospectively Assessed Psychosocial and Psychophysical Variables

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Introduction: Breast cancer is the most common form of female cancer, the treatment of which often involves surgery. Previous reports cite persistent postmastectomy pain (PPMP) incidence around 30%, and putative risk factors include younger age, type of surgery, axillary dissection, anesthetic technique, genetics, negative affect (psychosocial factors) and increased pain sensitivity (psychophysical factors). However, most previous studies of PPMP have been retrospective and cross sectional in design.

Methods: In the current study, a broad array of potential risk factors were assessed in women prospectively before surgery. Patients undergoing partial or total mastectomy were recruited and underwent preoperative assessment including validated psychosocial (anxiety, depression, catastrophizing, sleep disturbance etc) and psychophysical (quantitative sensory testing; pressure tolerance, pressure threshold, pinprick temporal summation and aftersensation pain) measures. Their degree of surgically related pain was then assessed using the Breast Cancer Pain Questionnaire, including frequency, severity and number of body areas assessments to determine a pain burden index (PBI) at several time points after surgery.

Results: Patients undergoing more extensive surgery reported higher acute pain (postoperative day 0 and 1), with severity correlating with surgical extent (bilateral mastectomy> unilateral mastectomy> lumpectomy), as well as younger age, and higher preoperative psychosocial dysfunction (high catastrophizing, anxiety, depression). Subacute postoperative pain (postoperative day 14) also correlated with younger age and preoperative psychosocial dysfunction, but not surgical extent and duration. By 90 days after surgery, PBI was no longer associated with age or surgical factors, but remained correlated with preoperative psychosocial factors, as well as heightened baseline sensory processing (higher temporal summation of pain and painful aftersensations).

Conclusions: These findings suggest that the factors influencing acute pain after surgery may differ somewhat from those that predict more persistent pain. By more extensively phenotyping individual differences in pain processing in the preoperative period, we may differentially identify those at greater risk of acute vs chronic postsurgical pain, and design preventive therapies accordingly.

Pain 102 (176)

Sp1-like Transcription Factor Inhibitor Mithramycin – A, Reverses Platinum – Induced Pain Behaviors in Mice

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Introduction: Successful treatment of patients suffering from cancers often require the administration of chemotherapeutic agents that are associated with the development of acute and chronic painful conditions. Referred to as: Chemotherapy Induced Peripheral Neuropathy, CIPN includes painful states as mechanical allodynia and in the case of oxaliplatin cold allodynia. The pain associated with platinum - based anticancer agents such as oxaliplatin (mechanical and cold - allodynia) are resistant to effective treatment that degrades the quality of life of cancer survivors. Evidence suggests that binding of platinum - based compounds such as oxaliplatin to the DNA of peripheral sensory neurons results in the development of CIPN and may involve expression of TRPV1. Building on our understanding of Sp1 and Sp4 - dependent expression of TRPV1 in sensory neurons, we have investigated the ability of an inhibitor of Sp1-like transcription factors to block a mouse model of painful CIPN.

Methods: Following approval from the IACUC, we conducted behavioral studies (mechanical allodynia - von Frey and cold plate 10 C latency) on male wild type (wt) C57Bl/6 mice following i.p. injection of either vehicle or oxaliplatin (3mg/kg) as a single or twice weekly dose for four cycles of treatment. Two sequential daily doses of the Sp1-inhibitor, mithramycin-A (MTM), (100 mcg/kg) was then administered. Primary dorsal root ganglion (DRG) neurons were harvested from mice, cultured and changes in intracellular calcium to cold buffer (12 C) measured. Sp4 +/- knockdown mice were also studied. Differences ANOVA required a minimum of $n=6$; $p<0.05$.

Results: A single dose of oxaliplatin in wt mice induced a decrease in mechanical threshold and cold plate paw withdrawal latency beginning at 24 hours and lasting up to three weeks. MTM treatment at 48 hours reversed both the mechanical and cold plate allodynia seen with oxaliplatin. DRG neurons derived ex vivo from oxaliplatin-treated wt mice had the greatest percentage of cold-responding neurons. MTM-treatment showed a reversal of this observation with a reduction of cold responding neurons. Wt mice treated with repeated cycles of oxaliplatin developed persistent (1 month) mechanical and cold allodynia. MTM successfully reversed oxaliplatin mechanical and cold allodynia at one month. In a parallel genetic approach, Sp4+/- heterozygous knockdown mice injected with oxaliplatin failed to develop persistent mechanical or cold allodynia.

Conclusions: A small-molecule inhibitor of Sp1-like transcription factors, mithramycin-A, was found to reverse both short-term (days) and long-term (weeks) oxaliplatin-induced painful mechanical and cold-allodynia in mice. MTM-directed reversal of cold allodynia appeared to parallel ex vivo changes in cold-induced responses in cultured DRG neurons. Mice containing a genetic knockdown of transcription factor Sp4+/- (a target of MTM) failed to develop persistent oxaliplatin-induced mechanical and cold allodynia. Use of inhibitors of the Sp1-like transcription factor family may hold promise to better understand platinum-induce painful CIPN and one day help develop an effective strategy to block or reverse chemotherapy-induced pain.

Pain 103 (136)
Development of a Functional Connectivity Tool for Identifying Pain

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Introduction: The lack of an objective indicator for pain hampers disease diagnosis and the evaluation of treatment response needed for the development of both drug and non-drug chronic pain treatments. Attempts to objectively measure pain have been met with limited success[1]. Functional connectivity MRI (fcMRI) offers a promising new avenue toward a neuroimaging based method for differentiating between pain and non-pain states [2,3]. The insula is a key region for pain processing, with changes in both activity and functional connectivity shown for acute and chronic pain states[4].

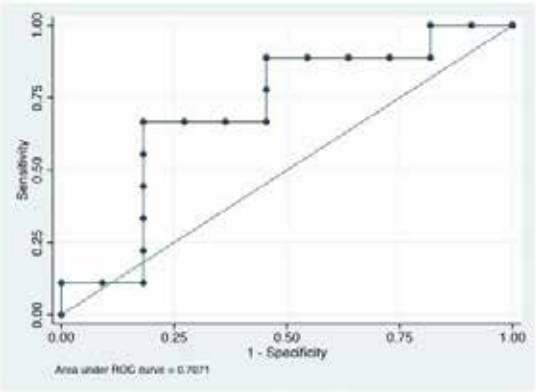

Figure 2. Receiver operating characteristic (ROC) curve for pIns-PCC connectivity in the detection of pain. Area under the curve is 0.71 (95% CI = 0.46 – 0.95).

Purpose: Prior work optimized the application of fcMRI to the study of pain[5], and demonstrated that functional connectivity between the posterior insula (pIns) and posterior cingulate cortex (PCC) is uniquely altered by pain perception[6]. Further, using a carefully selected pIns-PCC connectivity threshold value, we were able to differentiate pain scans from non-pain scans with 92% accuracy. The current study sought to validate our previous findings with the use of an independent sample that included an innocuous touch as a non-painful control condition.

Methods: We present interim results of 3T BOLD functional imaging data from 5 healthy adults in each of 4 conditions: rest, innocuous touch, light pain, and moderate pain. Innocuous touch consisted of a researcher moving a gauze pad around the left volar forearm of each subject randomly to ensure the salience of this stimulus. Pain was induced with a 30-minute topical application of capsaicin to the same region of the left volar forearm. The light pain condition occurred at the beginning of this period; the moderate pain condition occurred at the end. Functional connectivity maps were generated using the CONN toolbox for SPM. ROC curves were generated to assess the capacity of pIns to PCC connectivity to identify the presence of pain. Our previously determined pIns-PCC connectivity threshold was assessed for overall accuracy of classification, sensitivity, and specificity.

Results: Group average functional connectivity maps revealed altered pIns to PCC connectivity in response to pain, consistent with our previous findings. The area under the ROC curve for pIns-PCC connectivity in predicting the presence of pain was 0.71 (95% CI = 0.46-0.95; Figure). Using our previously determined connectivity threshold value, we were able to differentiate non-pain scans (i.e., rest, innocuous touch) from pain scans (i.e., light pain, moderate pain) with 70% overall accuracy (sensitivity = 0.9, specificity = 0.5).

Conclusions: These preliminary results support our prior and suggests that a pIns-PCC connectivity threshold is sensitive to pain state, although improvements are needed to increase the specificity. Future work will build upon these finding by varying pain stimulus modality and intensity, enabling us to refine our imaging technique for detecting acute pain. This more accurate model will then be tested in patients with chronic osteoarthritis hip pain pre and post arthroplasty.

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Pain 104 (53)
Modulation of Long-Term Auditory Memory by Acute Pain, Including During Sedation with Midazolam and Dexmedetomidine

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Introduction: Acute pain is an attention-demanding stimulus that impairs explicit memory in awake subjects[1] This contrasts with conflicting evidence from patients under general anesthesia that opioid analgesia may reduce [2] or have no effect [3] on implicit memory. The purpose of this study was to determine if long-term memory for auditory stimuli would be modulated when paired with pain stimulation during infusion of saline versus low-dose midazolam (Mdz) or dexmedetomidine (Dex). Our hypotheses were that pain would impair memory under saline, but attenuate the memory-impairing effects of the anesthetic agents by transiently heightening arousal.

Methods: This preliminary study includes 5 healthy adults (2 male), with mean (sd) age 23.2 (1.7) years. A list of 90 words was played 3 times (random order), and subjects made classifications (e.g. alive or not) about each. Thirty of the words were consistently followed by a 1 s painful (rated 7/10) electrical stimulation. Either drug was then administered via target-controlled infusion to effect site concentrations: 20 ng/ml for Mdz or 0.15 ng/ml for Dex. After steady-state was reached, the same experimental procedures were repeated with a new word list. During memory testing (24 hours later), previous words were intermixed with an equal number of novel words. Subjects responded using the Remember-Know-New procedure [4]. "Remember" indicated recall of specific (episodic) details. "Know" was for familiarity with no specific association recalled. "New" indicated no recognition. Subjects received the other drug during a subsequent visit (with different words). As in a similar study [5], d' (d-prime) was calculated for each condition; d' reflects the proportion of words correctly identified with the false-alarm rate incorporated to account for subject's discrimination threshold. Paired t-tests were performed on the d' values.

Table 1. Memory testing results separated by response category, drug condition, and pair pairing.

Drug Condition & Pain Pairing	Remember + Know			Remember Only			Know Only		
	Average Hit Rate	Average FAR	Average d'	Average Hit Rate	Average FAR	Average d'	Average Hit Rate	Average FAR	Average d'
Saline									
No Pain	0.87	0.23	2.10	0.57	0.07	2.05	0.30	0.16	0.49
+ Pain	0.86	0.23	2.09	0.57	0.07	2.06	0.29	0.16	0.42
Midazolam									
No Pain	0.42	0.23	0.59	0.10	0.07	0.34	0.31	0.16	0.58
+ Pain	0.39	0.23	0.51	0.06	0.07	-0.01 *	0.33	0.16	0.64
Dexmedetomidine									
No Pain	0.63	0.23	1.19	0.31	0.06	1.48	0.42	0.17	0.77
+ Pain	0.62	0.23	1.29	0.33	0.06	1.56	0.35	0.17	0.55

Hit Rate is number of words correctly identified in each response category. FAR = false-alarm rate. Statistically significant differences due to pain pairing are denoted by an asterisk (*).

Results: The group average memory results are shown in Table 1. Driven by large differences in "Remember" responses, d' was significantly lower with both Dex and Mdz, compared to saline. Decreased "Remember" responses with pain under Mdz were significant across subjects ($p = 0.006$). Examination of the individual subject results revealed wide variability in memory under either anesthetic agent, with pain-pairing resulting in memory improvements, memory worsening, and no difference in memory performance.

Conclusions: We have developed an experimental framework for determining how pain influences auditory memory at baseline and under light sedation with two distinct anesthetic agents. Preliminary findings suggest decreased memory with pain, but subjects varied greatly in memory performance as functions of both pain-pairing and sedative given. Additional data collected in more subjects should allow more definitive conclusions to be drawn.

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Pain 105 (49)
Stem Cells Reversed Morphine Tolerance and Opioid-induced Hyperalgesia

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Background: More than 240 million opioid prescriptions are dispensed annually to treat moderate to severe pain. However, the use of opioids is commonly associated with opioid tolerance (OT) and opioid-induced hyperalgesia (OIH), which limit efficacy and compromise safety of opioid therapy. We aim to develop an effective way to prevent or treat OT and OIH, which are major clinical challenges to a wide range of medical professionals and patients alike on a daily basis. One of the most important discoveries in recent years is the recognition that both OT and chronic pain are associated with neuroinflammation mediated, at least in part, by activation of immune cells and glial cells in the central nervous system. Mesenchymal stem cells (MSCs) have been shown to possess remarkable anti-inflammatory and immune modulatory properties and MSC transplantation (MSC-TP) has shown promise to reduce pain consequent to nerve injuries. We hypothesized MSC-TP prevents OT and OIH in rats and mice.

Methods: With IACUC approval, we isolated MSCs from the rat bone marrow, characterized their properties by flow cytometry and functional differentiations. MSC-TP was performed in rats and mice either intravenously or intrathecally one day or 7 days before the initiation of repeated daily morphine injections or 14 days after daily morphine injection. OT and OIH were evaluated by foot paw withdrawal thresholds in response to mechanical or thermal stimulation and tail flick test by two groups of investigators who were blinded to the treatment. Immunohistochemistry was used to evaluate the levels of activation of microglia and astrocytes. The long term safety and toxicity of MSC-TP were evaluated by vital functions and histopathology.

Results: We found that the development of OT and OIH was effectively prevented by either intravenous or intrathecal MSCs, which were transplanted before morphine treatment. Remarkably, established OT and OIH were significantly reversed by either intravenous or intrathecal MSCs when the cells were transplanted after repeated morphine injections. These effects were observed in rats and mice and were confirmed by two groups of investigators independently. The animals did not show any abnormality in vital organs or functions. Immunohistochemistry revealed that the treatments significantly reduced the level of activation of microglia and astrocytes in the spinal cord.

Conclusions: Daily morphine injections produced OT and OIH and activated microglia and astrocytes in the spinal cord dorsal horn. MSC-TP was safe and effective to prevent and treat OT and OIH regardless the route and timing of administration in both rats and mice. MSC-TP may have achieved these effects by attenuating the levels of activation of microglia and astrocytes. We have thus demonstrated that MSC-TP promises to be a safe and effective way to prevent and reverse two of the major problems of opioid therapy.

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Disclosure to Learners (May 17, 2016)

Association of University Anesthesiologists 63rd Annual Meeting

Continuing Medical Education (CME) Activity Information

Activity Overview
Findings from new research and the evolution of anesthesiology practice based on emerging evidence create an inherent gap between existing practice and new practice models. The purpose of the Association of University Anesthesiologists (AUA) 63rd Annual Meeting is to provide an evidence-based and clinically-oriented educational activity that will improve competence and performance in the anesthesiology specialty, resulting in improved patient care and outcomes.

Target Audience
The AUA 63rd Annual Meeting is designed to address the continuing medical education needs of anesthesiologists, anesthesiologists-in-training, and anesthesia investigators in academic, clinical and laboratory settings.

Educational Objectives
As a result of participating in this live CME activity, learners will be able to:

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

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

CME Credit
The International Anesthesia Research Society (IARS) designates this live activity for a maximum of 14.5 *AMA PRA Category 1 Credits.™* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Claiming CME Credit
The IARS will provide online program evaluation and session tracking to support claiming CME credit immediately following the close of the live activity.

Disclosure to Learners

Disclosure
The International Anesthesia Research Society (IARS) makes every effort to develop CME activities that are independent, objective, scientifically balanced presentations of information. The IARS has implemented mechanisms requiring everyone in a position to control content to disclose all relevant financial relationships with commercial interests. Relevant financial relationships are defined as financial relationships in any amount occurring within the past 12 months, including financial relationships of the spouse or partner of the person in control of content. Disclosure of any or no relationships is made available in advance of all educational activities. The IARS evaluates, and if necessary, resolves any conflicts of interest prior to the start of the activity. Individuals who refuse or fail to provide the required disclosures are disqualified from being a planning committee member, teacher, or author of CME, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.

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Disclaimer
The information provided in this CME activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient's medical condition.

Commercial Support
This CME activity is supported entirely by the Association of University Anesthesiologists. There is no commercial support for this activity.

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Disclosure to Learners

Course Faculty, Moderators, Reviewers, and Abstract Authors/Presenters Disclosures
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Name of Individual:	**Name of Commercial Interest(s):**	**Nature of Relationship(s):**
David W Kaczka, MD, PhD	Self-owned patent	Intellectual Property Rights
Alex Macario, MD, MBA	Merck	Consulting Fees
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