Syllabus

AUA 64th Annual Meeting | May 4–5, 2017

Grand Hyatt Washington, Washington, DC

Hosted by

Johns Hopkins Medicine and University of Maryland School of Medicine

AUA
Association of University Anesthesiologists

JOHNS HOPKINS
MEDICINE

UNIVERSITY OF MARYLAND

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Welcome to the AUA 64th Annual Meeting!

Welcome to the AUA 64th Annual Meeting, co-hosted by Johns Hopkins Medicine and the University of Maryland School of Medicine, May 4-5, in the nation's capital, Washington, DC. The Educational Advisory Board (EAB), Scientific Advisory Board (SAB), and the Host Institutions, Drs. Robert R. Gaiser, Y.S. Prakash, Colleen Koch, and Peter Rock have developed a compelling program with valuable insight into current discoveries in academic anesthesia and the practice as a whole.

Here are some of the highlights of this year's Annual Meeting:

Thursday, May 4

The ***Scientific Advisory Board (SAB)*** will highlight original research in the clinic and laboratory during two ***Oral Sessions I and II***, and the first of two ***Moderated Poster Discussion Sessions*** where attendees and abstract presenters will exchange ideas on a wide range of original research. The first ***EAB Program Panel Part I: The Science of Assessment of Clinical Performance*** will discuss the application of clinical performance and performance assessment in academic anesthesia. Johns Hopkins Medicine and the University of Maryland School of Medicine will share what makes their programs unique during two panels, ***Host Program Panel I and II***. Plus, be sure to relax and meet your colleagues from the United Kingdom, who are joining us for the second year, for an evening of networking at the **British Journal of Anaesthesia &** ***Anaesthetic Research Society Reception***, from 6:30 pm to 8:00 pm.

Friday, May 5

Friday includes two more engaging ***SAB Oral Sessions III and IV*** and offers an opportunity to hear from your colleagues about their research at the second ***Moderated Poster Discussion Session***. The ***EAB Program Panel Part II: The Evidence Behind the "Hot" Topics in Anesthesia***, will focus on a variety of learning methods such as the flipped classroom, space education and test-enhanced learning. The ***President's Panel*** will aim to answer the important question, ***Hypoxia is Not Always Bad for You?*** Be sure to sign-up to attend the ***Social Event Reception***, hosted by Johns Hopkins Medicine and University of Maryland School of Medicine, at the home of the world's largest and most significant collection of aviation and space artifacts, the Smithsonian's National Air and Space Museum.

Saturday, May 6 – Aligned Meeting Day at the IARS Annual Meeting

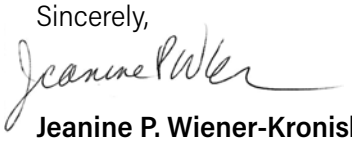
Stay an extra day and attend the Aligned Meeting Day sessions at the IARS 2017 Annual Meeting, included with your AUA registration fee.

Aligned Meeting Day Sessions include:

- **T.H. Seldon Memorial Lecture with Dr. Victor J. Dzau, MD** – 8:00 am - 9:00 am
- **AUA Symposium: Recognizing the "Painful" Truths of the Opioid Abuse Epidemic** – 9:30 am - 12:30 pm
- **IARS Scholars' Program** – 9:30 am - 6:00 pm
- **IARS Alignment Reception** – 6:00 pm to 7:30 pm

I am certain you will find the educational and networking opportunities, available at the AUA Annual Meeting, to be thought-provoking and rewarding while experiencing some of the meaningful history, beauty, and culture of our nation's capital, Washington, DC! I look forward to sharing this time together!

Sincerely,



Jeanine P. Wiener-Kronish, MD
President, Association of University Anesthesiologists (AUA)

Welcome from Your Co-Hosts

Dear Colleagues:

We are excited to co-host our Annual AUA Meeting in Washington, DC As the local co-hosts, we would like to welcome you to Baltimore and Washington, DC and provide recommendations for local Washington, DC and Baltimore attractions.

May is the best time of the year in Baltimore (Charm City)! Baltimore, home of your host institutions, is only a 45-minute train ride from Washington's Union Station, using either MARC (commuter) or Amtrak service. Did you know that Baltimore's Fort McHenry, birthplace of the National Anthem and penned by Francis Scott Key, defended the Baltimore Harbor during the War of 1812? Baltimore is home to the last Civil War vessel afloat, the USS Constellation. The Baltimore Museum of Art, founded in 1914, has the largest holdings in the world from the artist Henri Matisse. You can tour American writer Edgar Allen Poe's House and Museum and learn more of his life and death in Baltimore. Ride a water taxi and explore centuries-old sea-faring neighborhoods of Fells Point, Canton, Locust Point and Baltimore's Inner Harbor. Look blacktip reef sharks in the eye at the National Aquarium, visit the Science Center, catch a college lacrosse game, or bet on a thoroughbred at old Pimlico! The Orioles will be at home at Camden yards the weekend of the AUA and IARS Annual Meetings. On May 5–7, they play the White Sox. On May 8–9, the Washington Nationals visit Baltimore for a 4-game at home and away series with the Orioles.

Washington, DC is among the most beautiful cities in the USA. Our nation's capital is situated along the Potomac River and has countless museums, monuments, neoclassical buildings, and gardens. Of note, the Smithsonian's National Museum of African Art celebrated their historic opening of the National Museum of African American History and Culture in September 2016. This is a gem! We encourage you to visit. Visit the following links for updated information on "things to do" in Washington – food, wine, cultural events, history and more: **travel.nationalgeographic.com/travel/city-guides/free-baltimore-traveler/**; and **washington.org/things-do-washington-dc** With the influx of young government and tech workers, Washington has turned into a "foodie-paradise." A quick search of the internet will reveal many unexpected gustatory delights, including many traditional, ethnic or contemporary cuisines. The individual museum websites will provide you with updated gallery information and exhibits. Please take advantage of the many sightseeing opportunities, museums, monument government buildings and landscape vistas provided by our nation's capital.

Best,

Colleen Koch, MD, MS, MBA
Mark Rogers Professor of Anesthesiology and Critical Care Medicine,
Anesthesiologist-in-Chief,
Johns Hopkins Medicine
Baltimore, Maryland

Peter Rock, MD, MBA, FCCM
Helrich Professor and Chair,
Departments of Medicine,
Surgery and Anesthesiology
University of Maryland School of Medicine
Baltimore, Maryland

WE ARE WASHINGTON DC

Welcome

Association of University Anesthesiologists
International Anesthesia Research Society
Society of Critical Care Anesthesiologists
2017 Annual Meetings

May 4, 2017

As Mayor of the District of Columbia, I am pleased to welcome participants and members of the Association of University Anesthesiologists (AUA), the International Anesthesia Research Society (IARS), and the Society of Critical Care Anesthesiologists (SOCCA) to the nation's capital for your 2017 Annual Meetings.

The AUA, IARS and SOCCA 2017 Annual Meetings bring together the leaders in anesthesiology to exchange ideas and information with the goal of improving patient care around the world.

I am delighted that you have chosen Washington, DC, to host your event this year. While you are here, I invite you to enjoy all that our city has to offer and I encourage you to visit our museums, monuments, restaurants and diverse neighborhoods.

On behalf of the residents of the District of Columbia, I wish you a successful event.

Muriel Bowser
Mayor, District of Columbia

General Information

How to Use the Syllabus

In this Syllabus, you will find the information you need to make the most of your Annual Meeting experience. Included is a complete listing of Annual Meeting events and a Schedule-at-a-Glance grid for both days.

The education sessions and Moderated Poster Discussion Sessions are listed by day and then by time in each specific section within the Syllabus.

See page 8 of this Syllabus for a map of the AUA Headquarters Hotel, Grand Hyatt Washington, with meeting rooms and registration area.

Location

AUA 64th Annual Meeting Headquarters Hotel
Grand Hyatt Washington Hotel, 1000 H St. NW, Washington, DC 20001 | 202-582-1234

Registration Hours

Thursday, May 4, 6:00 am – 6:00 pm

Friday, May 5, 6:00 am – 6:00 pm

Registration Materials

Your registration materials will be available for pick up at the Registration Desk in the Independence Foyer. Registration materials will include a general information sheet, room locator, a Moderated Poster Discussion Sessions schedule, and an attendee list.

Registration Fee

The registration fee includes the Educational Advisory Board Program, Scientific Advisory Board Program, Host Program, meeting syllabus, coffee breaks, Thursday and Friday lunches, and the Aligned Meeting Day sessions taking place at the IARS 2017 Annual Meeting and International Science Symposium on Saturday, May 6. The AUA Social Event Reception on Friday, May 5, from 6:30 pm - 9:30 pm, requires an additional fee. Transportation will be provided to all special events not located at the Grand Hyatt Washington.

Name Badges

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

Services

Internet Availability

Complimentary wireless internet is available in the conference area and all AUA scheduled meeting rooms. Open your internet browser and choose the network labeled, **"Hyatt Meetings".** When prompted for an access code, enter **IARS2017**. Please no streaming or video downloads.

Official App of the IARS, AUA and SOCCA 2017 Annual Meetings

The IARS, AUA and SOCCA 2017 Annual Meetings feature an interactive app that will allow you to view the complete event schedule, explore all sessions, and get detailed presenter information. Expand your professional network and make the most of your Annual Meeting experience! Download the interactive IARS, AUA and SOCCA 2017 Annual Meetings app, **IARS Mtgs App**, available for iPhone, iPad, Android, and HTML5 for Blackberry in the Google Play and Apple Stores. Your username for the app is the email with which you registered for the Annual

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General Information, *continued from page 6*

Meeting. The password for all users is: **iars2017**. For more information, visit the AUA website at www.auahq.org. Expand your professional network and make the most of your Annual Meeting experience!

Information

Electronic Devices

Please silence all electronic devices during education sessions. Videotaping and recording of sessions is not allowed without the written permission from the presenter.

Photography Release

The Association of University Anesthesiologists plans to take photographs at the AUA 64th Annual Meeting and to reproduce them in AUA news or promotional materials, whether in print, electronic or other media, including the AUA website. By participating in the AUA 64th Annual Meeting, you grant AUA the right to use your name, photograph, and biography for such purposes.

No Smoking Policy

Smoking is not permitted at AUA events. We respectfully request that you abide by our smoke-free policy. Thank you for your cooperation.

Special Services

If you are in need of any special services, please contact AUA staff at iarsmeeting@orchid.events or visit the Registration Desk during the annual meeting for special accommodations.

Washington, DC Travel Tips

Time Zone

Washington, DC follows Eastern Time Zone (EST).

Washington, DC Airports

There are three major airports in the Washington DC region to choose from: Ronald Reagan Washington National Airport (code: DCA), Washington Dulles International Airport (code: IAD) and Baltimore/ Washington International Thurgood Marshall Airport (code: BWI). Ronald Reagan Washington National Airport is the closest airport to the AUA Headquarters Hotel, Grand Hyatt Washington.

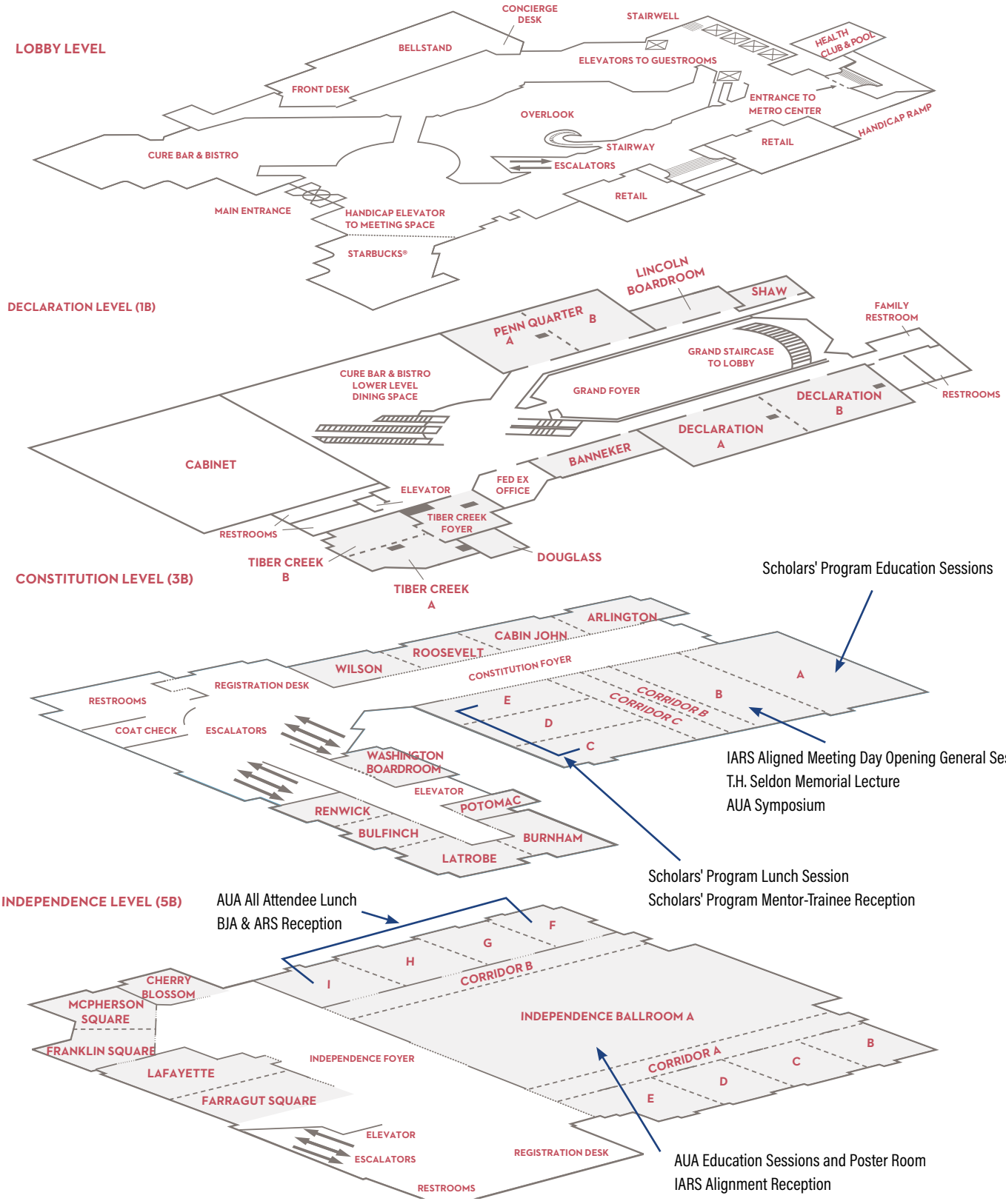
Transportation

Washington, DC is a bustling city with a great local public transportation system. The Metrorail and Metro bus offer the most clean and efficient transportation in the city providing routes to all parts of Washington, DC. The Metro Center station consists of light rail trains and buses. Base Fares range anywhere from $1.75 to $4.00, to calculate the exact cost of fare visit wmata.com/schedules/trip-planner/index.cfm. The closest Metro Center station the Grand Hyatt is located on 607 13th St NW, Washington, DC 20005, approximately 3 minutes from the Grand Hyatt Washington Hotel. Taxis, rental car services and Uber cars are also available throughout the city. For more information on traveling, visit washington.org/DC-guide-to/getting-around-washington-dc.

Weather

Although Washington, DC's weather can be extreme, the spring is milder with temperatures in the 60s and occasional showers. Pack for both rain and sunshine!

AUA Headquarters Hotel Floor Plan



What to Do in Washington, DC

Discover Washington, DC

Discover America's rich history in the nation's capital, Washington, DC and recall the significant moments in time where they first occurred. Walk the two-mile green expanse of the National Mall and take in the neoclassical monuments and buildings, including the iconic ones that house the federal government's three branches: The Capitol, White House and Supreme Court. Roam the many halls of free Smithsonian Museums, paddle on the Potomac River or sit back on a double-decker tour bus and soak in the beautiful sights of the city. Indulge in the food, wine, local breweries and funky marketplaces available in DC. From American history to culinary delicacies to cultural events, you can find it all in Washington, DC. Make the most of your time in the nation's capital! See the next page to find out how.

Washington, DC by the Numbers

2015 was the first time visitors were allowed to take photos on their White House tour as announced by Former First Lady Michelle Obama.

535 miles of book shelves and 162 million objects can be found at the Library of Congress, giving DC the largest library in the world.

60,000 objects, ranging in size from Saturn V rockets to jetliners to gliders to space helmets to microchips, can be found at the Smithsonian's National Air and Space Museum.

1,800 animals from 300 different species call the Smithsonian National Zoo home.

1884 was the year the Washington Monument was unveiled as the tallest structure in the world, standing at 555 feet and 5 1/8 inches in height, until the Eiffel Tower opened in 1889 and took the title.

59 pieces of Chinese granite make up the MLK Memorial, commemorating civil rights leader Martin Luther King, Jr., and designed and assembled by Chinese sculptor Lei Yixin.

1929 was the first year a phone was installed on the president's desk in the White House. The original phone number for the White House in 1878 was just the number 1.

2 Former presidents, Herbert Hoover and John Quincy Adams, kept pet alligators at the White House.

1800 was the year the White House was completed, a year after President George Washington's death. President John Quincy Adams was the first president to live in it.

19 feet tall and weighing almost 15,000 pounds, the bronze Statue of Freedom sculpture on the top of the U.S. Capitol Building is larger than it looks.

1901 was the year DC's first baseball team began playing as the Washington Senators. Not until 1971 was their name changed to the Washington Nationals.

180 embassies and international cultural centers are located in Washington, DC. More than 16 percent of DC residents speak a language other than English.

200 bonsai trees can be found at the National Bonsai and Penjing Museum, one of the 19 Smithsonian Museums in the city.

64,000 square feet and over 200 artifacts make up the first and only public museum in the United States solely dedicated to espionage, the International Spy Museum.

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What to Do in Washington, DC, *continued from page 9*

Explore the Top Sites in Washington, DC

National Mall and Memorial Parks

America's most visited national park, where the past, present and future come together. The monuments and memorials in this park honor American forefathers and veterans.

The 8 Must-See Memorials at the National Mall

1. The Franklin Delano Roosevelt Memorial
2. Korean War Veterans Memorial
3. Vietnam Veterans Memorial
4. Thomas Jefferson Memorial
5. Martin Luther King, Jr. Memorial
6. World War II Memorial
7. Washington Monument
8. The Lincoln Memorial

DC Neighborhoods

Find out why the District is such a unique city. There's so much to love about each one of DC's neighborhoods, from history on Capitol Hill and high-end boutiques in Georgetown to performing arts in Penn Quarter and a 24-hour diner in Adams Morgan. Get familiar with the lay of the land and find your place in DC.

Southwest Waterfront

Native Americans, European Settlers, and now, the new Wharf development, this quadrant of Washington, DC has one constant — it's always evolving. Today, visitors have much to see in this unique neighborhood a few blocks from the National Mall, including the new District Wharf, the Mead Center, Maine Avenue Fish Market, East Potomac Tennis Center, Women's Titanic Memorial, Mandarin Oriental Hotel Spa and the tiki-style bar Cantina Marina to name a few hot spots.

The Smithsonian National Museum of Natural History

Opened in 1910 to invoke discovery and education of the natural world, its green dome and immense size (comparable to 18 football fields) are signatures, as well as the 126 million natural science specimens and cultural artifacts that the museum contains. The Museum of Natural History is centrally located in Washington, DC on the National Mall. Like all Smithsonian Institution Museums, admission is free. Its regular hours are 10:00 am to 5:30 pm, but hours are extended during the summer with a closing time of 7:30 pm. Click here to learn more about all The Smithsonian Museums in Washington, DC.

DC's Arts & Culture

The backbone of the city is built on arts and culture. Enjoy awe-inspiring art galleries, unmatched museums, thriving performing arts and music scenes and so much more.

Famous places to visit include:

The John F. Kennedy Center for the Performing Arts
Ford's Theatre
The Smithsonian National Portrait Gallery

Click here to learn more about DC's arts and culture.

For more information on What to Do in Washington, DC, click here.

Restaurants

Restaurants at the Grand Hyatt Washington

Starbucks
Coffee
Lobby
Hours: Daily 5:30 am – 8:00 pm

Cabinet
Breakfast, Special Lunch on Weekends $$
Declaration Level (1B)
Hours: M-F 6:30 am – 11:00 am;
Sat-Sun 6:20 am - 3:00 pm

Cure Bar & Bistro
Lunch, Dinner and Late Night, $$ - $$$
Lobby and Declaration Level (1B)
Hours: M-F 11:00 am – 1:00 am;
Sat-Sun 3:00 pm – 1:00 am

Restaurants near the Grand Hyatt Washington

DBGB DC
French Bistro, $$$
931 H Street NW / 202-695-7660
Distance from hotel: 1 min (233 ft.)
dbgb.com/dc

Capitol City Brewing Company
American, Bar, Pub, Contemporary, Gluten Free Option, $$-$$$
1100 New York Avenue Northwest
202-628-2222
Distance from hotel: 1 min (305 ft.)
capcitybrew.com

Centrolina
Seasonal Italian, $$
974 Palmer Aly NW / 202-898-2426
Distance from hotel: 2 min (492 ft.)
centrolinadc.com

Del Frisco's Double Eagle Steak House
American, Steakhouse, $$$$
950 I St NW # 501 / 202-289-0201
Distance from hotel: 3 min (0.1 miles)
delfriscos.com/steakhouse/washington-dc

Fig & Olive D.C
American, Mediterranean, European, $$$$
934 Palmer Aly NW / 202-559-5004
Distance from hotel: 3 min (0.1 miles)
figandolive.com/

Fire & Sage
American, Bar, Pub, $$ - $$$
775 12th Street Northwest / 202-661-8925
Distance from hotel: 2 min (0.1 miles)
marriott.com

Fruitive
Juice Bars & Smoothies, Vegan, Live/Raw Food, $$
1094 Palmer Aly NW / 202-836-7749
Distance from hotel: 2 min (0.1 miles)
fruitive.com

Mango Tree
Asian, Thai, Vegetarian Friendly, $$ - $$$
929 H St NW / 202-408-8100
Distance from hotel: 2 min (0.1 miles)
mangotreedc.com

Momofuku CCDC
Japanese, Asian, Gluten Free Options, $$ - $$$
1090 I St NW / 202-602-1832
Distance from hotel: 2 min (0.1 miles)
ccdc.momofuku.com

Haad Thai Restaurant
Asian, Thai,$$ - $$$
1100 New York Ave NW / 202-682-1111
Distance from hotel: 3 min (0.2 miles)
haadthairestaurant.com

Cuba Libre Restaurant & Rum Bar
Caribbean, Latin, Bar, Spanish, Cuban, Central American, Pub, Gluten Free Options, $$ - $$$
801 9th St NW, Penn Quarter, (Corner of 9th & H Streets) / 202-408-1600
Distance from hotel: 4 min (0.2 miles)
cubalibrerestaurant.com/en/washington

Pret A Manger
Soups, Cafe, Fast Food, Vegetarian Friendly, Vegan Options, $
1155 F Street NW / 202-464-2791
Distance from hotel: 4 min (0.2 miles)
www.pret.com/en-us

Zaytinya
Lebanese, Mediterranean, European, Turkish, Greek, Middle Eastern, Gluten Free Options, $$ - $$$
701 9th St NW, Edison Place
202-638-0800
Distance from hotel: 4 min (0.2 miles)
zaytinya.com

Ella's Wood-Fired Pizza
Italian, Pizza, Gluten-Free Options, $$ - $$$
610 9th St NW / 202-638-3434
Distance from hotel: 5 min (0.3 miles)
ellaspizza.com

Mayur Kabob
Indian, Pakistani, Halal , $$ - $$$
1108 K St NW / 202-637-9770
Distance from hotel: 6 min (0.3 miles)
mayurkababhousedc.com

Daikaya
Japanese, $$
705 6th Street Northwest / 202-589-1600
Distance from hotel: 9 min (0.4 miles)
daikaya.com

Corduroy
Upscale, Seasonal New American Menu, $$$
1122 9th St NW / 202-589-0699
Distance from hotel: 9 min (0.4 miles)
corduroydc.com

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Restaurants, *continued from page 11*

Coffee near the Grand Hyatt Washington Hotel

Rare Sweets
Dessert, Coffee, & Teas
963 Palmer Alley / 202-499-0077
Distance from hotel: 2 min (0.1 miles)
raresweets.com

Dolcezza Gelato and Coffee
904 Palmer Alley NW / 202-733-2879
Distance from hotel: 3 min (0.2 miles)
dolcezzagelato.com

Sip of Seattle
Coffee & Tea, Breakfast & Brunch, Juice Bars & Smoothies, $
1120 G St NW / 202-393-5058
Distance from hotel: 4 min (0.2 miles)
yelp.com/biz/sip-of-seattle-washington

Bluebird Bakery
918 F St NW / 202-510-9917
Distance from hotel: 5 min (0.3 miles)
bluebirdbakerydc.com

Peet's Coffee
435 11th St NW / 202-400-3258
Distance from hotel: 7 min (0.4 miles)
peets.com

Chinatown Coffee Co.
475 H St NW #1
202-320-0405
Distance from hotel: 9 min (0.4 miles)
chinatowncoffee.com

La Colombe Coffee
900 6th St NW / 202-795 7909
Distance from hotel: 9 min (0.4 miles)
lacolombe.com

Bakers & Baristas
501 7th St NW / 202-347-7895
Distance from hotel: 10 min (0.5 miles)
bakersandbaristas.net

Timgad Cafe
Cafes, Coffee & Tea, Sandwiches
1300 Pennsylvania Ave
202-289-6444
Distance from hotel: 10 min (0.5 miles)
timgadcafe.com

Other Restaurants of Note

Rasika
Indian, $$
633 D St, NW / 202-637.1222
Distance from hotel: (0.6 miles) 12 min walk; 9 min bus ride (M Red); 4 min car ride
rasikarestaurant.com

Fiola
Italian, $$$
601 Pennsylvania Ave NW / 202-628-2888
Distance from hotel: (0.7 miles) 15 min walk; 8 min bus ride (M Green/ Yellow); 6 min car ride
fioladc.com

Little Serow
Thai, $$$
1511 17th Street Northwest
Walk in; no reservations or phone.
Distance from hotel: (1.2 miles) 15 min bus ride/walk (M Red); 10 min car ride
littleserow.com

Red Hen
Italian, $$
1822 First Street NW
202-525-3021
Distance from hotel: (1.6 miles) 20 min bus ride/walk (M Green/ Yellow); 10 min car ride
theredhendc.com

Blue Duck Tavern
American, $$$
1201 24th St NW / 202-419-6755
Distance from hotel: (1.7 miles) 14 min bus ride/walk (M orange/ silver/blue); 12 min car ride
hyatt.com/corporate/restaurants/blue-duck-tavern/en/blue-duck-tavern-home

Lincoln Park Kitchen & Wine Bar
Wine Bars, American, $$
106 13th St SE / 202-765-0449
Distance from hotel: (2.3 miles) 29 min bus ride/walk (M orange/ silver/blue); 13 min car ride
lincolnparkdc.com

Rose's Luxury
New American, $$
717 8th Street SE / 202-580-8889
Distance from hotel: (2.6 miles) 19 min bus ride/walk (M orange/ silver/blue); 10 min car ride
rosesluxury.com

BlackSalt Fish Market & Restaurant
Seafood, Palisades, $$$
4883 MacArthur Blvd / 202-342-9101
Distance from hotel: (4.4 miles) 36 min bus ride/walk (D6); 17 min car ride
blacksaltrestaurant.com/market

Special Events

Thursday, May 4

***British Journal of Anaesthesia* & Anaesthetic Research Society Reception**
6:30 pm to 8:00 pm, Grand Hyatt Washington

AUA attendees are invited to attend the *British Journal of Anaesthesia* & Anaesthetic Research Society Reception on Thursday, May 4, from 6:30 pm to 8:00 pm, at the Grand Hyatt Washington. Please sign up for this event when registering for the Annual Meeting if you and/or your guest will attend. A ticket will be provided with your badge for attendance to this reception.

Friday, May 5

AUA Social Event Reception
6:30 pm to 9:30 pm, Smithsonian's National Air and Space Museum (600 Independence Ave SW)

The AUA Social Event Reception, hosted by Johns Hopkins Medicine and University of Maryland School of Medicine, will take place on Friday, May 5, from 6:30 pm to 9:30 pm, at the Smithsonian's National Air and Space Museum, home to the world's largest and most significant collection of aviation and space artifacts. The event includes a buffet dinner and drinks, as well as access to the museum. Busing will be provided to this event. An additional fee is required to attend this special event, and a ticket will be provided with your badge for attendance to this reception. Please visit the Registration Desk to check availability.

Saturday, May 6

Aligned Meeting Day at the IARS 2017 Annual Meeting and International Science Symposium
The IARS Aligned Meeting Day offers AUA attendees complimentary access to cutting-edge sessions on a variety of anesthesia topics. Pre-registration is required to attend these sessions.

IARS Alignment Reception
6:00 pm to 7:30 pm, Grand Hyatt Washington

Come together and celebrate the convergence of the IARS, AUA and SOCCA Annual Meetings and meet the leaders in all subspecialties in anesthesiology in one location, Washington, DC.

Scholars' Program Mentor-Trainee Reception
Saturday, May 6, 5:00 pm - 6:00 pm, Grand Hyatt Washington
Meet your mentor, socialize and discuss the curriculum and tips for advancing your career with your fellow scholars at the Scholars' Program Mentor-Trainee Reception.

The Scholars' Program and the Scholars' Program Mentor-Trainee Reception require pre-registration and an additional $50.00 fee.

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) 64th 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 64th 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.
- 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. Meeting participants will have 45 days post-meeting to claim CME credit.

Disclosure

The International Anesthesia Research Society (IARS) makes every effort to develop CME activities that are independent, objective, and 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.

It is IARS policy that an employment relationship with a commercial interest presents an inherent conflict of interest that cannot be resolved successfully with respect to CME activities. Therefore, employees of commercial interests are prohibited from serving in any position to control CME content (planner, reviewer, presenter, speaker, moderator, etc.).

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 (AUA). There is no commercial support for this activity.

Planning Committee and Program Faculty

Planning Committee

Robert R. Gaiser, MD
Chair, Educational Advisory Board
Professor and Chair, Department of Anesthesiology, University of Kentucky Health Care, Lexington, Kentucky

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Co-Chair, Host Institution, AUA 64th Annual Meeting
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Chair, Scientific Advisory Board
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Jeanine P. Wiener-Kronish, MD
President, 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

Program Faculty

Lorenzo Berra, MD
Assistant Professor, Anaesthesia, Harvard Medical School; Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

John (Jack) R. Boulet, PhD
Vice President, Research and Data Resources, Educational Commission for Foreign Medical Graduates, Foundation for Advancement of International Medical Education and Research, Philadelphia, Pennsylvania

Lucy Chen, MD
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Robert R. Gaiser, MD
Chair, Educational Advisory Board
Professor and Chair, Anesthesiology, University of Kentucky Health Care, Lexington, Kentucky

Peter Goldstein, MD
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Joshua Epstein, PhD
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Michael Grocott, BSc, MBBS, MD, FRCA, FRCP, FFICM
Professor of Anaesthesia and Critical Care Medicine, Head, Critical Care Research Area, Southampton NIHR Respiratory Biomedical Research Unit, Head, Integrative Physiology and Critical Illness Group, University of Southampton, Southampton, England, United Kingdom

Tomoki Hashimoto, MD
Professor of Anesthesiology, UCSF School of Medicine, University of California, San Francisco, San Francisco, California

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Planning Committee and Program Faculty, *continued from page 15*

Douglas E. Hough, PhD
Associate Scientist & Associate Director, Master of Health Administration Program, Department of Health Policy & Management, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland

Colleen Koch, MD, MS, MBA, FACC
Co-Chair, Host Institution, AUA 64th Annual Meeting
Mark C. Rogers Professor of Anesthesiology and Critical Care Medicine and Anesthesiologist-in-Chief, Johns Hopkins Medicine, Baltimore, Maryland

Shyamasundaran Kottilil, MD
Associate Chief of the Division of Infectious Diseases, Director of the Clinical Trials Unit, Institute of Human Virology (IHV), University of Maryland School of Medicine, Baltimore, Maryland; Scientific Director, Program for AIDS Progress, National Institute of Health, Bethesda, Maryland

Adam Levine, MD
Professor, Anesthesiology, Professor, Pharmacological Sciences, Professor, Otolaryngology, Icahn School of Medicine, The Mount Sinai Hospital, New York, New York

Feroze-Ud-Din Mahmood, MBBS
Associate Professor, Anaesthesia, Harvard Medical School; Director, Vascular Anesthesia/Perioperative Echocardiography at Beth Israel Deaconess Medical Center, Anesthesiology; Beth Israel Deaconess Medical Center, Harvard Medical School; Boston, Massachusetts

Susan M. Martinelli, MD
Associate Professor, Anesthesiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Matthew D. McEvoy, MD
Associate Professor of Anesthesiology, Division of Multispecialty Adult Anesthesiology, Vice-Chair, Educational Affairs, Vanderbilt University Medical Center, Nashville, Tennessee

Vamsi K. Mootha, MD
Investigator, Howard Hughes Medical Institute, Professor, Department of Systems Biology, Department of Medicine, Harvard Medical School; Massachusetts General Hospital, Boston, Massachusetts

Kathleen M. Neuzil, MD, MPH, FIDSA
Director, Center For Vaccine Development (CVD); Deputy Director, Institute for Global Health; Division Head, Geographic Medicine, Professor and Director, Center for Vaccine Development, Deputy Director, Institute for Global Health, University of Maryland School of Medicine, Baltimore, Maryland

Peter Rock, MD, MBA, FCCM
Co-Chair, Host Institution, AUA 64th Annual Meeting
Professor, Anesthesiology, and Dr. Martin A. Helrich Chair for Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland

Randall Schell, MD, MACM
Academic Vice-Chairman and Program Director, Professor of Anesthesiology, Surgery, and Pediatrics, University of Kentucky Department of Anesthesiology, Lexington, Kentucky

Edward Sherwood, MD, PhD
Professor, Vice Chair for Research, Vanderbilt University Medical Center, Nashville, Tennessee

Jeanine P. Wiener-Kronish, MD
President, 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

Program Schedule

Thursday, May 4

6:00 am – 6:00 pm **Registration**

8:30 am – 9:00 am **Welcome from AUA President and Host Institution Chairs –**
Colleen Koch, MD, MS, MBA, FACC
Peter Rock, MD, MBA, FCCM
Jeanine P. Wiener-Kronish, MD

9:00 am – 10:00 am **Scientific Advisory Board (SAB) Oral Session I**
Moderators: Lucy Chen, MD, and Edward Sherwood, MD, PhD

Junior Faculty Research Award

- ***Photo-Relaxation: Light Mediated Airway Smooth Muscle Relaxation***
  Peter Yim, MD, Columbia University Medical Center, New York, New York
- ***Alteration in Bitter Taste Receptor (TAS_2R) Expression and Function in the Airway Smooth Muscle Cells of a Murine Model of Cystic Fibrosis***
  Nicholas M. Dalesio, MD, Johns Hopkins Medicine, Baltimore, Maryland

Junior Faculty Research Award

- ***Implication of LDL Receptors in the Development of Pulmonary Hypertension***
  Soban Umar, MD, PhD, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California
- ***Spinal Cord Stimulation Reduces Ventricular Arrhythmias During Acute Ischemia Through Attenuation of Regional Myocardial Excitability in A Porcine Model***
  Kimberley Howard-Quijano, MD, MS, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, California

Learner Objectives: After participating in this activity, the learner will be able to: (1) Discuss novel mechanisms to bronchodilation; (2) Appraise light-based approaches to bronchodilation; (3) Define the implications of lipid signaling in vascular disease; and (4) Identify emerging interventions for arrhythmias.

10:00 am – 11:30 am **Moderated Poster Discussion Session I**

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 anesthesiology research programs.

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11:30 am – 12:30 pm **SAB Oral Session II**
Moderators: Lucy Chen, MD, and Edward Sherwood, MD, PhD

Resident Travel Award

- ***Sensitivity to Volatile Anesthetics Predicts Postoperative Delirium***
  Bradley A. Fritz, MD, Washington University School of Medicine in St. Louis, St. Louis, Missouri

Margaret Wood Resident Research Award

- ***Weak EEG α-Power During General Anesthesia as a Marker of Delirium in the PACU***
  Matthias Kreuzer, PhD, Emory University School of Medicine;, Atlanta VA Medical Center, Decatur, Georgia
- ***Astrocyte-Specific Knockout of a Mitochondrial Protein in Mice Increases Neural Inertia***
  Renjini Ramadasan Nair, PhD, Seattle Children's Research Institute, Seattle, Washington
- ***GABA Neurons in the Rostromedial Tegmental Nucleus Modulate Arousal and Anesthetic Sensitivity in Mice***
  Ken Solt, MD, Harvard Medical School; Massachusetts General Hospital, Boston, Massachusetts

Learner Objectives: After participating in this activity, the learner will be able to: (1) Discuss the mechanisms contributing to postoperative delirium; (2) Illustrate the role of mitochondrial pathways in neuronal dysfunction; and (3) Interpret the role of inhibitory transmission pathways in arousal and anesthetic sensitivity.

12:30 pm – 1:30 pm **All Attendee Lunch**

12:30 pm – 1:30 pm **Educational Advisory Board Lunch — Invite Only**

12:30 pm – 1:30 pm **President's Lunch — Invite Only**

1:30 pm – 3:00 pm **Educational Advisory Board (EAB) Program Panel I: The Science of Assessment of Clinical Performance**
Moderator: Robert R. Gaiser, MD

- ***The Science of Clinical Performance Assessment***
  John (Jack) R. Boulet, PhD
- ***Clinical Application of Clinical Performance Assessment***
  Feroze-Ud-Din Mahmood, MBBS

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Program Schedule, *continued from page 18*

- ***Performance Assessment for Re-entry***
  Adam Levine, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Summarize the various types of simulation-based assessment currently employed in medical education; (2) Discuss how meaningful scores can be obtained from performance-based assessments; (3) Identify psychometric evidence that must be gathered to support the use of assessment scores; (4) Evaluate the challenges and potential benefits of using clinical performance assessment; (5) Discuss the need for healthcare reentry programs; (6) Identify the reasons healthcare provides require reentry programs; (7) Evaluate the role for competency assessment for healthcare re-entry; and (8) Evaluate the role of simulation for reentry assessment.

3:00 pm – 4:15 pm **Host Program Panel I**
Moderators: Colleen Koch, MD, MS, MBA, FACC and
Peter Rock, MD, MBA, FCCM

Presenters:

- ***Agent-Based Modeling in Health Science: From Playground to Planet***
  Joshua Epstein, PhD
- ***Irrationality in Health Care: Why Patients and Physicians Do Not Always Choose Wisely***
  Douglas E. Hough, PhD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify the ubiquity of models; (2) Examine the cutting edge of computer simulation in Health Science; (3) Assess how this flexible technology could apply to your field, be it infectious disease, critical care, environmental health, at scales from the ICU to the Globe; (4) Identify the situations in which health care behavior can be irrational; (5) Review the major concepts of behavioral economics that can explain irrational behavior; and (6) Assess the challenge of changing patient and physician behavior.

4:15 pm – 4:30 pm **Break**

4:30 pm – 5:45 pm **Host Program Panel II**
Moderators: Colleen Koch, MD, MS, MBA, FACC, and

Peter Rock, MD, MBA, FCCM

- ***Developing and Deploying Influenza Vaccines: The Pandemic-Seasonal Interplay***
  Kathleen M. Neuzil, MD, MPH, FIDSA

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- ***The Beginning of the End of Hepatitis C — 2017***
  Shyamasundaran Kottilil, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Review the currently licensed influenza vaccines and those in development; (2) Discuss the role of market forces in shaping the influenza vaccine pipeline; (3) Discuss the global public health burden of chronic hepatitis C infection; (4) Describe recent advances in the treatment of HCV; (5) Assess the impact of HCV treatment on long term complications including cancer and transplantation; and (6) Identify challenges in global elimination of HCV.

6:30 pm – 8:00 pm ***British Journal of Anaesthesia*** **& Anaesthetic Research Society Reception**

Friday, May 5

6:00 am – 6:00 pm **Registration**

7:30 am – 8:00 am **AUA Sunrise Session –** *Non-CME Session*

8:00 am – 9:00 am **SAB Oral Session III**
Moderators: Peter A. Goldstein, MD, and Tomoki Hashimoto, MD

- ***CX_3CR1^+ Cells in the PNS Play A Key Role in Development of Neuropathic Pain in Mice***
  Jianguo Cheng, MD, PhD, Cleveland Clinic, Cleveland, Ohio
- ***Corticostriatal Circuit Regulates Acute and Chronic Pain in Rodents***
  Jing Wang, MD, PhD, New York University School of Medicine, New York, New York

Junior Faculty Travel Award in Perioperative Medicine

- ***A Randomized Trial of Perioperative Gabapentin to Promote Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort***
  Jennifer Hah, MD, MS, Stanford University School of Medicine, Stanford, California
- ***Dezocine for Opioid Addiction in A Rat Morphine Dependence Model***
  Renyu Liu, MD, PhD, University of Pennsyvania Perelman School of Medicine, Philadelphia, Pennsylvania

Learner Objectives: After participating in this activity, the learner will be able to: (1) Discuss novel immune mechanisms in neuropathic pain; (2) Identify the role of descending pathways in acute and chronic pain regulation; and (3) Assess novel approaches to reducing opioid use.

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Program Schedule, *continued from page 20*

9:00 am – 9:15 am **Break**

9:15 am – 10:15 am **SAB Oral Session IV**
Moderators: Peter A. Goldstein, MD, and Tomoki Hashimoto, MD

- ***How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?***
  Peter Hu, PhD, University of Maryland School of Medicine, Baltimore, Baltimore, Maryland

Junior Faculty Travel Award in Pediatric Anesthesia

- ***Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis***
  Caleb Ing, MD, MS, Columbia University Medical Center, New York, New York

- ***Perioperative Decline in High Density Lipoprotein Particles is Associated with Increased Risk of AKI after Cardiac Surgery***
  Loren Smith, MD, PhD, Vanderbilt University Medical Center, Nashville, Tennessee

Learner Objectives: After participating in this activity, the learner will be able to: (1) Evaluate the use of non-invasive approaches to assessing fluid responsiveness; (2) Evaluate approaches to reducing alarm fatigue in the ICU; (3) Discuss the implications of anesthesia in pediatric neurodevelopment; and (4) Interpret the effect of lipid particles in postoperative kidney injury.

10:15 am – 10:30 am **Break**

10:30 am – 12:00 pm **EAB Program Panel II: The Evidence Behind the "Hot" Topics in Anesthesia**
Moderator: Robert R. Gaiser, MD

- ***Flipped Classroom***
  Susan Martinelli, MD

- ***Spaced Education – What Is That and Why Should I Use It?***
  Matthew McEvoy, MD

- ***Test Enhanced Learning: Stop Studying and Take a Test!***
  Randall Schell, MD, MACM

Learner Objectives: After participating in this activity, the learner will be able to: (1) List the components of the flipped classroom method of education; (2) Describe the current state of the evidence supporting the flipped classroom educational method in graduate medical education; (3) Propose ways of implementing flipped classroom in anesthesiology education; (4) Assess how tests can be used beyond assessment to promoting learning; (5) Describe the benefit of retrieval practice in improving longer term retention of information; (6) Review select evidence in support of test-enhanced

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learning; (7) Discuss evidence-based ways to optimize test-enhanced learning including question type, repeated testing, and feedback; (8) Compare Spaced Education and traditional didactic education; (9) Discuss the evidence for using Spaced Education for driving knowledge acquisition and clinical practice improvement; and (10) Describe potential opportunities for applying Spaced Education in the perioperative arena.

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

12:00 pm – 1:00 pm **Scientific Advisory Board Lunch — Invite Only**

12:00 pm – 1:00 pm **Junior Faculty, Fellow, Resident and Medical Student Lunch**
Tables will be reserved for junior faculty members, fellows, residents and medical students and their sponsoring chair. AUA Council Members will also be present.

1:00 pm – 2:30 pm **Moderated Poster Discussion Session II**

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 anesthesiology research programs.

2:30 pm – 2:45 pm **Break**

2:45 pm – 4:45 pm **President's Panel: *Hypoxia is Not Always Bad for You?***
Moderator: Jeanine P. Wiener-Kronish, MD

Panelists:

- ***Oxygen and Humans: The Good, The Bad and The Ugly?***
  Michael Grocott, BSc, MBBS, MD, FRCA, FRCP, FFICM
- ***Hypoxia and Damaged Mitochondria: Good News***
  Vamsi K. Mootha, MD
- ***Mitochondrial Disorders: Towards a Therapy from Thin Air***
  Lorenzo Berra, MD

Learner Objectives: After participating in this activity, the learner will be able to: (1) Discuss the effect of hypoxia on normal individuals as well as those with mitochondrial dysfunction; (2) Analyze why hypoxia may be beneficial in mitochondrial disease; and (3) Identify why too much oxygen is dangerous to our patients.

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4:45 pm – 5:45 pm **AUA Annual Business Meeting**

6:30 pm – 9:30 pm **AUA Social Event Reception**
Hosted by Johns Hopkins Medicine and University of Maryland School of Medicine
Smithsonian's National Air and Space Museum (600 Independence Ave SW)

Busing will be provided to this reception from the side door of the AUA Headquarters Hotel.

Saturday, May 6

Aligned Meeting Day at the IARS 2017 Annual Meeting

The following sessions are part of the IARS 2017 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 and Opening Remarks**

8:00 am – 9:00 am **T.H. Seldon Memorial Lecture: *Vital Directions in Health and Medicine in Uncertain Times***
Victor J. Dzau, MD, President, National Academy of Medicine; Chancellor Emeritus and James B. Duke Professor of Medicine, Duke University School of Medicine, Durham, North Carolina

9:00 am – 9:30 am **Break**

9:30 am – 12:30 pm **AUA Symposium: *Recognizing the "Painful" Truths of the Opioid Abuse Epidemic***
Moderator: Y.S. Prakash, MD, PhD, Chair, Scientific Advisory Board; Professor of Anesthesiology and Physiology, Chair, Division of Anesthesia Research, Vice Chair, Department of Anesthesiology and Perioperative Medicine, Chair, Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota

Panelists:

- ***Understanding and Responding to the Intersecting Issues Related to Pain and Opioid Misuse***
  Wilson Compton, MD, MPE, Deputy Director, National Institute on Drug Abuse, Bethesda, Maryland
- ***FDA's Role in Addressing the Opioid Epidemic***
  Ellen Fields, MD, MPH, Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Office of New Drugs, Center for Drug Evaluation and Research, FDA, Silver Spring, Maryland

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- ***Frontlines of the Opioid Epidemic***
  Lynn Webster, MD, Vice President of Scientific Affairs, PRA Health Sciences; Immediate Past President, American Academy of Pain Medicine, Raleigh, North Carolina

- ***Mechanisms of Opioid Abuse: Dissecting Necessary from Unnecessary Need***
  Mary Jeanne Kreek, MD, Senior Attending Physician, Patrick E. and Beatrice M. Haggerty Professor, Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, New York

6:00 pm – 7:30 pm **IARS Alignment Reception**
Grand Hyatt Washington
AUA Attendees Invited to Attend

Scholars' Program

The Scholars' Program requires pre-registration and an additional $50 fee to attend.

9:30 am – 10:30 am **Scholar–01: Introduction to the Translational Research Continuum**

Moderator: Michael Montana, MD, PhD, Pediatric Fellow, Department of Anesthesiology, Washington University School of Medicine in St. Louis, St. Louis, Missouri

Presenter:

George Mashour, MD, PhD, Executive Director, Translational Research, Office of Research, Executive Director, Michigan Institute for Clinical and Health Research, Associate Dean for Clinical and Translational Research, Medical School, Director, Center for Consciousness Science, Bert N. La Du Professor and Associate Chair of Anesthesiology Research, Associate Professor, Department of Neurosurgery, University of Michigan Medical School, Ann Arbor, Michigan

10:45 am – 11:45 am **Scholar–02: Keynote Session: Rigor and Reproducibility Across the Translational Spectrum**

Moderators: Sinziana Avramescu, MD, PhD, FRCPC, Assistant Professor, Department of Anesthesia, University of Toronto; Staff Anesthesiologist, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Regional Representative: International, eSAS, and

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Katie J. Schenning, MD, MPH, Assistant Professor, Department of Anesthesiology & Perioperative Medicine, Oregon Health & Science University, Portland, Oregon, Co-Chair Membership, eSAS

- ***Trouble in the Laboratory: Problems with Rigor and Precision***
  James Eisenach, MD, President, Foundation for Anesthesia Education and Research, Immediate Past Editor-in-Chief, *Anesthesiology*
- ***Reproducibility Crisis in Scientific Research***
  Steven L. Shafer, MD, Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California; Adjunct Associate Professor of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, California; Immediate Past Editor-in-Chief, *Anesthesia & Analgesia*

12:00 pm – 1:00 pm **Scholar–03: Plenary Session I: Expanding Our Horizons in Anesthesiology Research Training**

Moderators: Julie Freed, MD, PhD, Adult Cardio-Thoracic Anesthesiology Fellow, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin; Co-Chair Partnerships, eSAS, and

James W. Ibinson, MD, PhD, Assistant Professor, Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Panelists:

- ***Developing Skills in Commercialization: Adapting Elements of the NSF I-CORPs Program to Create A Customized Program for Academic Physicians***
  Connie Chang, MBA, Managing Director, Fast Forward Medical Innovation, University of Michigan Health System, Ann Arbor, Michigan
- ***The Challenges of Building Diversity in Academic Anesthesiology***
  Paloma Toledo, MD, MPH, Assistant Professor of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

1:00 pm – 2:00 pm **Scholar–04: Lunch Session: Inspirational Tales of Career Success**

Moderator: Michael S. Avidan, MBBCh, Professor, Anesthesiology and Cardiothoracic Surgery, Director, INQUIRI, Division Chief, Cardiothoracic Anesthesiology and Cardiothoracic Intensive Care, Washington University School of Medicine in St. Louis, St. Louis, Missouri; President-Elect, AUA

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Panelists:

- ***How to Maximize Your Success in Academia: Tips for Junior Faculty***

  Oluwaseun Johnson-Akeju, MD, Assistant Professor of Anaesthesia, Harvard Medical School; Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachussetts

- ***Anesthesia, Informatics & Health Policy: My Unexpected Journey to Nashville***

  Jesse Ehrenfeld, MD, MPH, Associate Professor of Anesthesiology, Bioinformatics, Surgery, and Health Policy; Director of Education Research, Vanderbilt Office of Health Sciences Education; Associate Director, Anesthesiology & Perioperative Informatics Research Division, Vanderbilt University Medical Center, Nashville, Tennessee; Chair, Massachusetts Committee on LGBT Health, Chair, Massachusetts General Hospital LGBT Employee Resource Group, Member, Board Committee on Quality at Fenway Community Health Center

2:00 pm – 3:30 pm **Scholar–05: NIH Funding for Transition to an Early Independence: Information Session and Q&A with NIH Representatives**

Moderators: Aaron Norris, MD, PhD, Fellow, Neuroanesthesiology, Washington University School of Medicine in St. Louis, St. Louis, Missouri, Special Events Chair, eSAS, and

Vivianne Tawfik, MD, PhD, Instructor, Department of Anesthesiology, Perioperative and Pain Medicine, Assistant Director, Fellowship in Anesthesia Research & Medicine Program, Stanford University School of Medicine, Stanford, California; Co-President, eSAS

Presenters:

- ***Funding Opportunities for Early Career Investigators at the National Institute of General Medical Sciences (NIGMS)***

  Alison Cole, PhD, Branch Chief, Pharmacological and Physiological Sciences Branch, Division of Pharmacology, Physiology, and Biological Chemistry, National Institute for General Medical Sciences, National Institutes of Health (NIH), Bethesda, Maryland

- ***Funding Opportunities for Early Career Investigators at the National Institute on Aging***

  Luci Roberts, PhD, Director, Division of Planning, Evaluation & Analysis, Office of Planning, Analysis and Communication (OPAC), National Institutes of Health (NIH), Bethesda, Maryland

  Jane Scott, ScD, MSN, Director, Office of Research Training & Career Development, National Heart, Lung, and Blood Institutes, National Institutes of Health (NIH), Bethesda, Maryland

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4:00 pm – 5:00 pm **Scholar–06: Plenary Session II: Precision Medicine: What Anesthesiology Can Contribute**

Moderators: Michael Mathis, MD, Clinical Lecturer and T32 Research Fellow, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan, and

Elizabeth Whitlock, MD, MSc, Clinical Instructor and T32 Research Fellow, Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California; Co-President, eSAS

Panelists:

- ***Pharmacogenomics in Anesthesiology***
  Debra A. Schwinn, MD, Associate Vice President for Medical Affairs, Professor of Anesthesiology, Pharmacology & Biochemistry, University of Iowa Carver College of Medicine, Iowa City, Iowa
- ***The National Precision Medicine Initiative***
  Sachin Kheterpal, MD, MBA, Associate Professor of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan; Member, NIH Advisory Panel on Precision Medicine

5:00 pm – 6:00 pm **Scholars' Program Mentor-Trainee Reception**
Grand Hyatt Washington

Based on rigorous evaluation of both mentors' skills and trainees' needs, goal-directed interactions will be catalyzed.

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Thursday, May 4

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Scientific Advisory Board Oral Session I

11:30 am – 12:30 pm

Scientific Advisory Board Oral Session II

1:30 pm – 3:00 pm

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Host Program Panel I

4:30 pm – 5:45 pm

Host Program Panel II

Friday, May 5

8:00 am – 9:00 am

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9:15 am – 10:15 am

Scientific Advisory Board Oral Session IV

10:30 am – 12:00 pm

Educational Advisory Board Program Panel II

2:45 pm - 4:45 pm

President's Panel: Hypoxia is Not Always Bad for You?

Junior Faculty Award Winner

Thursday, May 4

Scientific Advisory Board Oral Session I

Photo-Relaxation: Light Mediated Airway Smooth Muscle Relaxation

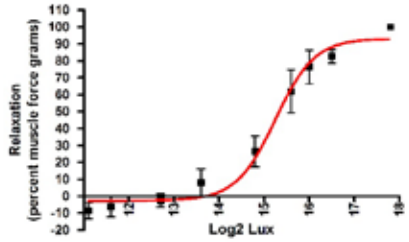
Peter Yim, MD

Opsins (OPN) are light sensitive receptors and are members of the seven transmembrane G protein coupled receptor (GPCR) family. More than 1,000 subtypes of the opsin receptors have been identified. A lysine residue on the seventh helix of the protein structure differentiates opsin receptors from other GPCRs and serves as a retinal/chromophore binding site. In vertebrate visual opsins, 11-cis retinal forms a covalent bond with the lysine residue and forms a "Schiff base". This retinylidene protein (opsin+chromophore) is light sensitive and the opsin/retinal complex determines the wavelength sensitivity. Classically, the photoactivated opsin activates G transducin and increases phosphodiesterase activity, thereby decreasing cGMP leading to a decrease release of glutamate by the photoreceptor cell.

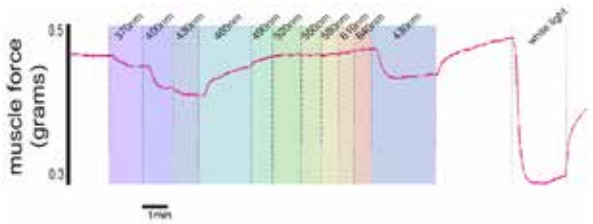
Recently, light was shown to relax blood vessels via activation of the opsin 4 receptor. Characteristics of this response included a sensitivity to blue wavelengths of light (~455nm) and increased relaxation when the tissues were pretreated with a methyl-5-[9E0-2-(5-nitrofuran-2-yl)ethenyl] furan-2-carboxylate, an inhibitor of G protein receptor kinase 2 (GRK2). We hypothesized that airway smooth muscle (ASM) demonstrates a similar physiologic response to light and shares mechanistic similarities.

We have demonstrated for the first time that airway smooth muscle expresses opsin 3 and exhibits photorelaxation. We have characterized the light mediated relaxation of airway smooth muscle, including light intensity dependent relaxation (EC5038,967 lux units) and a wavelength dependent relaxation (maximum relaxation at 430nm light) (figures above). The average relaxation of murine airway smooth muscle contracted with acetylcholine in the presence of a GRK2 inhibitor was 66% when treated with 405nm blue light and 21% in the absence of GRK2 inhibition. Human airway smooth muscle contracted with acetylcholine was completely relaxed (103% of contractile tone abolished) when exposed to blue light in the presence of GRK2 inhibition.

Conclusion: Airway smooth muscle from multiple species including human, demonstrated specific wavelength dependent light mediated photorelaxation that was augmented by GRK2 inhibition. This presentation introduces a novel endogenous human airway response to light and a novel field of human photo-physiology.



Dose response curve of mouse airway smooth muscle relaxation at different light intensities plotted in transformed units of log2 Lux. The light intensity that induced 50% relaxation was 15.25 Log2 Lux, approximately 38,967 Lux.



Representative mouse airway smooth muscle force tracing in response to light at different wavelengths depicted by the colored bars. Maximal relaxation of mouse airway smooth muscle occurred at 430nm light.

Scientific Advisory Board Oral Session I

Bitter Taste Receptors in Airway Smooth Muscle Cells of a Cystic Fibrosis Mouse Model

Nicholas M. Dalesio, MD

Cystic Fibrosis (CF) is caused by the loss-of-function of cystic fibrosis transmembrane conductance regulator (CFTR) and, in the lungs, is characterized by the respiratory sequelae leading to airflow obstruction. Approximately 50% of patients with CF have hyper-reactive airway disease with unclear contributing mechanisms. CFTR protein expression and function has recently been detected in airway smooth muscle (ASM) cells. ASM cells also express certain subtypes of the bitter taste receptor (TAS2R), which mediate relaxation of ASM upon activation via release of intra-cellular calcium. We hypothesized that this TAS2R signaling pathway is disrupted in a murine model of CF.

To evaluate TAS2R in CF, we examined changes in receptor expression using quantitative PCR (qPCR) and function using magnetic torsion cytometry. Changes in expression using qPCR were conducted to determine the expression of TAS2R10, TAS2R14, TAS2R31 and TAS2R38 in the tracheal and lung tissues of mice homozygous for the S489X (CFTR -/-) mutation and wild-type (WT) (CFTR +/+). Changes in function required ASM cell isolation and culture from male and female mice tracheas of CF and WT controls. Magnetic twisting cytometry was used to measure dynamic changes in stiffness of isolated mouse ASM cells, first contracted with 5-HT and then relaxed with either isoproterenol or chloroquine. Tracheal and lung tissue were collected from 4 WT compared to 4 homozygous CFTR -/- mice. Expression of the TAS2R's were not statistically different in the lung and trachea of WT versus CFTR -/- mice. Interestingly, CF ASM pre-constricted with 5-HT demonstrated enhanced relaxation to increasing doses of isoproterenol compared to WT. However, CF ASM cells demonstrated impaired relaxation to increasing doses of the bitter taste receptor agonist, chloroquine compared to WT ASM.

In conclusion, while expression of TAS2R was not different between CF and controls in mouse tracheobronchial ASM tissue, TAS2R- mediated relaxation was attenuated in CF. We conclude that TAS2R-mediated ASM-relaxation is impaired in CF and propose further work to understand the mechanism and identify potential therapeutic targets.

Junior Faculty Award Winner

Scientific Advisory Board Oral Session I

Implication of LDL Receptors in the Development of Pulmonary Hypertension

Soban Umar, MD

Notes:

Scientific Advisory Board Oral Session I

Spinal Cord Stimulation Reduces Ventricular Arrhythmias During Acute Ischemia Through Attenuation of Regional Myocardial Excitability in A Porcine Model

Kimberley Howard-Quijano, MD, MS

Introduction: Myocardial ischemia creates autonomic nervous system imbalance and can trigger lethal cardiac arrhythmias.[1,2] Neuraxial interventions such as spinal cord stimulation (SCS) have shown promising therapeutic benefits in reducing ventricular arrhythmias.[3] While regulation of myocardial excitability in cardiac tissues is understood, there are major gaps in our understanding of the mechanism of the sympathetic neural control of cardiac excitability. We hypothesize that neuromodulation by SCS will reduce cardiac sympathoexcitation from ischemia-induced increases in afferent signaling, reduce ventricular arrhythmias, and improve myocardial function during acute ischemia.

Methods: After approval by the animal research committee, anesthetized Yorkshire pigs (n=20) were randomized to SCS (50 Hz at 200μsec duration, current 90% of motor threshold) or Sham for 30 min prior to ischemia. A 4 pole SCS lead was placed percutaneously in the epidural space (T1-T4) with fluoroscopy guidance and a 56-electrode mesh placed over the heart for high resolution electrophysiological recordings including; activation recovery intervals (ARIs), activation time, repolarization time, and dispersion of repolarization. Activation recovery interval is an established surrogate for action potential duration that decreases with sympathoexcitation and increased dispersion is a measure of ventricular arrhythmogenicity. Hemodynamics and electrophysiologic measures were recorded; at baseline, after SCS/sham, during acute ischemia (300 sec ligation of the left anterior descending coronary artery), and throughout reperfusion.

Results: SCS reduced ischemia-induced myocardial sympathoexcitation as demonstrated by; 1) attenuation of ventricular activation recovery interval shortening, 2) decrease in repolarization time shortening, 3) an increase activation time (Figure 1), and 4) suppression of the increase in ventricular dispersion (Figure 2) in ischemic myocardium. In addition, SCS was associated with improved left ventricular function (dP/dt reduction: Sham 13% vs. SCS 3%, $p<0.01$) and less ventricular arrhythmias (non-sustained VT (arrhythmic events in # of animals): Sham 24(3) vs. SCS 1(1) and PVCs: Sham 105(9) vs. 17(8) $p<0.001$) during ischemia and reperfusion. No change was observed in ventricular electrophysiology during baseline conditions without myocardial stress, nor in the non-ischemic myocardium.

Conclusion: In a porcine model of acute ventricular ischemia with increased cardiac afferent signaling, SCS reduced regional efferent myocardial sympathoexcitation, decreased ventricular arrhythmias, and improved myocardial function. SCS decreased sympathetic nerve activation regionally in ischemic myocardium with no effect observed in normal myocardium. These findings provide important mechanistic insight into the anti-arrhythmic and myocardial protective effects of thoracic neuromodulation with spinal cord stimulation.

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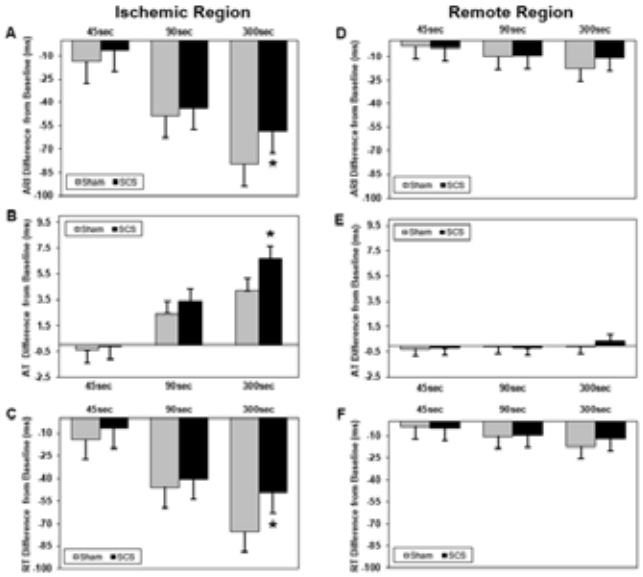

FIGURE 1: Change in electrophysiologic parameters in the ischemic and remote regions from baseline to 45, 90, and 300 seconds ischemia. Data presented as mean difference from baseline at each time point in Sham vs, SCS group. In ischemic myocardium SCS - A) attenuated sympathetic excitation associated ARI reduction (*p=0.035 vs. Sham), B) was associated with a greater increase in activation time (AT) (*p=0.001 vs. Sham), and C) was associated with a greater reduction in repolarization time (RT) (*p=0.008 vs. Sham). In remote unaffected myocardium - there was no change in D) activation recovery interval, E) activation time, or F) repolarization time in SCS or sham treated groups, all p>0.28. All Sham n=9, SCS n=10.

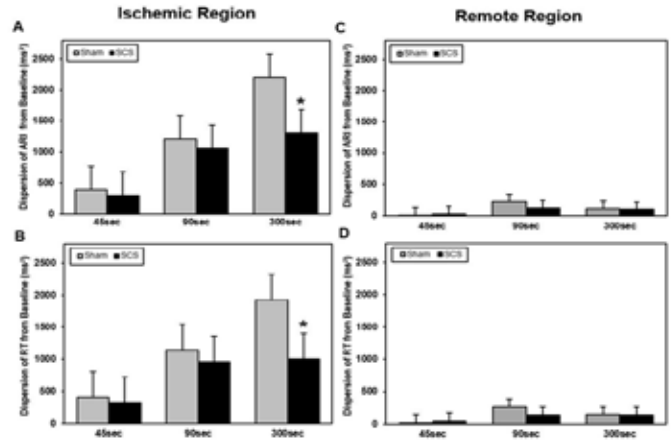

FIGURE 2: Change in dispersion in the ischemic and remote regions from baseline to 45, 90, and 300 seconds ischemia. Data presented as mean difference from baseline at each time point in Sham vs. SCS group. In ischemic myocardium SCS attenuated increase in - A) dispersion of ARI (*p=0.006 vs. Sham) and B) dispersion of repolarization time (*p=0.002 vs. Sham). In remote unaffected myocardium there was no change in - C) dispersion of ARI or D) dispersion of repolarization time, all p>0.16 in SCS or sham treated groups. All Sham n=9, SCS n=10.

Resident Travel Award Winner

Scientific Advisory Board Oral Session II

Sensitivity to Volatile Anesthetics Predicts Postoperative Delirium

Bradley A. Fritz, MD

Introduction: Postoperative delirium is a common surgical complication that is associated with morbidity and mortality [1-3]. Our group recently described an association between increased duration of electroencephalogram (EEG) suppression during surgery and postoperative delirium [4]. Some patients with diagnosed or undiagnosed brain pathology may have increased sensitivity to volatile anesthetic agents, which might manifest during general anesthesia as EEG suppression at relatively low anesthetic concentration. We hypothesized that patients who experience EEG suppression at lower volatile anesthetic concentrations would have increased incidence of postoperative delirium.

Methods: This is a substudy of our previous study examining EEG suppression and postoperative delirium, for which IRB approval was obtained [4]. The population included 618 elective surgery patients with planned intensive care unit admission, who received intraoperative EEG monitoring and had delirium assessments documented in the medical record. Sensitivity to volatile anesthetics was assessed using a mixed effects model predicting the likelihood of EEG suppression at each time point based on the current end-tidal anesthetic concentration. Patients with a random intercept below the population median (i.e. EEG suppression at lower anesthetic concentrations) were classified as having heightened sensitivity to volatile anesthetics. Delirium was defined as a positive Confusion Assessment Method for the ICU (CAM-ICU) assessment at any point in the first five postoperative days. Logistic regression was used to determine whether patients with heightened sensitivity to volatile anesthetics had a greater incidence of delirium.

Results: Postoperative delirium was observed in 162 of the 618 patients (26%). Patients who experienced EEG suppression at lower volatile anesthetic concentrations had a higher incidence of postoperative delirium (107/301 [36%]) than other patients (55/317 [17%]) (unadjusted odds ratio 2.63; 95% CI, 2.22 to 3.11, $p<0.001$). This association remained significant after adjusting for patient characteristics, surgical variables, and duration of EEG suppression (adjusted odds ratio 2.08; 95% CI 1.31 to 3.29, $p=0.001$).

Conclusion: These data support the hypothesis that patients who are more sensitive to volatile anesthetic agents have an increased incidence of postoperative delirium. Underlying pathology may contribute directly to delirium, or it may act through EEG suppression to cause delirium. If there is a causal link between EEG suppression and postoperative delirium, then interventional studies may address whether avoidance of EEG suppression can reduce the incidence of postoperative delirium.

References:

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2. Witlox J, et al. JAMA 2010; 304:443-51
3. Leslie D, et al. Arch Intern Med 2008; 168:27-326
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Margaret Wood Resident Research Award Winner

Scientific Advisory Board Oral Session II

Weak EEG α-Power During General Anesthesia as A Marker of Research Award Delirium in the PACU

Matthias Kreuzer, PhD

Introduction: Recent studies showed that intraprocedural EEG signatures are correlated with delirium in the PACU (PACU-D) as determined by CAM-ICU. Patients that emerge from anesthesia without transitioning through α-spindle dominant EEG are at higher risk PACU-D. The EEG α-band seems of special interest, because of an existing correlation between α-power and intraoperative noxious stimulation[1] as well as absolute alpha power being an indicator for "brain age"[2,3]. We investigated the association of EEG spectral properties during episodes of "no surgical stimulation" (NoStim) and "surgical stimulation" (Stim) and the adverse outcome of hypoactive PACU-D, a transient phenomenon that correlates with negative long-term effects[4].

Methods: We included EEG from 232 patients, collected during a multicenter study, receiving propofol induction and sevoflurane maintenance. EEG was recorded with 250 Hz using a SEDLine monitor. For each patient we calculated the median power spectral density (PSD) and the interhemsipheric spectral coherence for NoStim, i.e. the period 30s after intubation until 30s before start of surgery, and for Stim, the episode from 30s after start surgery until 30s before start of emergence, i.e., gas turn off. We also evaluated the correlation between PSD or coherence in the α-band and the patients' age. We defined PACU-D as positive CAM-ICU assessment as described in[4].

Results: 33 patients developed PACU-D. Age, BMI, and ASA-status were not significantly different. PACU-D patients underwent longer surgeries of 140 (47-346; median and range) min versus 96 (14-398) min ($p<0.05$, Mann-Whitney U). The duration of NoStim was not different. Patients with PACU-D had significantly lower absolute and relative α-band power during Stim and NoStim conditions (Chronux two group test, $p<0.05$). We could further observe a decline in absolute α-power and α-coherence with age for both groups. The ANCOVA analysis did not reveal significant differences between the PACU-D and no PACU-D group, but may show trend ($p=0.059$) towards a steeper decreasing slope in the no PACU-D group. This may indicate that younger PACU-D patients expressed spectral EEG features resembling an older brain, while this difference was not as pronounced for older PACU-D patients. Coherence analysis did not reveal differences between patients with and without PACU-D. The age to α-band coherence relationship was not statistically different between PACU-D and no PACU-D patients.

Conclusion: Our findings emphasize the use of intraoperative α-power as a possible marker of "anesthesia quality". Commercial monitoring systems currently focus on a reliable separation of different anesthetic levels during general anesthesia but not on association of the monitoring with adverse outcomes. Since frontal α-oscillations contain information involving thalamocortical connections[5], our results indicate that patients, who develop PACU-D, may be less robust in maintaining the thalamocortical state that generates α-oscillations. Hence an inclusion of distinct parameters evaluating α-oscillations may represent a valuable contribution to monitoring for preventing/predicting PACU-D.

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Program Materials, *continued from page 37*

Scientific Advisory Board Oral Session II

Astrocyte-Specific Knockout of a Mitochondrial Protein in Mice Increases Neural Inertia

Renjini Ramadasan Nair, PhD

Introduction: The cell types in the CNS which contribute to the anesthetic response are unknown. Animals with defects in mitochondrial complex I have been shown to be hypersensitive to volatile anesthetics (VAs)[1, 2]. Restriction of the knock out of the mitochondrial complex I protein, NDUFS4, to glutamatergic neurons confers the VA hypersensitivity[3]. While the importance of neuronal circuitry in mediating the anesthetic state is undisputed, recent research shows that astrocytes may also play a role by altering Ca2+ transients independent of neuronal activity[4]. In addition, norepinephrine inputs from the locus coeruleus (LC) have been implicated in astrocyte-mediated cortical state switching[5]. We analyzed the effects of knocking out Ndufs4 in astrocytes and in the LC on anesthetic sensitivity.

Methods: The SCRI IACUC approved all studies. We constructed a transgenic mouse line Pgfap-CreERT2, which conditionally expresses Cre-recombinase in GFAP-expressing cells (astrocytes). These mice were injected with 4-hydroxytamoxifen (50 μg/g, once a day, PND33-40) to generate animals lacking Ndufs4 in astrocytes (GFAP-KO) and were subjected to behavioral tests three weeks post injections. Successful astrocytic KO was confirmed by immunohistochemistry. Cre-positive sibling mice (Ndufs4 Δ/+ or Ndufs4 lox/+) were used as controls. For the LC-specific knockout (KO), we injected adeno-associated viruses (109 pfu) encoding Cre-recombinase (WT-Cre) or inactive virus (Δ-Cre) bilaterally into the LC of Ndufs4 floxed mice, and allowed them to recover for 1-2 months. The injected mice were exposed to isoflurane or halothane and tested for the loss of righting reflex or response to a tail clamp both during induction of and emergence from anesthesia.

Results: EC50s for each VA defined by the first loss of tail flick or righting reflex were not different between the GFAP-KOs and control animals. In contrast, EC50s for emergence from ISO and HAL for the GFAP-KO mice were markedly different from controls, at both 1 and 2 months post tamoxifen injection. The values of hysteresis (ΔAD, difference between EC50s for induction and emergence) were not altered by prolonged times (30 minutes) of anesthetic exposure, eliminating a pharmacokinetic effect. Preliminary results indicate that loss of Ndufs4 in the LC is sufficient to recapitulate the hysteresis phenotype of the GFAP-KO for both anesthetics.

Conclusion: Our conditional GFAP-KO uncovered a surprising role of astrocytes in response to VAs: recovery from the anesthetized state. Although the astrocytic KO animal has normal anesthetic sensitivity during induction, it emerges from general anesthesia at a much lower concentration than controls. The hysteresis between the induction of and emergence from anesthesia, termed neural inertia by Kelz6, is not explained by pharmacokinetics. Our study shows that astrocytes play a role in generating neural inertia, likely by supporting metabolism in glutamatergic neurons. We hypothesize that energy deficits in astrocytes disrupt Ca2+ homeostasis, thereby delaying glutamate cycling leading to inability to regain synaptic function in the presence of low concentrations of VA. Preliminary results from KO of Ndufs4 in the LC lend support to the hypothesis that the LC mediates arousal from anesthesia through modulation of astrocytes.

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Acknowledgements:

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Scientific Advisory Board Oral Session II

GABA Neurons in the Rostromedial Tegmental Nucleus Modulate Arousal and Anesthetic Sensitivity in Mice

Ken Solt, MD

Introduction: Many anesthetic drugs potentiate GABA-A receptors in the brain, but their neuroanatomic sites of action are less clear. A population of GABA neurons in the rostromedial tegmental nucleus (RMTg) was recently discovered [1]. These neurons have dense projections to the neighboring ventral tegmental area (VTA), and recent studies show that VTA dopamine neurons promote wakefulness [2] and induce emergence from isoflurane anesthesia [3]. Using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), we tested the hypothesis that RMTg GABA neurons modulate arousal and anesthetic sensitivity.

Methods: To target GABA neurons, male mice that express cre recombinase under the transcriptional control of the Vesicular GABA Transporter (VGAT-cre mice, n=4) underwent bilateral RMTg injections of viral constructs that elicit cre-dependent expression of DREADDs. A mixture of two constructs was used to induce expression of both stimulatory (Gq-coupled) human muscarinic receptor-based DREADDs (hM3Dq) and inhibitory (Gi-coupled) kappa opioid receptor-based DREADDs (KORD) [4]. hM3Dq and KORD do not respond to their native ligands, but are activated by the inert ligands clozapine-N-oxide (CNO) and salvinorin B (SalB), respectively. Two additional VGAT-cre mice received the same injections for immunohistochemical confirmation that DREADDs co-localize with the GABA-synthesizing enzymes GAD65 and GAD67 in RMTg neurons (Fig. 1). Control male VGAT-cre mice (n=4) underwent bilateral RMTg injections of viral constructs that only encode a reporter gene (mCherry). After full recovery, normal saline, CNO (1 mg/kg i.p.) or SalB (15 mg/kg i.p.) was administered, and the open field test (5 min) and accelerating rotarod (4 to 50 RPM over 5 min) were used to assess motor activity and coordination. In addition, EEG and EMG were recorded in both groups before and after CNO. To test for altered anesthetic sensitivity, mice received CNO and were placed in an anesthetizing chamber 20 min later. The sevoflurane concentration (in oxygen) was increased by 0.2% every 10 minutes until loss of righting (LOR) occurred. At least 3 days of rest were provided between experiments.

Results: In the open field test (Fig. 2) CNO greatly decreased the distance traveled in hM3Dq/KORD mice (median 0.3 cm) compared to controls (median 15.6 cm), and the difference was statistically significant (p=0.014, Mann-Whitney test). Saline and SalB had no significant effect on distance traveled. CNO significantly decreased time on the accelerating rotarod (Fig. 3) in hM3Dq/KORD mice (median 33 sec) compared to controls (median 113 sec, p=0.014), but saline and SalB had no significant effect. CNO induced slow-delta oscillations in hM3Dq/KORD mice, but not control mice (Fig. 4). After CNO, LOR occurred at a median sevoflurane dose of 1.60% in controls, and 0.87% in hM3Dq/KORD mice (Fig. 5). This difference was statistically significant (p=0.014).

Conclusion: The results of behavioral testing suggest that activation of RMTg GABA neurons decreases arousal, whereas inhibition does not appreciably increase arousal when the animal is already awake. CNO induced slow-delta oscillations similar to non-REM sleep in hM3Dq/KORD mice but not controls, suggesting that RMTg GABA neurons may be part of an endogenous sleep-promoting circuit. Activation of RMTg GABA neurons greatly increased sensitivity to sevoflurane-induced loss of righting, suggesting that these neurons may play a role in the mechanism of sevoflurane hypnosis.

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Acknowledgements:

Supported by NIH grant R01-GM104948

Program Materials, *continued from page 39*

Educational Advisory Board Program Panel I

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

AUA 64th Annual Meeting
May 4-5, 2017 • Washington, DC

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

Educational Commission for Foreign Medical Graduates
Foundation for Advancement of International Medical Education and Research

AUA 64th Annual Meeting
May 4-5, 2017 • Washington, DC
DISCLOSURES

Nothing to Declare

Overview

- The need for performance assessment?
  - Simulation-based assessments currently used in medicine
  - Generating "meaningful" scores
  - Need to gather psychometric evidence to support the use of the scores
  - Challenges of clinical performance assessment
    - What comes next?

Need for Performance Assessment

- Knowledge
- Skills
  - Communication
  - Professionalism
  - Teamwork
- Procedures
  - Physical examination
  - Procedures
- Clinical reasoning
  - Patient management
  - Resource utilization

Developing Performance Assessments

- What do you want to assess?
- Will simulation technology improve the assessment?
- What are the expected outcomes?
- How will the results be used?
- How reliable and valid are the assessment mechanisms (scores)?

Competency Contamination

- Need to be very explicit about what you want to measure
  - Professionalism, Situational Awareness, etc.
- Competencies overlap
- Definitions vary
  - CANMEDs
  - ACGME

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Program Materials, *continued from page 40*

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

Clinical Performance Assessments

- Workplace-based assessment
  - Observation of practitioners
- **Simulation-based assessment**

Standardized (Simulated) Patients

- Performance-based
- "Standardized"
  - Same conditions for all test takers
- Individuals trained to portray patients with specific conditions
  - Chest pain
  - Depression
  - Shortness of breath

Part-Task Trainers

- **Vascular**
  - Plastic "IV arm"
- **Pelvic**
  - Birthing trainer
- **Respiratory**
  - Airway management
- **Abdominal**
  - Laparoscopic trainer
- **Breast**
  - Detection of lesions
- **Dermal**
  - Skin sheets for suturing

Full-Body Mannequins

Simulation-Based Assessment in Medicine

- United States Medical Licensing Examination (USMLE™)
  - Step 2 CS (ECFMG Clinical Skills Assessment)
  - Step 3 (clinical case simulations)
- National Board of Osteopathic Medical Examiners
  - COMLEX-USA-PE
- Medical Council of Canada
  - MCC QE Part II
- General Medical Council (UK)
- Various specialty board examinations
  - American Board of Emergency Medicine
  - American Board of Internal Medicine
  - American Board of Anesthesiology
- Royal College of Physicians and Surgeons of Canada

Dillon, G.F., Boulet, J.R., Hawkins, R.E. & Swanson, D.B. (2004). Simulations in the United States Medical Licensing Examination™(USMLE™). Quality & Safety in Health Care, 13(Suppl 1), i41-i45.

Scoring Clinical Performance Assessments

- Link measures to scenario events
- Focus on observable behaviors
- If possible, incorporate multiple measures from different sources
- Capture performance processes in addition to outcomes

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Program Materials, *continued from page 41*

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

Types of Scores

- Explicit Process
  - Checklists
  - Key actions
- Implicit Process
  - Rating scales
    - Timing
    - Sequencing
- Explicit outcome
  - Patient status
  - Complications, etc.

Intraoperative Asthma Episode (simulator scenario)

- Review Vital Signs
- **(Key)Increase FIO_2 to 100 %**
- Increase Anesthesia Depth after Increase FiO_2
- Establish Lung Compliance is Increased by Hand Ventilation
- **(Key) Auscultate Chest**
- **(Key)Diagnose Presence of Bilateral Wheezing**
- Above Steps in Less than 60 seconds
- Pass Suction Catheter Through Endotracheal Tube
- (Key)Begin Nebulizer Therapy (Any B-agonist or Combined Atrovent)
- Corticosteroid IV
- Beta-Agonist IV
- Suggest Arterial Blood Gas
- Order Chest X-ray

Rating Scales (Mini-CEX)

- Evaluate student/resident in broad range of settings
  - Various patients, multiple tasks
- Interviewing skills, physical examination, professionalism, clinical judgment, counseling, organization and efficiency, overall competence

Advantages and Disadvantages of Explicit Process

- Fairly easy to develop
- "Objective"
- Record of what was done (feedback)
- Can be used by non-physicians
- Students/residents perceive that they are being evaluated by patients
- Difficult to assess complex skill sets

Advantages and Disadvantages of Implicit Process

- Rely on expert judgment
- Can consider many factors related to performance
  - Egregious actions
- Medical students/ residents prefer to be evaluated by their peers

Disadvantages of Global Ratings

- Need "experts"
  - cost
- Some evaluators may not be objective
  - training

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Program Materials, *continued from page 42*

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

Who Should Provide the Scores

- Expert (physician, nurse, etc.) examiners
  - "face" validity
  - Expertise
    - Practice of medicine is complex
  - Perceived subjectivity
- Other 'observers'
  - Objective
  - First-hand understanding of skill being measured
  - Economical/ efficient

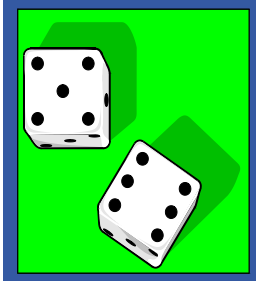
Let the Jury Decide (Sometimes)

- The "myth of subjectivity"
  - The aggregate opinions of "experts" should yield defensible scores/decisions
  - Training, quality assurance

Measurement Issues

- The development of reliable and valid assessment systems can be difficult
- For most simulations, there are equally acceptable treatment approaches
  - Prioritization of necessary actions?
- Separation of individual and group actions

Reliability



- How consistent are the examinee/trainee scores?
  - want to ensure that an examinee's observed score is a reasonable reflection of his/her "true" ability
  - Identify and minimize errors of measurement

Sampling Perspective

	Judge 1	Judge 2	Judge 3	…	Judge n
Case 1	A B C	A	A	A	A
Case 2	B	C			
Case 3	B		C		
…	B			C	
Case n	B				C

What are we Really Measuring?

- Validity is a property of the scores, or the inferences we make based on the scores
  - Choosing what to assess
  - Simulation modalities
  - Purpose of assessment
  - Scenario content

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Program Materials, *continued from page 43*

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

Validity

- Development of evidence providing "… a sound scientific basis for the proposed score interpretations"
- Does the assessment provide measure of what it is supposed to?

Content Validity

- Cases (simulations) and items are "vehicles" to measure skills & knowledge
  - Who are the "target" examinees?
  - Specificity
  - Difficulty
  - Essential maneuvers and questions?
  - Sampling from domain
    - Test blueprint

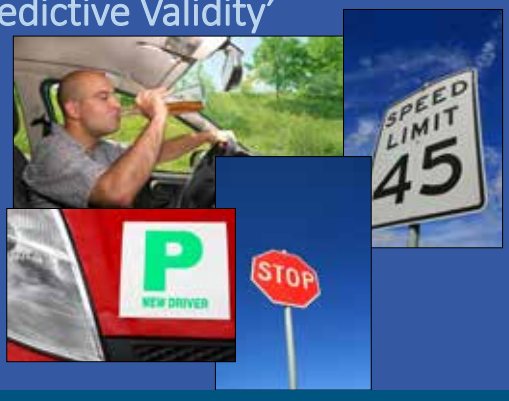
Content Under-representation

- For performance-based assessments, some conditions cannot be simulated very well
  - Not as important for basic skills
- Can sample more broadly for knowledge exams

Performance with "Real" Patients

- Difficult to establish "predictive" value … at least in the short term
  - Aviation simulation
  - Driver's test

'Predictive Validity'



'Predictive Validity'

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Program Materials, *continued from page 44*

The Science of Clinical Performance Assessment

John (Jack) R. Boulet, PhD

Consequences of Assessment

- Candidate self-selection / preparation
  - want to learn
  - specialized preparation courses
- Changes in curriculum
- Development of training centers

Issues and Challenges

- Cost
- Logistics
- Setting standards
- Interdisciplinary skills
- Integration

What Comes Next?

Technology-Enhanced Scoring

- Explicit outcome measures
  - Code actions and timing based on mannequin output
- Natural Language Processing (NLP)
  - Post simulation encounter exercises
- Analysis of Talk Time
  - Speech recognition
- Automated Computer Vision Analysis
  - Empathy, rapport

Future Directions

- Assessment of knowledge, skills and abilities
  - Teamwork
- Use of advanced technology to increase fidelity
  - Virtual reality
  - Haptic systems
- Electronic portfolios
- Combining simulation modalities
- Validation studies

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Program Materials, *continued from page 45*

Educational Advisory Board Program Panel I

Clinical Application of Clinical Performance Assessment

Feroze-Ud-Din Mahmood, MBBS

Notes:

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Educational Advisory Board Program Panel I

Performance Assessment for Re-eentry

Adam Levine, MD

AUA 64th Annual Meeting
May 4-5, 2017 • Washington, DC

Performance Assessment for ReEntry

Adam Levine, MD
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AUA 64th Annual Meeting
May 4-5, 2017 • Washington, DC

DISCLOSURES

- Springer, I receive royalties as Senior Editor of "The Comprehensive Textbook for Healthcare Simulation" and the Series "Comprehensive Healthcare Simulation"

- ASA, I receive honoraria and expenses as the Editor in Chief of the Interactive Computer-based Education Editorial Board and an editor on the Simulation Education Editorial Board
- Society of Simulation in Healthcare, I receive expenses as a member of the Board of Directors

Learning Objectives

1. Understand the need for healthcare reentry programs
2. Identify the reasons healthcare providers require reentry programs
3. Appreciate the role for competency assessment for healthcare reentry
4. Appreciate the role of simulation for reentry assessment

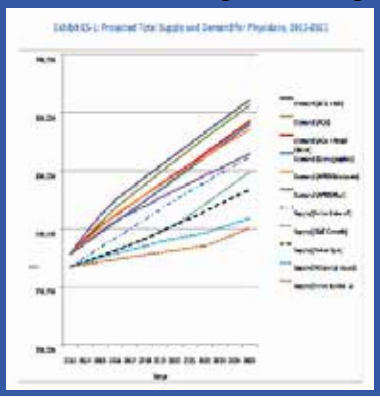
The Background

- AMA Council on Medical Education
  - Physician Supply and Demand Through 2025
    - Projects demand will increase 17% (130,000+)
    - By 2025 demand > supply by 46,000-90,000
    - Shortages
      - 12,500-31,100 primary care physicians
      - 28,200-63,700 non-primary care physicians
        - 5,100-12,300 medical specialists
        - 23,100-31,600 surgical specialists
        - 2,400-20,200 other specialists

What Can be done?

- Increased use of advance practice nurses
- Integrated care delivery (medical homes vs ACOs)
- Greater use of alternate healthcare settings (i.e. retail clinics)
- Reductions in avoidable hospitalizations
- Delay physician retirement
- Develop ReEntry Programs for those physicians with a protracted clinical hiatus.

What's Worse Than Having the Shortage?



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Program Materials, *continued from page 47*

Performance Assessment for Re-entry

Adam Levine, MD

State of ReEntry

- AMA, American Academy of Pediatrics, American College of Obstetricians and Gynecologists and American Board of Medical Specialties all recommend physician re-entry programs
- Formal re-entry programs have been created in multiple fields to bridge gap
  - Anesthesiology
  - Internal Medicine
  - Pediatrics
  - Family Medicine
- Currently ~35 programs exist for physician assessment and remedial education

AMA Guiding Principles for Reentry Programs

- **Accessible-** Including geography, time, and cost
- **Collaborative-** To improve communication and resource utilization
- **Comprehensive-** To cover relevant areas
- **Ethical-** On the basis of accepted principles of medical ethics
- **Flexible-** To maximize usefulness for the program and participant
- **Modular-** To meet the specific needs of individual physicians
- **Innovative-** Must use current education formats and up to date content
- **Accountable-** Need mechanism for assessment and evaluation
- **Stable-** To ensure adequate funding
- **Responsive-** To changing landscape of practice

Anesthesiology provides unique challenges for ReEntry

- Some skills are easy to acquire in low-risk settings (e.g. preoperative assessment clinic)
  - Communication, interpersonal skill
- But certain skill acquisition cannot be easily obtained in low-risk environments or with observership alone
  - Crisis management, vigilance, etc.

Role of Simulation for ReEntry

- Can fulfill the guiding principles set forth by the AMA
- Perfect environment for difficult skill acquisition with no patient harm
- No need for licensure or active credentials
- No ethical issues with patient exposure
- Provides development of unique curriculum tailored to specific practitioner's needs
- Well-suited for assessment and rating for reports to external bodies

Why People Leave Practice?

- **Voluntary**
  - Family obligations
  - Early retirement
  - Change of career
  - Limited scope of practice
    - Exclusive non-OR practice (e.g., 100% pain or ICU practice)
    - Exclusive sedation practice (e.g., ophthalmologic center, endoscopy)
- **Involuntary**
  - Injury/disability
  - Substance Abuse Disorder
  - Medico-legal
    - Suspended license due to incompetence, impairment, legal issues, etc.

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Performance Assessment for Re-entry

Adam Levine, MD


ORIGINAL INVESTIGATIONS IN EDUCATION

Simulation-based Assessment and Retraining for the Anesthesiologist Seeking Reentry to Clinical Practice

A Case Series

Samuel DeMaria, Jr., M.D.,* Stefan T. Samuelson, M.D.,† Andrew D. Schwartz, M.D.,‡ Alan J. Sim, M.D.,‡ Adam I. Levine, M.D.§

ABSTRACT

What We Already Know about This Topic

Background: Established models for assessment and maintenance of competency in anesthesiology may not be adequate for anesthesiologists wishing to reenter practice. The

Summative Assessment

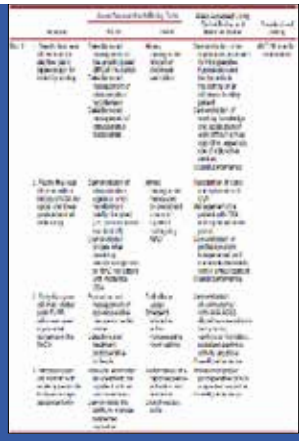
- Not always needed/desired
- Orientation done separately
- Two-day process
- Conducted with two board-certified anesthesiologist raters with extensive experience in simulation-based assessment
  - Two other support staff to serve as confederates
  - Critical Action Checklist
  - Anesthesia Non-Technical Skills
  - Holistic Rating

Summative Assessment

- Three (or more) standardized scenarios presented each day
- Establishes a baseline level of competency
- Need flexibility to tailor cases for second day
  - Anything identified as a gap in knowledge, judgment, or skill will reappear on day 2
  - Allows for reassessment, proof of learning and/or adjustments in technique
- Ratings provided by course instructors and confederates as needed

Sample Program Schedule:
Day 1

Sample Program Schedule:
Day 2



Retraining and Formative Assessment

- Unique program designed for each participant based on ongoing formative assessment
- Includes daily simulation (2-4 hrs) and operating room observation (3-4+ hrs)
- Length varies from 1-6 weeks
- Specific topics emphasized as appropriate (e.g. fiberoptic skills, professionalism, communication, etc.)
- Scenario repetition used to reinforce targeted competencies or problem areas

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Performance Assessment for Re-entry

Adam Levine, MD

Final Report

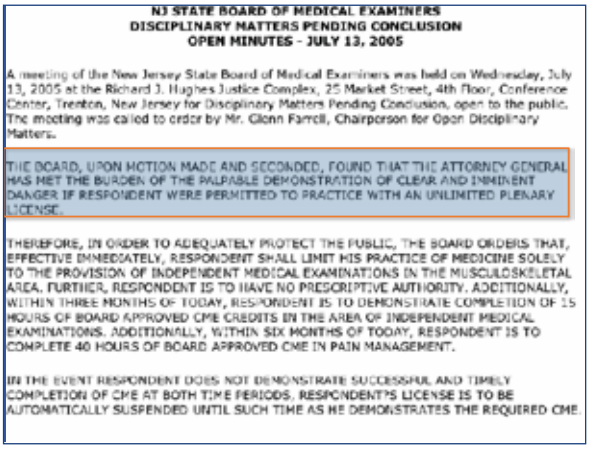
- All assessment scenarios are recorded
- Reviewed using standardized rating scales and narrative reports
- Report consist of three parts:
  - Brief description of assessment tools
  - Detailed description of each assessment case (scenario goals, objectives, events and assessment results)
  - Details of each retraining case (if applicable)
  - Final list of identified deficiencies and prescription for remediation
- Final summary statement documenting whether participant "did or did not practice within the standards of care ***in the simulated environment***"

Practice status following the program (first 20 participants)

Simulation-Based Education & Assessment for Re-entry

- **Remediation Assessment**
  - Physician with lapsed competence evaluated for possible remediation
  - referred from NY State Medical Board and NYSSA
    - based solely on traditional methods of assessment MCE and oral exam, physician was not considered a candidate for remediation.
  - 4 Simulation-Based Scenarios
    - simulations placed practitioner in their "natural environment" where they were able to demonstrate safe practice
    - Recommended for remediation
    - Remediation prescription was created

Rosenblatt MA, Abrams KJ: The use of a human patient simulator in the evaluation of and development of a remedial prescription for an anesthesiologist with lapsed medical skills. Anesth Analg 2002; 94:149 –53



NJ STATE BOARD OF MEDICAL EXAMINERS
DISCIPLINARY MATTERS PENDING CONCLUSION
OPEN MINUTES - JULY 13, 2005

A meeting of the New Jersey State Board of Medical Examiners was held on Wednesday, July 13, 2005 at the Richard J. Hughes Justice Complex, 25 Market Street, 4th Floor, Conference Center, Trenton, New Jersey for Disciplinary Matters Pending Conclusion, open to the public. The meeting was called to order by Mr. Glenn Farrell, Chairperson for Open Disciplinary Matters.

THE BOARD, UPON MOTION MADE AND SECONDED, FOUND THAT THE ATTORNEY GENERAL HAS MET THE BURDEN OF THE PALPABLE DEMONSTRATION OF CLEAR AND IMMINENT DANGER IF RESPONDENT WERE PERMITTED TO PRACTICE WITH AN UNLIMITED PLENARY LICENSE.

THEREFORE, IN ORDER TO ADEQUATELY PROTECT THE PUBLIC, THE BOARD ORDERS THAT, EFFECTIVE IMMEDIATELY, RESPONDENT SHALL LIMIT HIS PRACTICE OF MEDICINE SOLELY TO THE PROVISION OF INDEPENDENT MEDICAL EXAMINATIONS IN THE MUSCULOSKELETAL AREA. FURTHER, RESPONDENT IS TO HAVE NO PRESCRIPTIVE AUTHORITY. ADDITIONALLY, WITHIN THREE MONTHS OF TODAY, RESPONDENT IS TO DEMONSTRATE COMPLETION OF 15 HOURS OF BOARD APPROVED CME CREDITS IN THE AREA OF INDEPENDENT MEDICAL EXAMINATIONS. ADDITIONALLY, WITHIN SIX MONTHS OF TODAY, RESPONDENT IS TO COMPLETE 40 HOURS OF BOARD APPROVED CME IN PAIN MANAGEMENT.

IN THE EVENT RESPONDENT DOES NOT DEMONSTRATE SUCCESSFUL AND TIMELY COMPLETION OF CME AT BOTH TIME PERIODS, RESPONDENT'S LICENSE IS TO BE AUTOMATICALLY SUSPENDED UNTIL SUCH TIME AS HE DEMONSTRATES THE REQUIRED CME.

Simulation-Based Education/Assessment for Re-entry

- Practicing Anesthesiologist over a 10 year hiatus from clinical medicine due to a non-medical reason
- New York State Department of Health State Board for Professional Medical Conduct (OPMC) Required the physician to obtain a retraining program before allowing them to regain their licensure and thus practice clinically
  - Approved retraining on a simulator
    - 6 week program
    - 20 hours of one on one simulation
    - 12 hours of integrated didactic sessions
    - Proctored departmental lectures and conferences

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Program Materials, *continued from page 50*

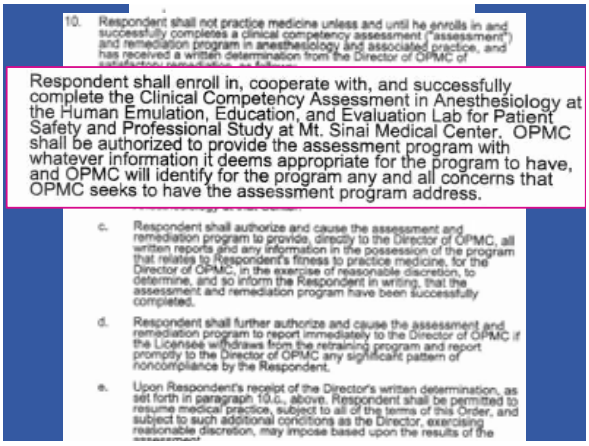
Performance Assessment for Re-entry

Adam Levine, MD

Simulation-Based Education & Assessment for Re-entry

- Upon completion the physician underwent a Simulation Based Assessment
  - 4 scenarios
  - Metrics exams
- Results
  - Improved confidence
  - Modernized practice, modernization of practice, e.g. ACLS protocols, new agents.
  - For the most part practiced "with in the standard of care" in a simulated environment.
  - Recommend to resume clinical practice, but should be supervised for no less then 6 months.

Levine A, Bryson E: The Use of Multi-modality Simulation for Competency Assessment: Journal of Critical Care, Volume 23, Issue 2, pages 197-202
DeMaria S Jr, Levine AI, Bryson EO, The use of multi-modality simulation in the retraining of the physician for medical licensure; J Clin Anesth. 2010 Jun;22(4):294-9.



10. Respondent shall not practice medicine unless and until he enrolls in and successfully completes a clinical competency assessment ("assessment") and remediation program in anesthesiology and associated practice, and has received a written determination from the Director of OPMC of

Respondent shall enroll in, cooperate with, and successfully complete the Clinical Competency Assessment in Anesthesiology at the Human Emulation, Education, and Evaluation Lab for Patient Safety and Professional Study at Mt. Sinai Medical Center. OPMC shall be authorized to provide the assessment program with whatever information it deems appropriate for the program to have, and OPMC will identify for the program any and all concerns that OPMC seeks to have the assessment program address.

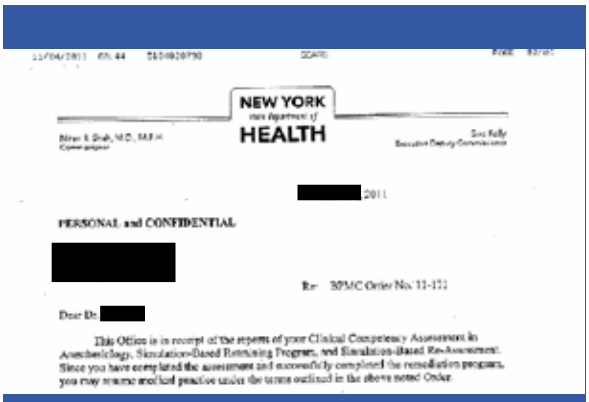
c. Respondent shall authorize and cause the assessment and remediation program to provide, directly to the Director of OPMC, all written reports and any information in the possession of the program that relates to Respondent's fitness to practice medicine, for the Director of OPMC, in the exercise of reasonable discretion, to determine, and so inform the Respondent in writing, that the assessment and remediation program have been successfully completed.

d. Respondent shall further authorize and cause the assessment and remediation program to report immediately to the Director of OPMC if the Licensee withdraws from the retraining program and report promptly to the Director of OPMC any significant pattern of noncompliance by the Respondent.

e. Upon Respondent's receipt of the Director's written determination, as set forth in paragraph 10.c., above, Respondent shall be permitted to resume medical practice, subject to all of the terms of this Order, and subject to such additional conditions as the Director, exercising reasonable discretion, may impose based upon the results of the

The assessment revealed the following deviations from standards of care.

1. Ability to adequately perform ACLS protocols either solo or as a team member.
2. Ability to maintain vigilance and recognize lost or failing standard ASA monitors.
3. Ability to appreciate and manage more complex patients with significant co-morbities.
4. Ability to demonstrate the ability to evaluate cardiac patients for non-cardiac surgery.
5. Ability to deviate from a set practice patterns regardless of the patient's co-morbities.



NEW YORK
State Department of
HEALTH

[redacted] 2011

PERSONAL and CONFIDENTIAL

[redacted]

Re: BPMC Order No. 11-111

Dear Dr. [redacted]

This Office is in receipt of the reports of your Clinical Competency Assessment in Anesthesiology, Simulation-Based Retraining Program, and Simulation-Based Re-Assessment. Since you have completed the assessment and successfully completed the remediation program, you may resume medical practice under the terms outlined in the above noted Order.

VERMONT

VERMONT BOARD OF MEDICAL PRACTICE – VERMONT DEPARTMENT OF HEALTH
LETTER OF AGREEMENT:
EXPERT REVIEWS AND LICENSEE ASSESSMENTS

The undersigned will provide a simulator-based clinical assessment of a Vermont Board of Medical Practice licensee pursuant to a contract entered into directly between the undersigned and the licensee. As part of the assessment, the Vermont Board of Medical Practice and Vermont Department of Health will provide to and receive from the undersigned relevant information relating to the licensee. To the extent applicable, protected health information contained therein will be treated pursuant to the terms of the attached Business Associate Agreement.

Simulation-Based Education & Assessment for Re-entry

- Practicing, boarded, Anesthesiologists with unblemished record for over 15 years
- Sustained an Achilles tendon injury
- Out of work for 2.5 years
- Attempted to be re-credentialed
- The Medical Staff Credentialing committee required the physician to undergo a simulation-based competency assessment

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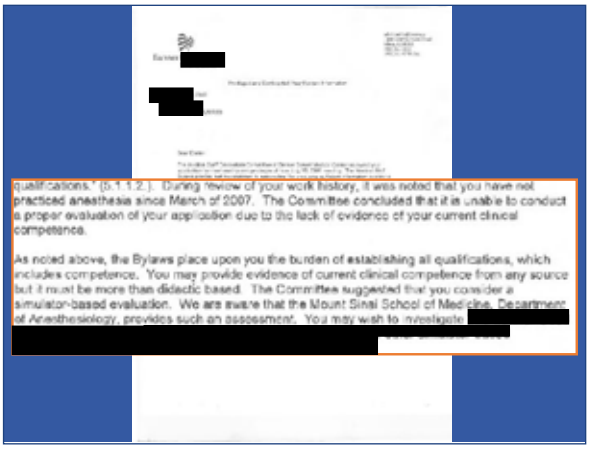
Program Materials, *continued from page 51*

Performance Assessment for Re-entry

Adam Levine, MD



qualifications." (b.1.1.2.). During review of your work history, it was noted that you have not practiced anesthesia since March of 2007. The Committee concluded that it is unable to conduct a proper evaluation of your application due to the lack of evidence of your current clinical competence.

As noted above, the Bylaws place upon you the burden of establishing all qualifications, which includes competence. You may provide evidence of current clinical competence from any source but it must be more than didactic based. The Committee suggested that you consider a simulator-based evaluation. We are aware that the Mount Sinai School of Medicine, Department of Anesthesiology, provides such an assessment. You may wish to investigate

Characteristics of Success

- Competence at the Time of Hiatus
- Maintained of CME/Licensure during hiatus
- Maintained relationships with anesthesia community

Summary

- To date there is no standard program for anesthesiologist to reenter clinical practice
- Anesthesiologists are a heterogeneous group of people
- Ideal re-entry programs are tailor-made to suit the individual
- Simulation-based education and formative and summative assessment can be used effectively as a critical component for reentry.

Program Materials, *continued from page 52*

Host Program Panel I

Agent-Based Modeling in Health Science: From Playground to Planet

Presenter: Joshua Epstein, PhD

Joshua M. Epstein, PhD, is Professor of Emergency Medicine at Johns Hopkins University, with Joint Appointments in the Departments of Applied Mathematics and Statistics, Economics, Biostatistics, International Health, and Civil Engineering. He is Founding Director of the JHU Center for Advanced Modeling in the Social, Behavioral, and Health Sciences. He is an External Professor at the Santa Fe Institute, a member of the New York Academy of Sciences, and was recently appointed to the Institute of Medicine's Committee on New Preventive Vaccines. Earlier, Epstein was Senior Fellow in Economic Studies and Director of the Center on Social and Economic Dynamics at the Brookings Institution. He is a pioneer in agent-based computational modeling of social dynamics. He has authored or co-authored several books including Growing Artificial Societies: Social Science from the Bottom Up, with Robert Axtell (MIT Press/Brookings Institution); Nonlinear Dynamics, Mathematical Biology, and Social Science (Addison-Wesley); Generative Social Science: Studies in Agent-Based Computational Modeling (Princeton University Press); and most-recently, Agent_ Zero: Toward Neurocognitive Foundations for Generative Social Science (Princeton University Press). Epstein holds a Ph.D. from MIT, and has taught at Princeton, and lectured worldwide. In 2008, he received an NIH Director's Pioneer Award, and in 2010 an Honorary Doctorate of Science from Amherst College, his alma mater.

Presentation Description: A pioneer of agent-based computational modeling, Epstein will demonstrate its applications to Pandemic Influenza, Smallpox, Ebola, Zika, and environmental health, at scales ranging from the local playground to artificial cites (New York and Los Angeles), to the US, to entire planet. Epidemic dynamics depend on human behavior, which—particularly in stressful settings—may be very far from canonically rational. Under an NIH Director's Pioneer Award, Epstein has developed a formal competitor to the rational actor, one driven by emotions (like fear), bounded rationality, and social conformity effects. These affective, deliberative, and social "modules" of Agent_Zero, as this creature is known, are based on contemporary cognitive neuroscience. Epstein is populating his large-scale models with cognitively plausible agents, to produce a transformative synthesis for global public health modeling.

Learner Objectives: After participating in this activity, the learner will be able to: (1) Identify the ubiquity of models; (2) Examine the cutting edge of computer simulation in Health Science; and (3) Assess how this flexible technology could apply to your field, be it infectious disease, critical care, environmental health, at scales from the ICU to the Globe.

Host Program Panel I

Irrationality in Health Care: Why Patients and Physicians Do Not Always Choose Wisely

Douglas E. Hough, PhD

Abstract: Most proposals to improve health care — whether national health policy or admonitions to patients to improve their lifestyle — are predicated on the assumption that people are rational. They understand that they need to buy health insurance in order to avoid potential bankruptcy in case of a serious illness. Patients understand that they need to take their medications as prescribed in order to recover from an illness. Physicians adjust their practice patterns when presented with evidence-based medical advances.

Yet, people don't always do these things. The "young invincibles" do not always buy health insurance (unless forced to). Patients are only 60% adherent to treatment regimens, even if they agree in principle with their physician's advice — and can afford the treatment. Physicians continue to prescribe treatments (such as MRIs for low-back pain) even if research demonstrates that the treatments have little or no clinical value.

The emerging field of behavioral economics provides a variety of tools and concepts that can be useful in understanding why people sometimes do not act rationally regarding health care. In this talk, I will describe some of the more robust concepts in behavioral economics – loss aversion, the endowment effect, framing, the power of the default, hyperbolic discounting, and System 1/System 2 thinking – and explain how they can be applied to health care behavior in the US.

Learning Objectives: After participating in this activity, the learner will be able to: (1) Identify the situations in which health care behavior can be irrational; (2) Review the major concepts of behavioral economics that can explain irrational behavior; and (3) Assess the challenge of changing patient and physician behavior.

Program Materials, *continued from page 54*

Host Program Panel II

Developing and Deploying Influenza Vaccines: The Pandemic-Seasonal Interplay

Presenter: Kathleen M. Neuzil, MD, MPH, FIDSA

Notes:

Host Program Panel II

The Beginning of the End of Hepatitis C — 2017

Presenter: Shyamasundaran Kottilil, MD

Chronic hepatitis C (HCV) is estimated to infect more than 130 million people worldwide. A significant proportion of patients with chronic HCV will progress to develop liver cirrhosis, and subsequently hepatic decompensation and hepatocellular cancer. Of these, approximately 700,000 die each year of liver complication related to hepatitis C. Chronic hepatitis C was once deemed to be a very difficult to treat infection until recent advancement in HCV therapy with the availability of newer highly efficacious direct acting antiviral (DAA) drugs.

For more than a decade, HCV standard of care therapy involved treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV), which was associated with significant dose limiting adverse events and modest cure rates. The breakthrough in HCV therapy happened when all oral directly acting antiviral agents were approved for the treatment of hepatitis C. Hence, HCV therapy has evolved rapidly from an injectable interferon based regimen of poor tolerability, modest efficacy to all oral well tolerated and highly efficacious DAA treatment. Today, combination therapy that is capable of attaining SVR rates of 95-99% regardless of HCV genotypes was approved in the U.S.

Though having safe and highly effective drug regimens that can "virtually" cure all HCV infected individuals is an integral part of any hepatitis C eradication strategy, it still is just one component to achieving disease elimination. An optimal approach to eliminate hepatitis C involves identifying all chronically infected patients, linking them all to care, and successively treating them, as well as addressing the social and economic issues that increases risk of reinfection. As majority of chronic hepatitis C infected individuals are asymptomatic, only a fraction are aware that they have the disease. As a result, hepatitis C is a silent disease with a global epidemiology that is not fully understood. Another shortfall in the cure cascade of hepatitis C, is that only a fraction of those tested positive gets linked to care and subsequently treated. This is primarily hindered by the limited access to specialists that treats hepatitis C. To overcome this barrier, there needs to be an expansion of the pool of healthcare providers that are trained and therefore have expertise in caring for patients with chronic hepatitis C. Once linkage to care is established, all that have chronic HCV infection regardless of fibrosis stage should be treated. Therefore, in order to cause a significantly reduction in the transmission of hepatitis C, treatment of all infected patients should be the goal.

Hepatitis C is a global disease that needs global attention. With the availability of highly effective anti-HCV drug regimens, it is one step closer to being eliminated as a public health problem, but several hurdles remain and needs to be addressed to attain this vision. Today, availability of DAAs is no longer the limiting factor for escalation of HCV care.

Scientific Advisory Board Oral Session III

CX_3CR1^+ Cells in the PNS Play a Key Role in Development of Neuropathic Pain in Mice

Jianguo Cheng. MD, PhD

Introduction: The mechanisms of neuropathic pain are complex and far from clear (1). Neuroinflammation in both the central nervous system (CNS) and peripheral nervous system (PNS) has been specifically implicated (2-4). Fractalkine receptor (CX3CR1) is expressed constitutively in microglia and has been used as a specific marker for microglia in the CNS (3). It is a unique chemokine receptor that binds only to the chemokine, fractalkine (CX3CL1) (5). We identified a unique population of CX3CR1+ cells in the PNS and investigated the role of this population of cells in the development of neuropathic pain by utilization of CX3CR1GFP knock-in mice, CX3CR1 knock-out mice, and chimeric mice with CNS or PNS CX3CR1-deficiency.

Methods: With IACUC approval, CX3CR1GFP/+ and CX3CR1GFP/GFP transgenic mice were used to induce neuropathic pain by chronic constrictive injury (CCI) of the sciatic nerve. Paw withdrawal thresholds were evaluated on post-surgical days 0, 7, 14, 21 and 28. The animals were sacrificed and perfused at these time intervals to collect samples of the sciatic nerve, DRG, and spinal cord of both sides for immunohistochemistry and flow cytometry examination of CX3CR1+ cells. We reconstituted irradiated CCR2RFP/+ or CX3CR1GFP/GFP mice with CX3CR1GFP/GFP or CCR2RFP/+ bone marrow cells to produce PNS CX3CR1-deficiency mice (CX3CR1GFP/GFP → CCR2RFP/+) or CNS CX3CR1-deficiency mice (CCR2RFP/+ → CX3CR1GFP/GFP) and used these mice to determine the role of CX3CR1+ cells the development of neuropathic pain. Statistical analyses were made using two-way analysis of variance (ANOVA) followed by paired comparisons with Bonferroni corrections when comparisons were made between more than 3 groups.

Results: CX3CR1 was expressed not only in microglia in the CNS but also in cells residing in the sciatic nerve and DRG in mice. The morphology of CX3CR1+ cells in the sciatic nerve and DRG was different from that of microglia in the spinal cord. These cells were positive for IBA1, a macrophage/microglia marker, and positive for CD45, a hematopoietic marker, suggesting this population of cells is a subtype of macrophages residing in the PNS. We further demonstrate that these cells were negative for NF-H (neuronal marker), myelin basic protein (MBP, marker for myelin), glutamine synthetase and Kir4.2 (markers for satellite cells), suggesting they were neither neurons nor Schwann cells, nor satellite cells. Immuno-Electronic microscopy confirmed that CX3CR1 was exclusively expressed on these cells. Interestingly, the number and morphology of CX3CR1+ cells were dramatically increased in the sciatic nerve and DRG, started from post-surgical day 3 and peaked at the day 14, in sync with hyperalgesia. Mice with global CX3CR1-deficiency were resistant to the development of neuropathic pain. Mice with PNS CX3CR1-deficiency only (CX3CR1GFP/GFP → CCR2RFP/+) or CNS CX3CR1-deficiency only (CCR2RFP/+ → CX3CR1GFP/GFP) were partially resistant to the development of neuropathic pain.

Conclusion: We discovered a specific population of resident CX3CR1+ cells in the PNS (the sciatic nerve and DRG) which were morphologically different from blood CX3CR1+ cells and CNS CX3CR1+ microglia. PNS CX3CR1+ cells played a role in the development of neuropathic pain that was as important as microglia in the CNS. Further experiments will further clarify how this population of CX3CR1+ cells contribute to the initiation and/or maintenance of neuropathic pain.

Scientific Advisory Board Oral Session III

Corticostriatal Circuit Regulates Acute and Chronic Pain in Rodents

Jing Wang, MD, PhD

Synopsis: A better understanding of the brain circuits that determine the perception and modulation of pain is crucial to the development of novel analgesics. The prefrontal cortex (PFC) is a well-known cortical region that provides top-down regulation of sensory and affective processes. While previous studies have shown this region to be implicated in nociceptive regulation, the output target for the PFC in the context of acute and chronic pain remains poorly defined. The projection from the PFC to the nucleus accumbens (NAc) is an important component of the reward circuitry, and this projection has been implicated in chronic pain states. The function of this key corticostriatal projection in pain states, however, is not known, but its understanding can significantly impact our knowledge of central pain regulation. We took an optogenetic approach to study the role of the projection from PFC to NAc in pain regulation in rats. We examined both sensory and affective pain symptoms in the context of corticostriatal activation, using an acute postoperative pain model (paw incision or PI model) and a chronic neuropathic pain model (spared nerve injury or SNI model). We tested the anti-nociceptive effects of optogenetic activation of PFC neurons using mechanical allodynia and Hargreave's tests. We tested the affective symptoms of pain using conditioned place preference. Following this, we specifically targeted the projection from the PFC to the NAc using optogenetics and performed the same sensory and affective pain assays. We found that optogenetic activation of the PFC, compared with control, reduced both sensory and affective components of pain in both acute and chronic pain models. Furthermore, we showed that these analgesic effects are at in large part mediated by the projection from the prefrontal projections to the NAc core. These results show that this corticostriatal circuit has a critical role in pain regulation.

Scientific Advisory Board Oral Session III

Junior Faculty Travel Award in Perioperative Medicine

A Randomized Trial of Perioperative Gabapentin to Promote Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort

Jennifer Hah, MD, MS

Introduction: More than 51 million Americans undergo surgery every year, after which up to 13% of patients initiate chronic opioid use. Medicine is facing the considerable challenge of adequately managing pain while limiting opioid consumption. Gabapentin may reduce opioid use independent of its effect on decreasing pain, but research on gabapentin's effect on postoperative pain and opioid use has been methodologically limited and drawn conflicting conclusions. We conducted a randomized, double-blind, placebo-controlled trial of perioperative gabapentin in a mixed surgical cohort followed up to 2 years postoperatively.

Methods: 411 patients scheduled for an eligible surgery (thoracotomy, video-assisted thoracoscopic surgery, total hip replacement, total knee replacement, mastectomy, breast lumpectomy, hand surgery, carpal tunnel surgery, knee arthroscopy, shoulder arthroplasty, and shoulder arthroscopy) were randomly assigned to receive 1200 mg gabapentin preoperatively and 600mg gabapentin three times a day postoperatively, or active placebo (0.5mg lorazepam) preoperatively followed by inactive placebo postoperatively for 72 hours. Prior to surgery, participants completed assessments including the Brief Pain Inventory (BPI), self-reported likelihood of developing chronic pain after surgery, self-perceived sensitivity to pain, and self-perceived likelihood of addiction to pain medication after surgery. After discharge, a modified BPI was administered daily over the phone for 3 months, at which point the frequency reduced to weekly until 6 months, and then to monthly up to 2 years after surgery. Primary outcome was time to pain resolution (five consecutive reports of zero out of ten average pain at the surgical site). Secondary outcome was time to opioid cessation (five consecutive reports of zero opioid use even for participants taking opioids prior to surgery). These outcomes, were analyzed in the intention-to-treat population with the hazard ratio and two-sided 95% confidence intervals based on a Cox regression model stratified by surgery type as pre-specified in our analytic plan.

Results: 2075 patients were screened for eligibility between May 25, 2010 and July 25, 2014. 422 underwent randomization, with 215 assigned to receive perioperative gabapentin and 207 assigned to receive active placebo. Baseline sociodemographic characteristics were balanced between the two study groups. This longitudinal study represents 19,511 distinct assessments of postoperative pain. Perioperative gabapentin did not affect time to pain cessation after surgery. Nevertheless, participants receiving gabapentin had a 24% increase in the rate of opioid cessation after surgery (HR 1.24, 95% CI 1.00-1.54, p-value=0.05). No differences were noted in the number of adverse or serious adverse events. Patients receiving gabapentin reported more impaired coordination and rash, and reported less constipation. No differences were noted in pre-planned subgroup analyses.

Conclusion: Despite its lack of impact on pain resolution, perioperative gabapentin speeded cessation of opioids prescribed for postoperative pain management. This resonates with our earlier work suggesting that the determinants of the rate of opioid cessation are largely independent of the duration of pain and the determinants of time to pain resolution. Expanded use of this medication may lower the risks of opioid misuse, abuse, addiction, diversion, and overdose after surgery.

Scientific Advisory Board Oral Session III

Dezocine for Opioid Addiction in a Rat Morphine Dependence Model

Renyu Liu, MD, PhD

Synopsis: Opioid dependence continues to be a major public health issue without optimal therapeutics. The present study investigated the therapeutic potential of dezocine, a non-addictive opioid, to attenuate naloxone-precipitated morphine withdrawal syndrome in a rat addiction model. The intensity of the morphine withdrawal syndrome was reduced doze-dependently in rats treated with dezocine comparable to that with buprenorphine. Chronic morphine administration through repeated subcutaneous injections induced astrocytes activation in nucleus accumbens, which was attenuated by dezocine and buprenorphine. Dezocine blocked the agonist-induced kappa opioid receptor internalization, using a fluorescently tagged kappa opioid receptor over-expressed neuroblastoma cells in vitro. However, buprenorphine blocked the receptor internalization with higher potency than dezocine. Interrogation of 317 human G protein coupled receptors via a G protein-independent μ-arrestin-recruitment and radioligand binding assays for 44 G protein coupled receptors, ion channels and transporter proteins indicated that morphine, dezocine and buprenorphine have different sets of molecular targets. It was revealed that Neurokinin 1 Receptor is potentially novel unique molecular target for dezocine for its anti-addictive properties. Furthermore, while dezocine inhibits norepinephrine and serotonin reuptake as we demonstrated previously, buprenorphine did not interact with norepinephrine and serotonin transporters. Findings in this study suggest that dezocine could be an alternative medication for opioid addiction management and has different molecular targets from that of buprenorphine.

Significance Statement: This study provides evidence that dezocine, a partial mu opioid receptor agonist and kappa opioid receptor antagonist, could potentially be used for addiction management by using a rat morphine dependence model. It is important to note that dezocine is a non-addictive opioid that has been used in clinical practice for centuries. The molecular targets of dezocine are also investigated in parallel of morphine and buprenorphine, providing useful information for science communication in understanding molecular mechanisms for addiction and anti-addiction. Novel molecular targets are revealed for all three molecules. Dezocine is a neurokin 1 receptor agonist, which could potentially relate to its non-addictive property. Further studies are needed to confirm these newly discovered molecular targets and the related pharmacological significance.

References:

1. J Opioid Manag. 2016, 12: 109–18.
2. J Psychopharmacol 2006, 20: 806–814.
3. Anesthesiology. 2014–120:714-23.

Program Materials, *continued from page 60*

Scientific Advisory Board Oral Session IV

How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?

Peter Hu, PhD

How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?

Peter F. Hu, PhD[1,2], Li-Chien Lee, MS[1], Hsiao-Chi Li, PhD[1], Shiming Yang, PhD[1], Samuel Galvagno, MD[1], Samuel Tisherman, MD[2], Peter Rock, MD[1]
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Association of University Anesthesiologists 64th Annual Meeting
May 4-5, 2017. Washington, DC

The Joint Commission Announces 2014 National Patient Safety Goal

In June 2013, The Joint Commission approved new National Patient Safety Goal NPSG.06.01.01 on **clinical alarm safety** for **hospitals** and **critical access hospitals**.

The implementation for NPSG.06.01.01 will occur in two phases:

- In Phase I (beginning **January 2014**), hospitals will be required to establish alarms as an **organization priority** and identify the most important alarms to manage based on their own internal situations.
- In Phase II (beginning **January 2016**), hospitals will be expected to **develop** and **implement** specific components of policies and procedures. Education of those in the organization about alarm system management will also be required in January 2016.

http://www.jointcommission.org/assets/1/18/JCP0713_Announce_New_NSPG.pdf

Current Status of Hospital Alarms

Alarm fatigue is

- When a nurse and clinicians or other caregiver is **overwhelmed** with **350** alarm conditions **per patient per day**.
- When a **patient can't rest** with the multitude of alarm signals going off in the room
- When a true **life-threatening event** is **lost** in a cacophony of noise because of the multitude of devices with competing alarm signals, all trying to capture someone's attention, **without clarity** around what that someone is supposed **to do**.
- Compounded by **inconsistent alarm system functions** (alerting, providing information, suggesting action, directing action, or taking action) or **inconsistent alarm system characteristics** (information provided, integration, degree of processing, prioritization)
- A systems failure that results from **technology driving processes** rather than **processes driving technology.**

Summary of Alarm Summit by AAMI

What's happened in our institution

University of Maryland Medical Center / Shock Trauma Center

- "We didn't hear it"
- "We couldn't tell what was alarming"
- "We just got too busy"
- "Things were just crazy that day"
- "The place is like a casino with so many bells and whistles"

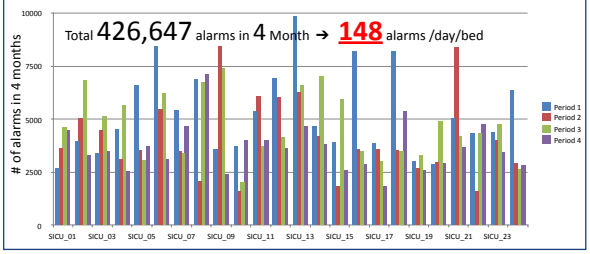
Methods

- We retrospectively analyzed patient Vital Signs (VS) in a **24-bed Surgical Intensive Care Unit (SICU)** and collected alarm data between October 12, 2015, and February 15, 2016, from networked patient VS monitors (GE Solar) using the BedMasterEX (Excel Medical LLC, FL) system.
- Alarm VS name, four industry defended alarm classifications, duration, and frequency were recorded and analyzed.
- Most alarms were found to be brief and transitory lasting just a few seconds. Specific duration (seconds) was analyzed to achieve 25% and 50% alarm reduction.
- To reduce individual VS alarms, different alarm limit settings were compared with the default settings of hypoxia (SpO2 low ≤ 90%,) and tachycardia (heart rate: HR, HR high ≥ 130 bpm).

Results

24-bed Surgical Intensive Care Unit (SICU)

120 Days: 4 periods , each period covers 30 days
Period 1 (10/12/15-11/10/15); Period 2 (11/11/15-12/10/15)
Period 3 (12/18/15-01/16/16); Period 4 (01/17/16-02/15/16)
Real time recording of All alarms (type and duration)
and Vital Signs (Trends 0.5Hz), Waveforms (240 Hz)



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Program Materials, *continued from page 61*

How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?

Peter Hu, PhD

Total 426,647 Alarms in 4 Month in 24 Bed SICU
Top 10 Reasons for Alarm in each of the 4 Categories

Alarm (Top 10) Level	Category	Total N	1	2	3	4	5	6	7	8	9	10
3 (C1)	System Warning	66300 (15.5%)	SPO2 PROBE	NO ECG	CONNECT PROBE	NBP MAX TIME	SENSOR	ARRHY SUSPEND	SPO2 SENSOR	NBP FAIL	RR LEADS FAIL	NBP OVER PRES
			33.4%	23.6%	16.2%	14.7%	5.8%	4.6%	1.0%	0.4%	0.4%	0.4%
5 (C2)	Patient Advisory	245779 (57.6%)	ART S LO	PVC	CHECK ADAPTER	ART S HI	NBP S LO	ART M LO	CO2 RSP HI	NBP S HI	ART D HI	ART M HI
			25.7%	15.7%	13.6%	13.3%	6.2%	4.7%	4.2%	3.5%	3.4%	2.7%
6 (C3)	Patient Warning	98024 (23.0%)	SPO2 LO	ART DISCONN	V TACH	VT > 2	NO BREATH	FEM2 DISCONN	HR HI			
			93.4%	2.8%	1.8%	1.1%	0.9%	0.0%	0.0%			
7 (C4)	Patient Crisis	16544 (3.9%)	VT > 2	LEADS FAIL	HR HI	HR LO	BRADY	V TACH	ASYSTOLE	V BRADY	VFIB/ VTAC	
			27.1%	25.0%	14.9%	12.4%	11.8%	6.5%	1.4%	0.6%	0.3%	

Total 426,647 Alarms in 4 Months with 24 Bed SICU
Durations (seconds) of alarms in each category

Alarm Levels	Categories	N	2s	4s	6s	8s	10s	1min
3 (C1)	System Warning	66300 (15.5%)	6.26%	10.97%	13.76%	15.61%	17.11%	31.61%
5 (C2)	Patient Advisory	245779 (57.6%)	26.55%	34.97%	39.98%	44.04%	47.45%	73.23%
6 (C3)	Patient Warning	98024 (23.0%)	24.70%	34.35%	41.65%	47.57%	52.38%	85.51%
7 (C4)	Patient Crisis	16544 (3.9%)	18.78%	28.93%	35.87%	41.36%	45.90%	81.10%
All	All Alarms	426647 (100.0%)	22.67%	30.87%	36.13%	40.33%	43.81%	69.89%

Can we wait **2s** to reduce **22%** or **4s** to reduce **30%** of alarms?

Total 426,647 Alarms in 4 Month in 24 Bed SICU
Top 10 Reasons for Alarm in each of the 4 Categories

Alarm (Top 10) Level	Category	Total N	1	2	3	4	5	6	7	8	9	10
3 (C1)	System Warning	66300 (15.5%)	SPO2 PROBE	NO ECG	CONNECT PROBE	NBP MAX TIME	SENSOR	ARRHY SUSPEND	SPO2 SENSOR	NBP FAIL	RR LEADS FAIL	NBP OVER PRES
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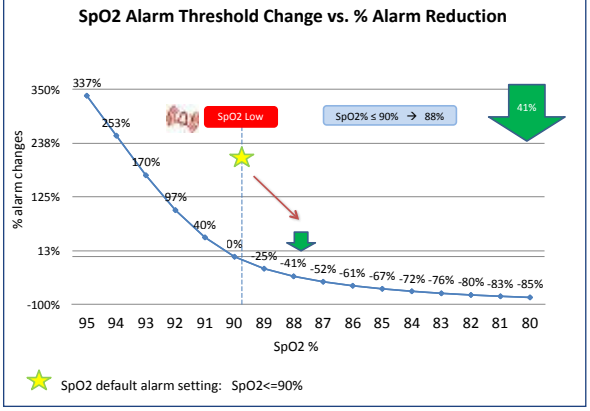
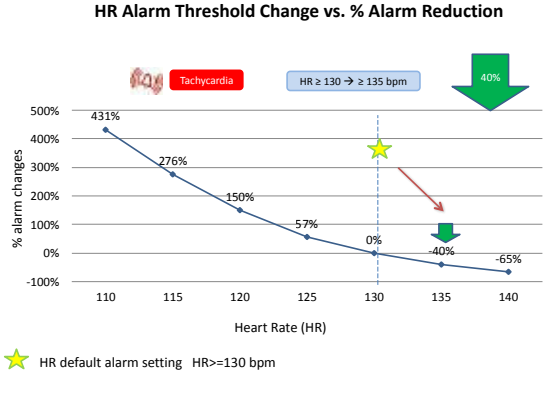
			93.4%	2.8%	1.8%	1.1%	0.9%	0.0%	0.0%			
7 (C4)	Patient Crisis	16544 (3.9%)	VT > 2	LEADS FAIL	HR HI	HR LO	BRADY	V TACH	ASYSTOLE	V BRADY	VFIB/ VTAC	
			27.1%	25.0%	14.9%	12.4%	11.8%	6.5%	1.4%	0.6%	0.3%	

PPG: SpO2 related alarms ECG: HR related alarms





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How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?

Peter Hu, PhD

What We Need: Smart Alarm

- High Sensitivity and Specificity alarms
- Limited alarms per patient per day. NOT 150-300 /day/bed

Personalized for individual patient and individual clinician

- Adoptive Alarm Settings (this patient and now)

- Tell me something that I do not know
  Status change notification for specific person (RN, MD)
  Patten vs. individual VS change

Additional use of alarms

- Provide patient physiological stability assessment
- Prediction of near future trajectory

Conclusion

Alarm fatigue from physiologic alarms in SICU is well recognized but a safe solution to safely reduce alarms has not been established.

Our study suggests that by delaying all alarms for **4 seconds** we could reduce **30%** of the total alarms.

By lowering alarm thresholds of SpO2 LO by **2%** and increasing the tachycardiac threshold by 5 bpm could reduce an additional **40%** of alarms in SICU.

Further study is needed to determine what impact such changes would have upon the safety of patients being cared for in the SICU.

Alarm Reduction Research Team at University of Maryland

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Thanks

Email: phu@umm.edu

Association of University Anesthesiologists 64th Annual Meeting
May 4-5, 2017. Washington, DC

Scientific Advisory Board Oral Session IV

Junior Faculty Travel Award in Pediatric Anesthesia

Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis

Caleb Ing, MD, MS

Introduction: Animals exposed to anesthetics during specific age periods of brain development experience neurotoxicity, with neurodevelopmental changes subsequently observed during adulthood.[1,2] The corresponding vulnerable age in children however is unclear. Despite this, the Food and Drug Administration recently released a new warning regarding the use of anesthetics in children before age 3 years. Since delaying necessary procedures may have unintended harmful consequences, whether delaying a procedure has any long-term clinical benefit is an important question to answer.

Methods: An observational cohort study was performed using a longitudinal dataset constructed by linking individual-level Medicaid claims from Texas and New York from 1999 to 2010. This dataset was evaluated to determine whether the timing of exposure to anesthesia under age 5 years for a single common procedure (pyloromyotomy, inguinal hernia, circumcision outside the perinatal period, or tonsillectomy and/or adenoidectomy) is associated with increased subsequent risk of diagnoses for any mental disorder, or specifically developmental delay (DD) such as reading and language disorders, and attention deficit hyperactivity disorder (ADHD). Exposure to anesthesia and surgery was evaluated in 11 separate age at exposure categories. Cox proportional hazards models were used to measure the hazard ratio of a mental disorder diagnosis associated with exposure to surgery and anesthesia. Procedure-specific models were also assessed.

Results: A total of 38,493 children with a single exposure and 192,465 propensity score matched children unexposed before age 5 were included in the analysis. Increased risk of mental disorder diagnosis was observed at all ages at exposure with an overall hazard ratio of 1.26 (95% confidence interval [CI], 1.22–1.30), which did not vary significantly with the timing of exposure. (Figure 1, Panel A) When evaluating children undergoing individual procedures, some minor variation in the risk of developing a mental disorder based on age at exposure was seen. (Figure 1, Panels B-E) Analysis of DD and ADHD showed similar results as those seen with any mental disorder diagnosis, with elevated hazard ratios distributed evenly across all ages, and overall hazard ratios of 1.26 (95% CI, 1.20–1.32) for DD and 1.31 (95% CI, 1.25–1.37) for ADHD. (Figure 2)

Conclusion: Children who undergo minor surgery requiring anesthesia under age 5 have a small but statistically significant increased risk of mental disorder diagnoses, and DD and ADHD diagnoses, but the timing of the surgical procedure does not alter the elevated risks. Based on these findings, there is little support for the concept of delaying a minor procedure to reduce neurotoxic risks of anesthesia in children.

References:

1. Disma et al. Paediatr Anaesth 2016; 26: 6-36
2. Loepke et al. Anesth Analg 2008; 106: 1681-707

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Program Materials, *continued from page 64*

Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis

Caleb Ing, MD, MS

Figure 1: Increased Hazard of Any Mental Disorder

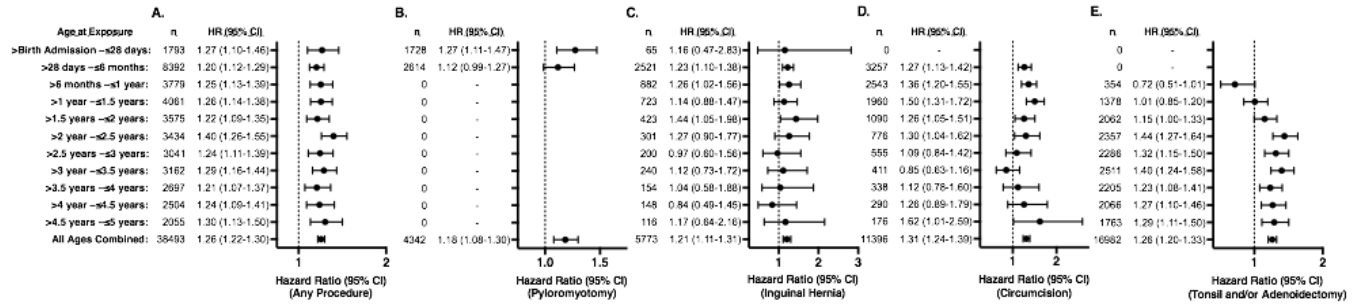
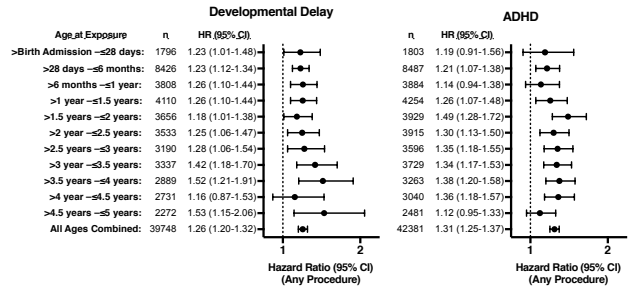


Figure 2: Increased Hazard of Developmental Delay or ADHD



Scientific Advisory Board Oral Session IV

Perioperative Decline in High Density Lipoprotein Particles is Associated with Increased Risk of AKI after Cardiac Surgery

Loren E. Smith, MD, PhD

Introduction: Acute kidney injury (AKI) after cardiac surgery occurs in up to 30% of patients and is an independent predictor of death.1 We previously reported that a higher preoperative high density lipoprotein (HDL) cholesterol concentration is associated with a decreased risk of AKI after cardiac surgery. HDL particle number and size better correlate with HDL's cardiovascular effects than HDL cholesterol levels,2 but the effect of HDL particle characteristics in the perioperative period has never been described. We measured HDL particle concentration and size at induction of anesthesia, at admission to the ICU following surgery, and on postoperative day two to test the hypothesis that perioperative HDL particles are associated with AKI following cardiac surgery.

Methods: After IRB approval, we selected 90 patients who developed mild, moderate, severe, or no AKI from a recently completed, prospective trial of perioperative atorvastatin to prevent post-cardiac surgery AKI.3 Plasma samples were analyzed using the NMR Lipoprofile test, a clinical assay of HDL particle concentration and size. HDL cholesterol concentration, particle concentration, and particle size changes over time were assessed with mixed effects models adjusted for AKI risk factors. A two-component latent variable mixture model was used to assess the association between the change in HDL particle concentration from anesthetic induction to postoperative day two and the maximum serum creatinine change from baseline in the first 48 postoperative hours. Similar modeling was used to assess the association between the change in average HDL particle size and postoperative serum creatinine change.

Results: HDL cholesterol concentration did not change during the perioperative period ($p=0.60$). HDL particle concentration, however, decreased over the same period ($p<0.001$), while HDL particle size increased ($p<0.001$). A larger decrease in HDL particle concentration from induction to postoperative day two was independently associated with a greater postoperative rise in serum creatinine ($p=0.02$), while a larger increase in average HDL particle size from induction to postoperative day two was not associated with a greater postoperative serum creatinine rise ($p=0.42$).

Conclusion: HDL particle concentrations decreased during the perioperative period while HDL particle sizes increased. HDL cholesterol concentrations did not change. A greater decrease in HDL particle concentration was independently associated with an increased risk of AKI after cardiac surgery. Further work will assess perioperative HDL protein composition and function changes, in a continued effort to identify the biological mechanism underlying the protective association between HDL and postoperative AKI.

References:

1. Perioperative Medicine, vol 1, pg 6, 2012
2. Cardiovasc Drugs Ther, vol 29(1), pg 41, 2015
3. JAMA, vol 315(9), pg 877, 2016

Program Materials, *continued from page 66*

Educational Advisory Board Program Panel II

Flipped Classroom

Susan M. Martinelli, MD

AUA 64th Annual Meeting
May 4-5, 2017 • Washington, DC

The Evidence Behind the "Hot" Topics in Anesthesia:
Flipped Classroom

Susan M Martinelli, MD
Associate Professor of Anesthesiology
University of North Carolina

AUA 64th Annual Meeting
May 4-5, 2017 • Washington, DC
DISCLOSURES

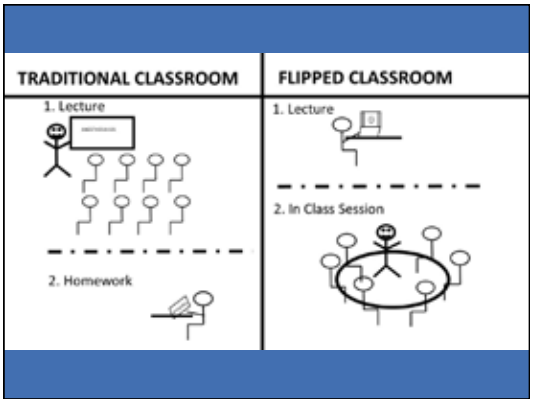
Foundation for Anesthesia Education and Research: Research in Education Grant 2014-2016

FAER
Foundation for Anesthesia Education and Research

Objectives:

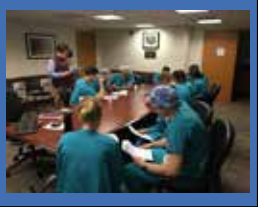
- Components of flipped classroom
- Evidence supporting flipped classroom
- Implementing flipped classroom

	Traditionalists	Baby Boomers	Gen X	Gen Y
Year Born	1935-1946	1946-1964	1965-1981	1982-2000
Learning Style	Dependent on educators Lecture format Books	Dependent on educators Lecture format Books	"Death by PowerPoint" Some small group	Teamwork Interactive
View on Technology	May be tech. challenged	Take it or leave it	Adept	Natives



In Classroom: Active Learning

- Audience response questions
- Think pair share
- Case based learning
- Educational games
- Role play



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Flipped Classroom

Susan M. Martinelli, MD

Suggested benefits of FC

- Efficient
- Flexible
- Engaging
- Promotes life-long learning
- Team work
- Assess understanding
- ↑knowledge gain
- ↑ knowledge retention

Pharmacy studies

- Wong et al
  - 3 sessions on cardiac arrhythmias
  - ↑knowledge gain (2 of 3)
- McLaughlin et al
  - Entire pharm course
  - ↑knowledge gain
- Pierce et al
  - 8 week renal pharm course
  - ↑knowledge gain

Systematic review of FC in Medical Education

- 46 articles
  - 11 GME
  - 9 controlled studies—none in GME
- Outcomes
  - ↑satisfaction with FC
  - Mixed results with knowledge/skill

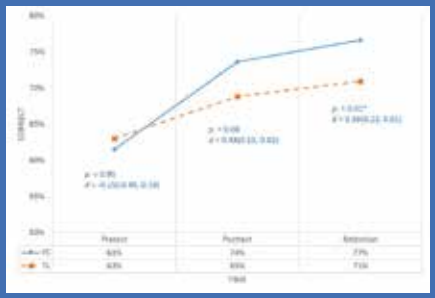
Chen F, Lui AM, Martinelli SM. A Systematic review of the effectiveness of flipped classroom in medical education. In press *Medical Education*.

Anesthesia Basic Board Preparation Experience

- 155 PGY-2s
- 8 institutions
  - Either TL or FC
- Multiple choice knowledge tests
- Preferred FC (p<.001)

Martinelli SM, Chen F, DiLorenzo AN, Mayer DC, Bowe EA, Fairbanks S, Hendrickse A, VanDyke K, Trawicki MC, Moran K, Rankin D, Guldan GJ, Hand W, Gallagher C, Jacob Z, Ku C, Mitchell JD, Royal KD, McEvoy MD, Zvara, DA, Schell RM. Flipped classroom led to increased knowledge acquisition and retention and is strongly preferred to traditional classroom in anesthesiology residents. Under review.

Adjusted means of the percent correct on the knowledge test over time



FC in Quality Improvement Education

- 143 internal medicine
  - PGY-1 and PGY-3—FC
  - PGY-2—non FC
- FC group
  - ↑ QI knowledge gain (p<.0001)
  - Preference for FC (p<.0001)
  - Felt that in-class sessions most enhanced learning

Bonnes SL, et al. Flipping the quality improvement classroom in residency education. *Acad Med* 2017 Jan; 92(1): 101-107.

continued on page 70

Program Materials, *continued from page 68*

Flipped Classroom

Susan M. Martinelli, MD

Impact of FC based on Bloom's Taxonomy

- FC goal for higher level thinking
- MS 1 in multi-disciplinary course
  - Focused on anatomy
  - TL (with some active learning) vs FC

http://www.learnnc.org/lp/media/misc/2008/blooms_new.png

Morton DA, Colbert—Getz JM. Measuring the impact of the flipped anatomy classroom: the importance of categorizing an assessment by Bloom's Taxonomy. *Anat Sci Educ*. 2017 Mar; 10(2): 170-175.

FC in Emergency Medicine Clerkship

- 69 MS3 and MS4
- 2 institutions
- FC—focused on designated theme during shift
- No difference in knowledge gain
- 31% did not follow protocol

Heitz C et al. Does the concept of the "flipped classroom" extend to the emergency medicine clinical clerkship? West J Emerg Med. 2015 Nov;16(6):851-5.

Implementation of FC

- Pre-session homework
  - Often video 15-20 min
  - Voice over slide based presentation
  - Ensure learners know expectations
- In class
  - Active learning
  - Problem solving
  - Function as facilitator/coach

Faculty Survey Regarding FC

- 244 faculty
- 57% understood FC
  - 57% used FC in previous year
- Perceived barriers
  - Learners prepared
  - Learners participation
  - More comfortable with TL
  - Time to prepare
  - Technology
- 89% interested in faculty development

Martinelli SM, Chen F, McEvoy MD, Zvara DA, Schell RM. Utilization of the flipped classroom in anesthesiology graduate medical education: a survey of faculty beliefs and practices. In preparation.

Faculty Perception: Anesthesia Basic Board Preparation Experience

- 16 faculty
- Residents prepared for FC sessions
- More professional satisfaction in FC
- Residents more engaged in FC
- Will use TL and FC in future

Conclusions

- Learners prefer FC
- ? Knowledge benefit
- Limited work in GME
- Barriers—improve with faculty development?
- Component of multi-modal curriculum

Educational Advisory Board Program Panel II

Spaced Education – What is That and Why Should I Use It?

Matthew D. McEvoy, MD

What are the best pedagogical approaches for transferring knowledge to the GME and CME learners of today? Based on current evidence, the answer would include "spaced education," a methodology created by Dr. Kerfoot a little over a decade ago. It has been tested in multiple medical specialties with over 10 large randomized controlled trials (RCTs) being completed to date. The results are significant and encouraging: compared to traditional "binge and purge" studying for tests and compared to online learning modules, "spaced education" learning consistently results in *>30% increase in knowledge acquisition and retention*.

What exactly is spaced education? It is a teaching and learning methodology based upon two core principles: spacing and testing. The spacing effect draws from well-described principles of learning and and how memory is encoded. Material is presented multiple times in small quanitites spaced out over time. The testing effect is simply that – presenting material in a test question format at the beginning of the learning process rather than the end, which improves learning. Taken together, these two principles greatly increase knowledge acquisition and long-term retention.

But, does that knowledge translate into clinical practice, and if so into improved patient outcomes? hile there are not as many trials looking into that question, several large RCTs have demonstrated that spaced education can improve process metrics of care delivery compared to traditional learning methods (classroom or online modules) in some clinical settings. One study looking at time to meeting blood pressure goals were shortened for clinicians receiving learning through spaced education than through traditional online learning modules. Another study in the VA health system showed a reduction in the number of inappropriate prostate cancer screening tests performed when spaced education was compared with other educational methods.

How does this apply to the field of aneshesiology and perioperative medicine? Little research has been performed with spaced education and anesthesiology trainees. But, small studies including anesthesiology residents suggest that spaced education is considered a beneficial and preferred pedagogical approach by anesthesiology trainees. Going forward our field should determine the optimal way in which to engage learners using spaced education: a replacement for classroom learning, in addition to case-based discussions, or as education during the workday and in the workplace? Some evidence is emerging to answer these questions.

What are the future directions for Spaced Education and anesthesiology? There are specific opportunities in our field due to the willingness to adopt technological solutions and due to particular challenges with maintaining a robust educational curriculum balanced with clinical duties. The use of Spaced Education specifically as workplace-based education provides excellent opportunities for research and improvements in care delivery, as well as a novel mechanism for delivering CME.

Educational Advisory Board Program Panel II

Test Enhanced Learning: Stop Studying and Take a Test!

Randall Schell, MD, MACM

"Exercise in repeatedly recalling a thing, strengthens the memory." —Aristotle

Summary Points

- We are poor judges of when we are learning well and when we're not. The level of performance immediately after learning (studying) is a poor indicator of future retention of knowledge.
- The "Forgetting Curve" trajectory after learning is initially very steep, with large amounts of forgetting occurring quickly and then a slower steady decline with time.
- **Retrieval Practice** is the act of recalling information to mind rather than re-reading it or re-hearing it. The act of retrieving a memory changes the memory, making it easier to retrieve again later and thus improving long-term retention.
- **Testing Effect:** When information is recalled from memory during testing, retention is better than if the material is simply re-studied.
- **Test Enhanced learning** is an approach that promotes retrieval practice via testing as a way to enhance retention of knowledge.
- Tests can be used for more than assessment, but also to promote learning. Learners should stop re-reading over and over the material attempting to be mastered and take a test. There is superior long-term retention relative to re-studying for an equivalent amount of time.
- Questions that require effortful recall and generation of information (short answer, oral answer) have potential benefits versus questions that require recognition, i.e., multiple-choice questions (MCQ).
- **Repeated testing** is better for improving long-term retention than taking a single test.
- **Spacing effect:** When testing (or studying) is distributed over time, information is more likely to be retained than if studying or testing is massed over a short period of time (cramming).
- Spacing and testing are evidence-based educational methods of increasing long-term retention without known boundary conditions, and are effective for many types of learners.
- Testing with feedback leads to greater benefits than taking practice tests without feedback.
- **Retrieval practice can be applied beyond written tests** to other aspects of learning. The key is that the information, procedure (e.g. how to perform a sciatic nerve block), or skill is retrieved from memory.

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Program Materials, *continued from page 71*

President's Panel: Hypoxia is Not Always Bad for You?

Oxygen and Humans: The Good, The Bad and The Ugly?

Michael Grocott, BSc, MBBS, MD, FRCA, FRCP, FFICM

Notes:

Program Materials, *continued from page 72*

Hypoxia is Not Always Bad for You?

Hypoxia and Damaged Mitochondria: Good News

Vamsi K. Mootha, MD

Notes:

Program Materials, *continued from page 74*

Hypoxia is Not Always Bad for You?

Mitochondrial Disorders: Towards a Therapy from Thin Air

Lorenzo Berra, MD

Notes:

2017 Abstract Award Winners

Margaret Wood Resident Research Award	**NR 50 (1707)** **Weak EEG α-Power During General Anesthesia as a Marker of Delirium in the PACU** **Matthias Kreuzer, PhD**[1]; September Hesse, PhD[1]; Darren F. Hight, BPhEd[2]; Jamie Sleigh, MBChD MD[2]; Paul S. Garcia, MD, PhD[1] *[1]Emory University/VAMC Atlanta, Decatur, GA, [2]Waikato Hospital, Hamilton, AK*	*Oral Presentation:* **SAB Oral Session II** Thursday, May 4, 2017▪ 11:30 am – 12:30 pm *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 4, 2017 ▪ 10:00 am – 11:30 am
Resident Travel Award	**NR 48 (1310)** **Sensitivity to Volatile Anesthetics Predicts Postoperative Selirium** **Bradley A. Fritz, MD**[1]; Hannah Maybrier, BS[1]; Michael S. Avidan, MBBCh[1]; *[1]Washington University School of Medicineat St. Louis, St. Louis, MO*	*Oral Presentation:* **SAB Oral Session II** Thursday, May 4, 2017 ▪ 11:30 am – 12:30 pm *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 4, 2017 ▪ 10:00 – 11:30 am
Junior Faculty Travel Award in Pediatric Anesthesia	**PED 61 (1287)** **Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis** **Caleb Ing, MD, MS**[1]; Ming Sun, MS[1]; Mark Olfson, MD, MPH[1]; Charles DiMaggio, PhD, MPH, PA-C[2]; Lena Sun, MD, MPH[1]; Melanie Wall, PhD[1]; Guohua Li, MD, DrPH[1] *[1]Columbia University College of Physicians and Surgeons, New York, NY*	*Oral Presentation:* **SAB Oral Session IV** Friday, May 5, 2017 ▪ 9:15 am – 10:15 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 5, 2017 ▪ 1:00 pm – 2:30 pm
Junior Faculty Travel Award in Perioperative Medicine	**PM 47 (1723)** **A Randomized Trial of Perioperative Gabapentin to Promote Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort** **Jennifer Hah, MD, MS**[1], Sean Mackey, MD[1], PhD; Bradley Efron, PhD[1]; Rebecca McCue, BS[1]; Stuart Goodman, MD, PhD[2]; Catherine Curtin, MD[2]; Ian Carroll, MD, MS[2] *[1]Stanford University, Stanford, CA, [2]Stanford University, Palo Alto, CA*	*Oral Presentation:* **SAB Oral Session III** Friday, May 5, 2017 ▪ 8:00 am - 9:00 am *Poster Discussion:* **Moderated Poster Discussion Session II** Friday, May 5, 2017 ▪ 1:00 pm - 2:30 pm

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2017 Abstract Award Winners, *continued from page 75*

Junior Faculty Research Award	**RES 40 (1386)** **Photo-Relaxation: Light Mediated Airway Smooth Muscle Relaxation** **Peter Yim, MD**[1]; Daniel Berkowitz, MD[2]; George Gallos, MD[1]; Charles W. Emala, MD[1] *[1]Columbia University, New York, NY, [2]Johns Hopkins University, Baltimore, MD*	*Oral Presentation:* **SAB Oral Session I** Thursday, May 4, 2017 • 9:00 am - 10:00 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 4, 2017 • 10:00 am - 11:30 am
Junior Faculty Research Award	**TRSL/BS 66 (1985)** **Implication of LDL Receptors in the Development of Pulmonary Hypertension** **Soban Umar, MD, PhD**; Mylene Vaillancourt, MSc; Christine Cunningham, BSc; Shayan Moazeni, BSc; Gregoire Ruffenach, PhD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD *University of California, Los Angeles, Los Angeles, CA*	*Oral Presentation:* **SAB Oral Session I** Thursday, May 4, 2017 • 9:00 am - 10:00 am *Poster Discussion:* **Moderated Poster Discussion Session I** Thursday, May 4, 2017 • 10:00 am - 11:30 am

Margaret Wood Resident Research Award Winner

NR 50 (1707)
Weak EEG α-Power During General Anesthesia as a Marker of Delirium in the PACU

Matthias Kreuzer, PhD[1], September Hesse, PhD[1]; Darren F. Hight, BPhEd[2]; Jamie Sleigh, MBChD MD[2]; Paul S. Garcia, MD, PhD[1]

[1]Emory University/VAMC Atlanta, Decatur, GA, [2]Waikato Hospital, Hamilton, AK

Introduction: The application of frontal EEG recording systems presents a convenient way to monitor the brain during general anesthesia. Recent case reports presented evidence for intraprocedural EEG signatures being correlated with delirium in the PACU (PACU-D) as determined by CAM-ICU.[1] Patients that emerge from anesthesia without transitioning through Î±-spindle dominant EEG are at higher risk PACU-D.[2] Further, the EEG Î±-band seems of special interest, because of an existing correlation between Î±-power and intraoperative noxious stimulation[3] as well as absolute Î±- power being an indicator for 'brain age'.[4-5] We investigated the association of EEG spectral properties during episodes of 'no surgical stimulation' (NOSTIM) and 'surgical stimulation' (STIM) and the adverse outcome of hypoactive PACU-D, a transient phenomenon that correlates with negative long-term effects.[6]

Methods: We examined frontal EEG recordings from 232 patients that received sevoflurane for maintenance of general anesthesia (after a propofol induction). For each patient, we calculated median power spectral density (PSD) and median interhemsipheric spectral coherence for NOSTIM, i.e. the period 30s after intubation until 30s before start of surgery and for STIM, the episode from 30s after start surgery until 30s before start of emergence, i.e., gas turn off. We also evaluated the correlation of PSD and coherence in the Î±-band and the patients, age. We defined PACU-D as positive CAM-ICU assessment as described in (6).

Results: 33 patients developed PACU-D. Their demographics (age, BMI, ASA) were not significantly different, but PACU-D patients underwent longer surgeries of 140 (47-346) min (median and range) versus 96 (14-398) min ($p<0.05$, Mann-Whitney U). Patients with PACU-D had significantly lower absolute and relative power in Î±-band frequencies during both NOSTIM and STIM conditions (Chronux two group test for spectra, $p<0.05$). A decline in absolute Î±-power and Î±-coherence was observed with increasing age for all patients regardless of PACU-D outcome. However the association of age with decreased absolute Î±-power was stronger for those without PACU-D. The younger patients with PACU-D exhibited lower absolute Î±-power, than might be predicted by their numerical age. The spectral EEG features in younger patients with PACU-D resembled that of older brains. The coherence analysis did not reveal differences between the patients with and without PACU-D during STIM or NOSTIM. The age to Î±-coherence relationship was not statistically different between the PACU-D and no PACU-D patients as well. As coherence indicates inter-hemispheric synchrony in the cortical network, these findings suggest that there is no difference in the effect of sevoflurane on inter-hemispheric communication between the groups.

Conclusion: Our findings emphasize the use of intraoperative Î±- power as a possible marker of 'anesthesia quality'. Commercial monitoring systems currently focus on a reliable separation of different anesthetic levels during general anesthesia but not on association of the monitoring with adverse outcomes. Since frontal Î±-oscillations contain information of interactions between thalamus and cortex (7) our results indicate that patients who develop PACU-D, may demonstrate less robust thalamocortical synchrony reflected as Î±-oscillations. Hence an inclusion of distinct parameters evaluating Î±-oscillations may represent a valuable contribution to monitoring for preventing/ predicting PACU-D.

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Margaret Wood Resident Research Award Winner, *continued from page77*

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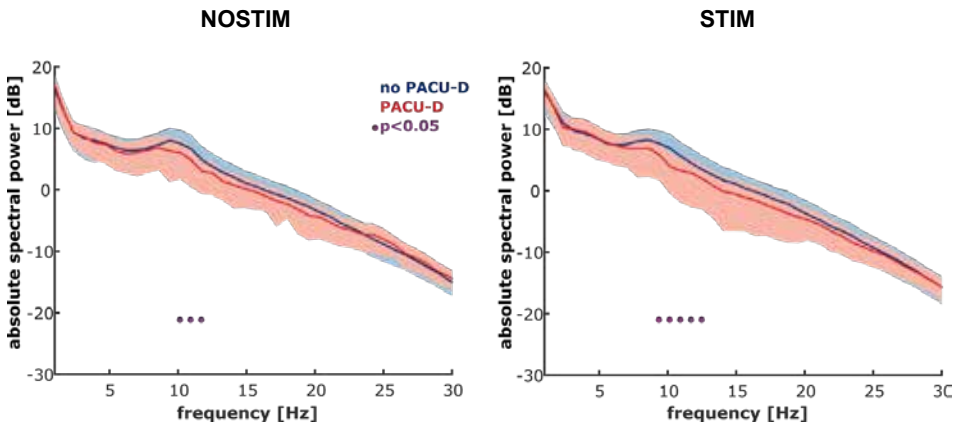

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Resident Travel Award Winner

NR 48 (1310)
Sensitivity to Volatile Anesthetics Predicts Postoperative Delirium

Bradley A. Fritz, MD[1], Hannah Maybrier, BS[1]; Michael S. Avidan, MBBCh[1]

[1]*Washington University School of Medicine, St. Louis, MO*

Introduction: Postoperative delirium is a common surgical complication that is associated with morbidity and mortality [1-3]. Our group recently described an association between increased duration of electroencephalogram (EEG) suppression during surgery and postoperative delirium [4]. Some patients with diagnosed or undiagnosed brain pathology may have increased sensitivity to volatile anesthetic agents, which might manifest during general anesthesia as EEG suppression at relatively low anesthetic concentration. We hypothesized that patients who experience EEG suppression at lower volatile anesthetic concentrations would have increased incidence of postoperative delirium.

Methods: This is a substudy of our previous study examining EEG suppression and postoperative delirium, for which IRB approval was obtained [4]. The population included 618 elective surgery patients with planned intensive care unit admission, who received intraoperative EEG monitoring and had delirium assessments documented in the medical record. Sensitivity to volatile anesthetics was assessed using a mixed effects model predicting the likelihood of EEG suppression at each time point based on the current end-tidal anesthetic concentration. Patients with a random intercept below the population median (i.e. EEG suppression at lower anesthetic concentrations) were classified as having heightened sensitivity to volatile anesthetics. Delirium was defined as a positive Confusion Assessment Method for the ICU (CAM-ICU) assessment at any point in the first five postoperative days. Logistic regression was used to determine whether patients with heightened sensitivity to volatile anesthetics had a greater incidence of delirium.

Results: Postoperative delirium was observed in 162 of the 618 patients (26%). Patients who experienced EEG suppression at lower volatile anesthetic concentrations had a higher incidence of postoperative delirium (107/301 [36%]) than other patients (55/317 [17%]) (unadjusted odds ratio 2.63; 95% CI, 2.22 to 3.11, p<0.001). This association remained significant after adjusting for patient characteristics, surgical variables, and duration of EEG suppression (adjusted odds ratio 2.08; 95% CI 1.31 to 3.29, p=0.001).

Conclusion: These data support the hypothesis that patients who are more sensitive to volatile anesthetic agents have an increased incidence of postoperative delirium. Underlying pathology may contribute directly to delirium, or it may act through EEG suppression to cause delirium. If there is a causal link between EEG suppression and postoperative delirium, then interventional studies may address whether avoidance of EEG suppression can reduce the incidence of postoperative delirium.

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Junior Faculty Travel Award Winner in Pediatric Anesthesia

PED 61 (1287)
Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis

Caleb Ing, MD, MS[1], Ming Sun, MS[1]; Mark Olfson, MD, MPH[1]; Charles DiMaggio, PhD, MPH, PA-C[1]; Lena Sun, MD, MPH[1]; Melanie Wall, PhD[1]; Guohua Li, MD, DrPH[1]

[1]*Columbia University College of Physicians and Surgeons, New York, NY*

Introduction: Animals exposed to anesthetics during specific age periods of brain development experience neurotoxicity, with neurodevelopmental changes subsequently observed during adulthood.[1,2] The corresponding vulnerable age in children however is unclear. Despite this, the Food and Drug Administration recently released a new warning regarding the use of anesthetics in children before age 3 years. Since delaying necessary procedures may have unintended harmful consequences, whether delaying a procedure has any long-term clinical benefit is an important question to answer.

Methods: An observational cohort study was performed using a longitudinal dataset constructed by linking individual-level Medicaid claims from Texas and New York from 1999 to 2010. This dataset was evaluated to determine whether the timing of exposure to anesthesia under age 5 years for a single common procedure (pyloromyotomy, inguinal hernia, circumcision outside the perinatal period, or tonsillectomy and/or adenoidectomy) is associated with increased subsequent risk of diagnoses for any mental disorder, or specifically developmental delay (DD) such as reading and language disorders, and attention deficit hyperactivity disorder (ADHD). Exposure to anesthesia and surgery was evaluated in 11 separate age at exposure categories: ‰¤28 days old, >28 days and ‰¤6 months, >6 months and ‰¤1 year, and 6 month age intervals between >1 year old and ‰¤5 years old. For each exposed child, five children matched on propensity score calculated using sociodemographic and clinical covariates were selected for comparison. Cox proportional hazards models were used to measure the hazard ratio of a mental disorder diagnosis associated with exposure to surgery and anesthesia. Procedure-specific models were also assessed to evaluate the association between the age at exposure to each specific procedure and subsequent mental disorder diagnoses.

Results: A total of 38,493 children with a single exposure and 192,465 propensity score matched children unexposed before age 5 were included in the analysis. Increased risk of mental disorder diagnosis was observed at all ages at exposure with an overall hazard ratio of 1.26 (95% confidence interval [CI], 1.22–1.30), which did not vary significantly with the timing of exposure. (Figure 1, Panel A) When evaluating children undergoing individual procedures, some minor variation in the risk of developing a mental disorder based on age at exposure was seen. (Figure 1, Panels B-E) Analysis of DD and ADHD showed similar results as those seen with any mental disorder diagnosis, with elevated hazard ratios distributed evenly across all ages, and overall hazard ratios of 1.26 (95% CI, 1.20–1.32) for DD and 1.31 (95% CI, 1.25–1.37) for ADHD. (Figure 2).

Conclusion: Children who undergo minor surgery requiring anesthesia under age 5 have a small but statistically significant increased risk of mental disorder diagnoses, and DD and ADHD diagnoses, but the timing of the surgical procedure does not alter the elevated risks. Based on these findings, there is little support for the concept of delaying a minor procedure to reduce neurotoxic risks of anesthesia in children. In evaluating the influence of age at exposure, the types of procedures included may need to be considered, as some procedures are associated with specific comorbid

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Junior Faculty Travel Award Winner in Pediatrics Anesthesia, *continued from page 80*

conditions and are only performed at certain ages.

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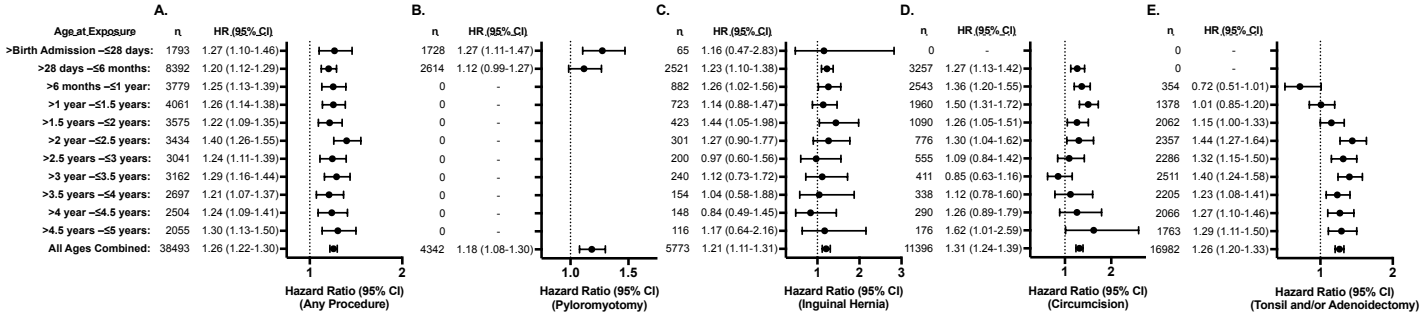

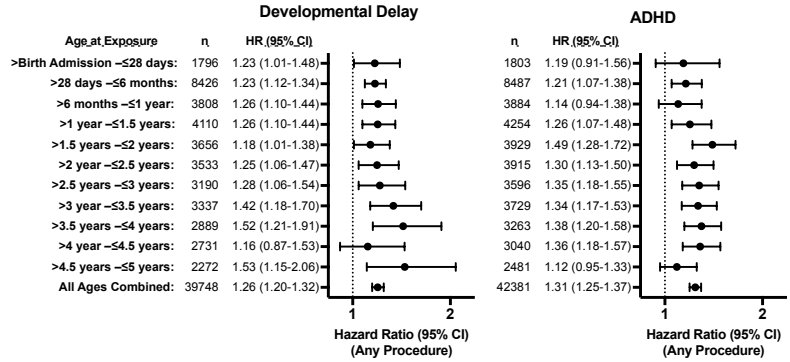

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Junior Faculty Travel Award Winner in Perioperative Medicine

PM 47 (1723)
A Randomized Trial of Perioperative Gabapentin to Promote Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort

Jennifer Hah, MD, MS[1], Sean Mackey, MD[1], PhD; Bradley Efron, PhD[1]; Rebecca McCue, BS[1]; Stuart Goodman, MD, PhD[1]; Catherine Curtin, MD[1]; Ian Carroll, MD, MS[1]

[1]*Stanford University, Stanford, CA*

Introduction: More than 51 million Americans undergo surgery every year, after which up to 13% of patients initiate chronic opioid use. Medicine is facing the considerable challenge of adequately managing pain while limiting opioid consumption. Gabapentin may reduce opioid use independent of its effect on decreasing pain,[1,2] but research on gabapentin's effect on postoperative pain and opioid use has been methodologically limited and drawn conflicting conclusions. We conducted a randomized, double-blind, placebo-controlled trial of perioperative gabapentin in a mixed surgical cohort followed up to 2 years postoperatively.

Methods: 411 patients scheduled for an eligible surgery (thoracotomy, video-assisted thoracoscopic surgery, total hip replacement, total knee replacement, mastectomy, breast lumpectomy, hand surgery, carpal tunnel surgery, knee arthroscopy, shoulder arthroplasty, and shoulder arthroscopy) were randomly assigned to receive 1200 mg gabapentin preoperatively and 600mg gabapentin three times a day postoperatively, or active placebo (0.5mg lorazepam) preoperatively followed by inactive placebo postoperatively for 72 hours. Prior to surgery, participants completed assessments including the Brief Pain Inventory (BPI), self-reported likelihood of developing chronic pain after surgery, self-perceived sensitivity to pain, and self-perceived likelihood of addiction to pain medication after surgery. After discharge, a modified BPI was administered daily over the phone for 3 months, at which point the frequency reduced to weekly until 6 months, and then to monthly up to 2 years after surgery. Primary outcome was time to pain resolution (five consecutive reports of zero out of ten average pain at the surgical site). Secondary outcome was time to opioid cessation (five consecutive reports of zero opioid use even for participants taking opioids prior to surgery). These outcomes, were analyzed in the intention-to-treat population with the hazard ratio and two-sided 95% confidence intervals based on a Cox regression model stratified by surgery type as pre-specified in our analytic plan.

Results: 2075 patients were screened for eligibility between May 25, 2010 and July 25, 2014. 422 underwent randomization, with 215 assigned to receive perioperative gabapentin and 207 assigned to receive active placebo (Figure 1). Baseline sociodemographic characteristics were balanced between the two study groups (Table 1). This longitudinal study represents 19,511 distinct assessments of postoperative pain. Perioperative gabapentin did not affect time to pain cessation after surgery. Nevertheless, participants receiving gabapentin had a 24% increase in the rate of opioid cessation after surgery (HR 1.24, 95% CI 1.00-1.54, p-value=0.05) (Table 2). No differences were noted in the number of adverse or serious adverse events (Table 3). Patients receiving gabapentin reported more impaired coordination and rash, and reported less constipation. No differences were noted in pre-planned subgroup analyses (Table 4).

Conclusion: Despite its lack of impact on pain resolution, perioperative gabapentin speeded cessation of opioids prescribed for postoperative pain management. This resonates with our earlier work suggesting that the determinants of the rate of opioid cessation are largely independent of the duration of pain and the determinants of time to pain resolution. (3,4) Expanded use of this medication may lower the risks of opioid misuse, abuse, addiction, diversion, and overdose after surgery.

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Junior Faculty Travel Award Winner in Perioperative Medicine, *continued from page 82*

2. Importance of gabapentin dose in treatment of opioid withdrawal.2011;31:593-6.
3. A pilot cohort study of the determinants of longitudinal opioid use after surgery. 2012;115:694-702.
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Table 1. **Baseline Preoperative Characteristics of Patients According to Treatment Group***

	Active Placebo	Gabapentin
Patients (no.)	202	208
Age-yr.	56.4 (11.8)	57.0(11.7)
Male Gender-no. (%)	73 (39)	81 (41)
Marital Status- no.(%)		
Never Married	16 (9)	17 (9)
Married	133 (72)	141 (73)
Living with someone	8 (4)	6 (3)
Divorced or separated	21 (11)	24 (12)
Widowed	7 (4)	6 (3)
Disability Claim Pending- no.(%)	25 (14)	21 (11)
Family History of Chronic Pain- no.(%)	61(34)	70(37)
Employment Status-no.(%)		
Full-time	83 (46)	80 (42)
Part-time	14 (8)	21 (11)
Unemployed, not interested in returning to work	8 (4)	11 (6)
Unemployed, looking for work	9 (5)	10 (5)
Unemployed, disabled	24 (13)	13 (7)
Retired, due to pain	8 (4)	11 (6)
Retired, not due to pain	36 (20)	44 (23)
Surgery- no. (%)		
Thoracotomy	6 (3)	7 (4)
Total Knee Replacement	66 (35)	79 (40)
Total Hip Replacement	48 (26)	40 (20)
Mastectomy	23 (12)	18 (9)
Lumpectomy	12 (6)	16 (8)
VATS	14 (7)	14 (7)
Hand Surgery	9 (5)	13 (7)
Carpal Tunnel Surgery	2 (1)	2 (1)
Knee Arthroscopy	3 (2)	4(2)
Shoulder Arthroplasty	2 (1)	2 (1)
Shoulder Arthroscopy	3 (2)	3(2)
Baseline pain at surgical site (0-10)	5.0(3.0)	5.4(3.2)
Baseline pain other than surgical site (0-10)	2.2(2.2)	2.5(2.5)
Median Time to Pain Resolution (days) (IQ range)	73(36-231)	84(36-203)
Median Time to Opioid Cessation (days) (IQ range)	32(9-55)	25(8-53)
Self-Perceived Likelihood of Developing Chronic Pain After Surgery	2.0(0.7)	2.0(0.7)
Self-Perceived Sensitivity to Pain	2.3(0.6)	2.2(0.6)
Ever use of Prescription Opioids- no.(%)	135(82)	148(86)
Self-Perceived Likelihood of Addiction to Pain Medication After Surgery	1.5(0.6)	1.6(0.6)
Opioid Risk Tool Score	2.4(3.0)	2.3(3.3)
Marlow-Crowne Social Desirability Scale Score	20.3(5.7)	20.4(5.8)
Barratt Impulsivity Scale Score	68.3(7.3)	69.0(6.3)
PTSD Checklist-Civilian Version (PCL-C) Score	23.8(7.6)	25.6(9.8)
State Anxiety Inventory Score	34.5(11.1)	35.1(11.1)
Trait Anxiety Inventory Score	32.7(10.7)	33.0(10.2)
Beck Depression Inventory-II Score	9.2(6.3)	10.3(7.5)
Euroqol VAS	70.2(20.3)	72.5(17.8)

*All values presented as mean(SD) unless otherwise noted. There were no significant differences between the treatment groups (P less than or equal to 0.002 was considered to indicate significance in these between-group comparisons)

Figure 1. Enrollment, Randomization, and Follow-Up

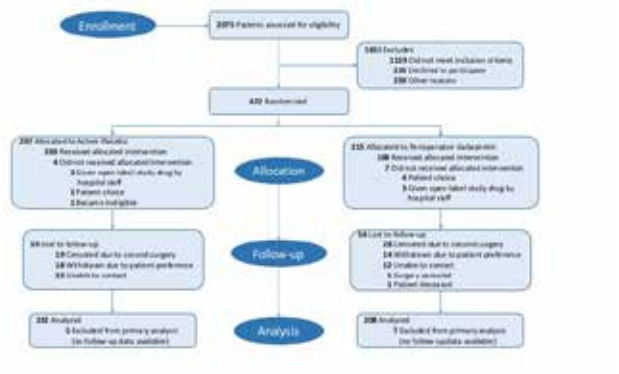

Table 2. **Primary and Secondary Outcomes**

Outcome	Active Placebo	Gabapentin	Hazard Ratio (95% CI)	P value
	Number of Events	Number of Events		
Primary Outcome: Time to Pain Cessation*	139	142	1.04(0.82-1.33)	0.70
Secondary Outcomes				
Time to Opioid Cessation*	176	179	1.24(1.00-1.54)	0.05
Time to Pain Cessation Per-Protocol Analysis(n=241)	90	82	1.08(0.79-1.48)	0.60
Time to Opioid Cessation Per-Protocol Analysis (n=241)	114	105	1.41(1.07-1.88)	0.01
			Odds Ratio (95% CI)	P value
Patients with Continued Pain at 6 months-no.(%)	37(18)	42(20)	1.07(0.64-1.78)	0.30
Patients with Continued Pain at 12 months-no.(%)	18(9)	21(10)	1.10(0.56-2.16)	0.80
Patients Continuing on Opioids at 6 months-no.(%)	4(2)	5(2.4)	1.22(0.32-4.66)	0.80
Patients Continuing on Opioids at 12 months-no.(%)	3(1.5)	4(1.9)	1.28(0.28-5.87)	0.70

*Intention-to-treat analysis

Table 3. **Frequency of Adverse Events**

Type of Event	Active Placebo (n=202)	Gabapentin (n=208)	P value*
	Number of patients with Events		
Serious adverse event	2	2	1.00
≥1 adverse event	191	195	0.70
Adverse event leading to discontinuation of trial drug	13	17	0.50
Leg swelling	56	49	0.40
Generalized weakness	122	119	0.60
Headache	68	81	0.20
Abdominal pain	44	30	0.06
Diarrhea	8	11	0.50
Dry mouth	184	192	0.40
Constipation	147	128	0.02
Nausea	125	117	0.30
Vomiting	55	49	0.40
Impaired Coordination	66	89	0.03
Memory	72	75	0.90
Sore Throat	113	104	0.30
Rash	14	27	0.04
Visual disturbance	45	63	0.06
Eye Pain	19	26	0.30
Ear Pain	3	6	0.50

*Chi-square test

Patients could have more than 1 event

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Junior Faculty Research Award Winner

RES 40 (1386)
Photo-relaxation: Light Mediated Airway Smooth Muscle Relaxation

Peter Yim, MD[1], Daniel Berkowitz, MD[2]; George Gallos, MD[1]; Charles W. Emala, MD[1]

[1]Columbia University, New York, NY, [2]Johns Hopkins University, Baltimore, MD

Introduction: Novel therapies directed towards the relaxation of airway smooth muscle (ASM) could improve the clinical management of asthma. Recently, light was shown to relax blood vessels via activation of opsin 4. Characteristics of this response included a sensitivity to blue wavelengths of light (~455mm) and greater relaxation when the tissues were pretreated with an inhibitor of G protein receptor kinase 2 (GRK2). Classically, opsins are coupled to G protein transducin family (GNAT) members and undergo rapid light-induced desensitization via GRKs. We hypothesized that airway smooth muscle (ASM) demonstrates the same physiologic response to light and shares mechanistic similarities.

Methods: Mouse and guinea pig studies were approved by IACUC. Human ASM strips were isolated from transplant discards (IRB exempt). ASM was suspended in organ baths at 37oC. Airway smooth muscle was contracted with an EC50 concentration of acetylcholine (Ach). In some experiments tissues were pretreated for 1hr in the dark and/or 15 min with a GRK2 inhibitor (Methyl 5-[(E)-2-(5-nitrofuran-2-yl)ethenyl] furan-2-carboxylate). When increased contractile force achieved a plateau (~15 min) the ASM was treated with white light or distinct wavelengths (370-640nm). The remaining contractile force was measured at a point of maximal relaxation (~10min) and expressed as the percent of the initial acetylcholine-induced contraction. RNA was isolated from freshly dissected and primary cultured mouse and human airway smooth muscle for RT-PCR detection of opsin and GNAT mRNA.

Results: ASM from all three species exhibited rapid relaxation of an acetylcholine-induced contraction in response to white light in the presence of a GRK2 inhibitor (e.g. guinea pig ASM relaxed to below baseline (108 +/- 8.9% of Ach-induced contraction) (n=5, p< 0.001 compared to no light treatment). No relaxation occurred with GRK2 inhibitor alone or its vehicle. Ach-contracted mouse ASM relaxed maximally in response to blue light when challenged with distinct wavelengths between 370-640nm. Pretreatment of mouse ASM for 1hr in the dark resulted in a blue-light induced relaxation of 21.3 +/- 1.0% when GRK2 inhibitor was omitted but 66.0 +/- 6.0% when GRK2 inhibitor was included in the buffer (n=3, p< 0.001 compared to no light treatment). mRNA encoding opsin 3 and GNAT2 was detected in both fresh and cultured ASM from mouse and human.

Conclusion: Airway smooth muscle from multiple species including human demonstrated light mediated photo-relaxation that was augmented by GRK2 inhibition. ASM expressed opsin and GNAT mRNA consistent with classical light mediated signaling pathways that may be targeted for relaxation.

References:

None

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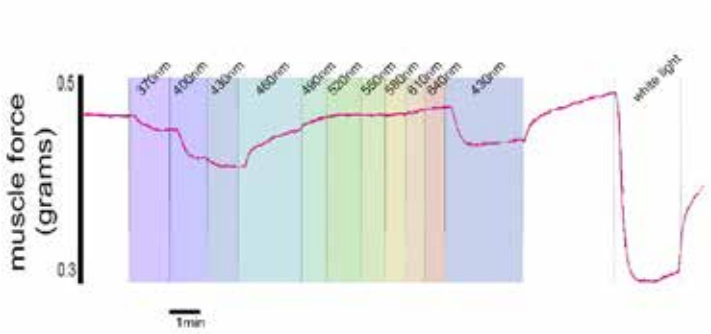
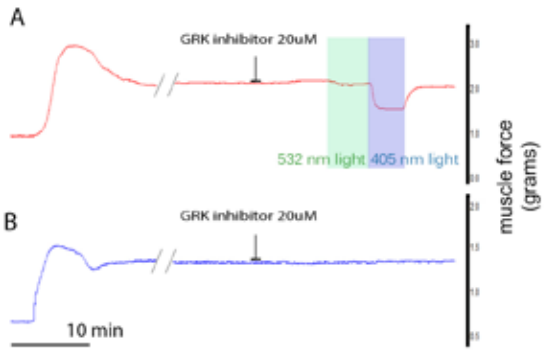
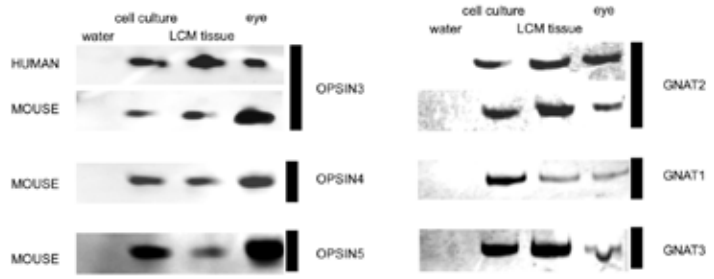
Junior Faculty Research Award Winner, *continued from page 84*



Representative tracing of mouse tracheal rings in an organ bath. Tracheal rings were precontracted with an EC_{50} concentration of acetylcholine. Tracheal rings were pretreated with 300uM of GRK2 inhibitor and exposed to light at discreet wavelengths 370-640 at 30nm intervals. A re-exposure to 430nm light was performed to demonstrate the continued sensitivity. A white light exposure at a much higher intensity was performed to demonstrate maximal light induced relaxation.



Representative tracing of human tracheal strips in an organ bath. Tracheal rings were precontrated with an EC50 dose of acetylcholine. All rings were treated with 1 hour of darkness (room with minimized ambient light) and 10min 20uM Methyl 5-[(E)-2-(5-nitrofuran-2-yl)ethenyl] furan-2-carboxylate (GRK inhibitor). Blue bars indicate treatment of 5mW 405 nm light and the green bar indicate 5mW 532 nm light treatment. A: Demonstration of small relaxation with green light and greater relaxation with blue light B: Demonstration of no light treatment shows no change in tension



Representative Gel images of RT-pcr products from primers targeting different Opsin and Transducin family proteins. Human airway smooth muscle cell culture, discrete areas of histological confirmed airway smooth muscle tissue obtain by laser capture microdissection (LCM) and positive control eye tissue demonstrates positive mRNA expression for OPSIN3 and GNAT2. In mouse airway smooth muscle (culture and tissue) demonstrated homolgous expression of OPSIN3 and GNAT2 in addition to OPSIN 4, OPSIN5, GNAT1 and GNAT3. Human airway smooth muscle did not demonstrate positive results for OPSIN4, OPSIN5,GNAT1 or GNAT3 (data not shown). Water demonstrated the lack of contamination and served as a negative control

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Junior Faculty Research Award Winner

TRSL/BS 66 (1985)
Implication of LDL Receptors in the Development of Pulmonary Hypertension

Soban Umar, MD, PhD, Mylene Vaillancourt, MSc; Christine Cunningham, BSc; Shayan Moazeni, BSc; Gregoire Ruffenach, PhD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD

University of California, Los Angeles, Los Angeles, CA

Introduction: Pulmonary hypertension (PH) is a pulmonary vascular disease with multifactorial etiology including pulmonary endothelial dysfunction, smooth muscle proliferation, extracellular matrix remodeling and inflammation. Long standing PH leads to right ventricular (RV) hypertrophy and failure. Recently, we and others[1,2] have reported a critical role for oxidized lipids in PH pathogenesis. An increase in the pro-inflammatory influence of low density lipoprotein (LDL) on high density lipids (HDL) dysfunction and oxidative stress was reported in PH patients. However, LDL receptor (LDL-R), which binds and internalizes LDL into the cell, has never been investigated for its role in PH. Here we examined the expression of LDL-R in the lung tissues of lung transplant patients with and without PH and aim to determine the potential role of LDL-R in development of PH in LDL-R knockout (LDL-R KO) mice.

Methods: Human explanted lung samples from patients with (PH group, n=7) and without PH (non-PH group, n=7) undergoing lung transplants were used. LDL-R and fatty acid transporter CD36 were assessed in lungs with RT-qPCR. For animal studies, male LDL-R KO mice were fed either chow (n=16) or Western diet (WD, n=27) for 12 weeks and monitored for the development of PH and RV dysfunction. Mice on WD were further divided into three groups, WD (n=9) and those treated with Apolipoprotein A1 mimetic (HDL mimetic) peptide 4F (n=11) or scramble peptide (n=7) in drinking water for 12 weeks. A group of chow fed mice received 4F (n=8). Echocardiography was performed to monitor cardiopulmonary hemodynamics. Direct RV and LV catheterization was performed terminally and RV hypertrophy index was calculated as weight ratio of RV/(LV+IVS). Aorta, RV, LV and lung tissue were collected. Trichrome and Oil Red O stains were performed. Data are expressed as mean+/-SEM.

Results: There was a significant decrease in human lung LDL-R and CD36 mRNA expression of PH group compared to non-PH group ($p<0.05$). Moreover, RV systolic pressure (RVSP) inversely correlated with lung LDL-R ($p<0.05$) and CD36 ($p<0.05$). We also found an increase in pulmonary arterial lipid deposits in lungs of PH patients, suggesting a potential link of decreased LDL-R with the increased lipid accumulation and its subsequent oxidation. As PH patients have lower lung LDL-R expression, we tested the hypothesis that WD fed LDL-R KO mice may develop PH and tested the potential of 4F peptide to prevent PH. We found that WD fed LDL-R KO mice developed PH, RV hypertrophy and RV dysfunction that were prevented by 4F (RVSP: 41.05 ±3.49 mmHg in WD vs. 28.49 ±1.12 mmHg in WD+4F, $p<0.05$; RV/(LV+IVS): 0.46 ±0.06 in WD vs. 0.28±0.01 in WD+4F; RVEF: 43.63±1.36% in WD vs. 65.5 ±1.05% in WD+4F, $p<0.05$). PH was associated with pulmonary vascular remodeling, fibrosis and lipid deposition in lungs that were prevented by 4F. WD fed mice also exhibited atherosclerosis in aorta and developed LV dysfunction (LVEF=46.18 ±2.09%) that was prevented by 4F (LVEF=63.79 ±1.72%, $p<0.05$). Interestingly, WD was not associated with either LV hypertrophy or LV pressure overload. WD+scramble group was similar to WD alone whereas Chow+4F was similar to Chow.

Conclusion: Human PH is associated with decreased LDL-R in lungs. WD fed LDL-R KO mice develop PH, RV and LV dysfunction, further implicating role of LDL-R and oxidized lipids in PH. This new model of PH can help us understand the involvement of oxidized lipids in PH. 4F peptide is a potential novel therapeutic agent for PH.

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1. Apolipoprotein A-I mimetic peptide 4F rescues pulmonary hypertension by inducing microRNA-193-3p. Circulation. 2014 Aug 26;130(9):776-85.
2. Proinflammatory high-density lipoprotein results from oxidized lipid mediators in the pathogenesis of both idiopathic and associated types of pulmonary arterial hypertension. Pulm Circ. 2015 Dec;5(4):640-8.

Oral Presentations on Thursday, May 4

Scientific Advisory Board (SAB) Oral Session I: Thursday, May 4, 2017 • 9:00 am – 10:00 am

Moderators: Lucy Chen, MD, and Edward Sherwood, MD, PhD

Moderated Poster Discussion Session I: Thursday, May 4, 2017 • 10:00 am - 11:30 am

Junior Faculty Research Award	**RES 40 (1386)** **Photo-relaxation: Light Mediated Airway Smooth Muscle Relaxation** **Peter Yim, MD**[1]; Daniel Berkowitz, MD[2]; George Gallos, MD[1]; Charles W. Emala, MD[1]; *[1]Columbia University, New York, NY, [2]Johns Hopkins University, Baltimore, MD* *See abstract on page 84*
	TRSL/BS 70 (1338) **Bitter Taste Receptors in Airway Smooth Muscle Cells of a Cystic Fibrosis Mouse Model** **Nicholas M. Dalesio, MD**[1]; Seakwoo Lee, PhD[1]; Steven S. An, PhD[2]; Charles W. Emala, MD[3]; Pamela L. Zeitlin, MD[4]; Daniel Berkowitz, MD[1] *[1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins School of Public Health, Baltimore, MD, [3]Columbia University, New York, NY, [4]National Jewish Health, Denver, CO*
Junior Faculty Research Award	**TRSL/BS 66 (1985)** **Implication of LDL Receptors in the Development of Pulmonary Hypertension** **Soban Umar, MD, PhD**; Mylene Vaillancourt, MSc; Christine Cunningham, BSc; Shayan Moazeni, BSc; Gregoire Ruffenach, PhD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD *University of California Los Angeles, Los Angeles, CA* *See abstract on page 86*
	TRSL/BS 68 (1783) **Spinal Cord Stimulation Reduces Ventricular Arrhythmias During Acute Ischemia Through Attenuation of Regional Myocardial Excitability in a Porcine Model** **Kimberly Howard-Quijano, MD, MS**[1]; Tatsuo Takamiya, MD[1]; Erica Dale, PhD[1]; Jasmine Kipke, BS[1]; Yukiko Kubo, MD[1]; Tristan Grogan, MS[1]; Aman Mahajan, MD, PhD[1] *[1]University of California at Los Angeles, Los Angeles, CA*

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Oral Presentations on Thursday, May 4, *continued from page 87*

SAB Oral Session II: Thursday, May 4, 2017 • 11:30 am - 12:30 pm

Moderators: Lucy Chen, MD, and Edward Sherwood, MD, PhD

Moderated Poster Discussion Session I: Thursday, May 4, 2017 • 10:00 am - 11:30 am

Resident Travel Award	**NR 48 (1310)** **Sensitivity to Volatile Anesthetics Predicts Postoperative Delirium** **Bradley A. Fritz, MD**[1]; Hannah Maybrier, BS[1]; Michael S. Avidan, MBBCh[1] *[1]Washington University School of Medicine, St. Louis, MO* *See abstract on page 79*
Margaret Wood Resident Research Award	**NR 50 (1707)** **Weak EEG α–Power During General Anesthesia as a Marker of Delirium in the PACU** **Matthias Kreuzer, PhD**[1]; September Hesse, PhD[1]; Darren Hight, BPhEd[2]; Jamie Sleigh, MBChD MD[2]; Paul S. Garcia, MD, PhD[1] *[1]Emory University/VAMC Atlanta, Decatur, GA, [2]Waikato Hospital, Hamilton, AK* *See abstract on page 77*
	NR 46 (1735) **Astrocyte-Specific Knockout of a Mitochondrial Protein in Mice Increases Neural Inertia** **Renjini Ramadasan Nair, PhD**[1]; Jessica Hui, BS[1]; Philip Morgan, MD[2]; Margaret Sedensky, MD[2] *[1]Seattle Children's Research Institute, Seattle, WA, [2]University of Washington, Seattle, WA*
	NR 44 (1803) **GABA Neurons in the Rostromedial Tegmental Nucleus Modulate Arousal and Anesthetic Sensitivity in Mice** Ksenia Y. Vlasov, BA[2]; JunZhu Pei, BS[2]; Norman E. Taylor, MD, PhD[1]; Christa J. Van Dort, PhD[1]; Jennifer A. Guidera, BA[1]; Emery N. Brown, MD, PhD[1] ; **Ken Solt, MD**[1] *[1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts Institute of Technology, Cambridge, MA*

Oral Session I

TRSL/BS 70 (1338)
Bitter Taste Receptors in Airway Smooth Muscle Cells of a Cystic Fibrosis Mouse Model

Nicholas M. Dalesio, MD[1], Seakwoo Lee, PhD[1]; Steven S. An, PhD[2]; Charles W. Emala, MD[3]; Pamela L. Zeitlin, MD[4]; Daniel Berkowitz, MD[1]

[1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins School of Public Health, Baltimore, MD, [3]Columbia University, New York, NY, [4]National Jewish Health, Denver, CO

Introduction: Cystic Fibrosis (CF) is caused by the loss-of-function of cystic fibrosis transmembrane conductance regulator (CFTR) and, in the lungs, is characterized by the respiratory sequelae leading to airflow obstruction. Approximately 50% of patients with CF have hyper-reactive airway disease with unclear contributing mechanisms. CFTR protein expression and function has recently been detected in airway smooth muscle (ASM) cells. ASM cells also express certain subtypes of the bitter taste receptor (TAS2R), which mediate relaxation of ASM upon activation via release of intra-cellular calcium. We hypothesized that this TAS2R signaling pathway is disrupted in a murine model of CF.

Lung	Mean Ct ± StDev				
	T2R10	T2R14	T2R31	T2R38	GAPDH
CFTR +/+	29.15 ± 1.04	29.47 ± 1.31	29.98 ± 1.21	32.65 ± 1.51	21.58 ± 0.25
CFTR -/-	29.46 ± 0.70	29.70 ± 0.85	30.30 ± 0.68	33.58 ± 0.97	21.66 ± 1.38
P Value	0.69	0.78	0.64	0.34	0.91

Trachea	Mean Ct ± StDev				
	T2R10	T2R14	T2R31	T2R38	GAPDH
CFTR +/+	32.64 ± 1.48	30.31 ± 1.38	32.26 ± 1.36	31.24 ± 1.57	22.07 ± 1.03
CFTR -/-	32.85 ± 0.40	30.69 ± 0.53	32.68 ± 0.42	32.13 ± 0.94	20.73 ± 1.20
P Value	0.79	0.63	0.58	0.08	0.14

Figure 1: mRNA expression via quantitative PCR (qPCR) of bitter taste receptors (T2R's) from wild-type CFTR +/+ and CFTR -/- mouse lung and trachea. T2R 10 was not detectable in mouse lung. StDev = standard deviation

Methods: To evaluate TAS2R in CF, we examined changes in receptor expression using quantitative PCR (qPCR) and function using magnetic torsion cytometry. Expression: qPCR was conducted to determine the expression of TAS2R10, TAS2R14, TAS2R31 and TAS2R38 in the tracheal and lung tissues of mice homozygous for the S489X (CFTR -/-) mutation and WT (CFTR +/+). Function: ASM cells were isolated and cultured from male and female mice tracheas of CF and WT controls. Magnetic twisting cytometry was used to measure dynamic changes in stiffness of isolated mouse ASM cells as previously described. For these studies, ASM cells were first contracted with 5-HT and then relaxed with either isoproterenol or chloroquine.

Results: Tracheal and lung tissue were collected from 4 WT compared to 4 homozygous CFTR -/- mice. Expression of the T2R10, T2R14, T2R31, and T2R38 were not statistically different in the lung and trachea of WT versus CFTR -/- mice. (Figure 1) Function: Results in (Mean ± SEM; 95% confidence interval; P value). Interestingly, CF ASM pre-constricted with 5-HT demonstrated enhanced relaxation to increasing doses of isoproterenol compared to WT (0.62 ± 0.02 versus 0.72 ± 0.02; 95%CI 0.05 to 0.15; P <0.002). However, CF ASM cells demonstrated impaired relaxation to increasing doses of the bitter taste receptor agonist, chloroquine compared to WT ASM (0.88 ± 0.02 versus 1.10 ± 0.04; 95%CI -0.3 to -0.13; P < 0.001) (Figure 2).

Conclusion: While expression of TAS2R was not different between CF and controls in mouse tracheobronchial ASM tissue, TAS2R- mediated relaxation was attenuated in CF. We conclude that TAS2R-mediated ASM-relaxation is impaired in CF and propose further work to understand the mechanism and identify potential therapeutic targets.

References:

Cystic fibrosis. N Engl J Med 2005; 352:1992–2001; Airways reactivity in patients with CF. Clin Rev Allergy Immunol 2002; 23:77–85; Cystic Fibrosis Transmembrane Conductance Regulator in Sarcoplasmic Reticulum of Airway Smooth Muscle. Implications for Airway Contractility. Am J Respir Crit Care Med 2016; 193:417–26; Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. Nat Med 2010; 16:1299–304

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TRSL/BS 68 (1783)
Spinal Cord Stimulation Reduces Ventricular Arrhythmias During Acute Ischemia through Attenuation of Regional Myocardial Excitability in a Porcine Model

Kimberly Howard-Quijano, MD, MS[1], Tatsuo Takamiya, MD[1]; Erica Dale, PhD[1]; Jasmine Kipke, BS[1]; Yukiko Kubo, MD[1]; Tristan Grogan, MS[1]; Aman Mahajan, MD, PhD[1]

[1]*University of California at Los Angeles, Los Angeles, CA*

Introduction: Myocardial ischemia creates autonomic nervous system imbalance and can trigger lethal cardiac arrhythmias. Neuraxial interventions such as spinal cord stimulation (SCS) have shown promising therapeutic benefits in reducing ventricular arrhythmias. While regulation of myocardial excitability in cardiac tissues is understood, there are major gaps in our understanding of the mechanism of the sympathetic neural control of cardiac excitability. We hypothesize that neuromodulation by SCS will reduce cardiac sympathoexcitation from ischemia-induced increases in afferent signaling, reduce ventricular arrhythmias, and improve myocardial function during acute ischemia.

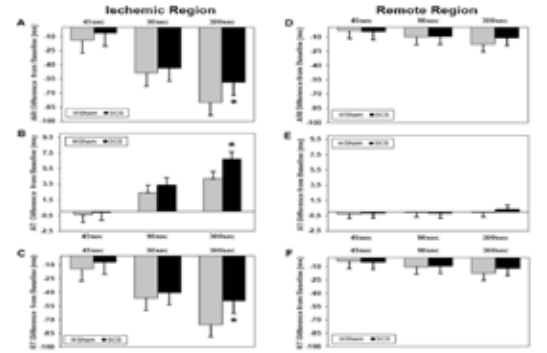

FIGURE 1: Change in electrophysiologic parameters in the ischemic and remote regions from baseline to 45, 90, and 300 seconds ischemia. Data presented as mean difference from baseline at each time point in Sham vs. SCS group. In ischemic myocardium SCS - A) attenuated sympathetic excitation associated ARI reduction (*p=0.035 vs. Sham), B) was associated with a greater increase in activation time (AT) (*p<0.001 vs. Sham), and C) was associated with a greater reduction in repolarization time (RT) (*p=0.008 vs. Sham). In remote unaffected myocardium - there was no change in D) activation recovery interval, E) activation time, or F) repolarization time in SCS or sham treated groups, all p>0.28. All Sham n=9, SCS n=10.

Methods: After approval by the animal research committee, anesthetized Yorkshire pigs (n=20) were randomized to SCS (50 Hz at 200Î¼sec duration, current 90% of motor threshold) or Sham for 30 min prior to ischemia. A 4 pole SCS lead was placed percutaneously in the epidural space (T1-T4) with fluoroscopy guidance and a 56-electrode mesh placed over the heart for high resolution electrophysiological recordings including; activation recovery intervals (ARIs), activation time, repolarization time, and dispersion of repolarization. Activation recovery interval is an established surrogate for action potential duration that decreases with sympathoexcitation and increased dispersion is a measure of ventricular arrhythmogenicity. Hemodynamics and electrophysiologic measures were recorded; at baseline, after SCS/sham, during acute ischemia (300 sec ligation of the left anterior descending coronary artery), and throughout reperfusion.

Results: SCS reduced ischemia-induced myocardial sympathoexcitation as demonstrated by; 1) attenuation of ventricular activation recovery interval shortening, 2) decrease in repolarization time shortening, 3) an increase activation time (Figure 1), and 4) suppression of increase in ventricular dispersion (Figure 2) in ischemic myocardium. In addition, SCS was associated with improved left ventricular function (dP/dt reduction: Sham 13% vs. SCS 3%, p<0.01) and less ventricular arrhythmias (non-sustained VT (arrhythmic events in # of animals): Sham 24(3) vs. SCS 1(1) and PVCs: Sham 105(9) vs. 17(8) p<0.001) during ischemia and reperfusion. No change was observed in ventricular electrophysiology during baseline conditions without myocardial stress, nor in the non-ischemic myocardium.

Conclusion: In a porcine model of acute ventricular ischemia with increased cardiac afferent signaling, SCS reduced regional efferent myocardial sympathoexcitation, decreased ventricular arrhythmias, and improved myocardial function. SCS decreased sympathetic nerve activation regionally in ischemic myocardium with no effect observed in normal myocardium. These findings provide important mechanistic insight into the anti-arrhythmic and myocardial protective effects of thoracic neuromodulation with spinal cord stimulation.

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Oral Session II

NR 46 (1735)
Astrocyte-Specific Knockout of a Mitochondrial Protein in Mice Increases Neural Inertia

Renjini Ramadasan Nair, PhD[1], Jessica Hui, BS[1]; Philip Morgan, MD[2]; Margaret Sedensky, MD[2]

[1]Seattle Children's Research Institute, Seattle, WA, [2]University of Washington, Seattle, WA

Introduction: The cell types in the CNS which contribute to the anesthetic response are unknown. Animals with defects in mitochondrial complex I have been shown to be hypersensitive to volatile anesthetics (VAs)[1,2]. Restriction of the knock out of the mitochondrial complex I protein, NDUFS4, to glutamatergic neurons confers the VA hypersensitivity[3]. While the importance of neuronal circuitry in mediating the anesthetic state is undisputed, recent research shows that astrocytes may also play a role by altering Ca2+ transients independent of neuronal activity[4]. In addition, norepinephrine inputs from the locus coeruleus (LC) have been implicated in astrocyte-mediated cortical state switching5. We analyzed the effects of knocking out Ndufs4 in astrocytes and in the LC on anesthetic sensitivity.

	Control	GFAP-KO	Control	GFAP-KO	Control	GFAP-KO	Control	GFAP-KO
1 month	0.93 1.18/1.27	0.56* 0.69/1.22	0.84 1.08/1.28	0.45* 0.55/1.20	0.98 0.98/1.01	0.67* 0.68/0.89	0.97 1.0/1.03	0.58* 0.56/1.0
2 months	0.97 1.23/1.24	0.57* 0.67/1.18	0.98 1.15/1.19	0.56* 0.66/1.22	0.97 0.89/0.92	0.66* 0.67/0.98	0.96 0.98/0.98	0.59* 0.55/0.93

Table. Ratios of EC_{50}s for emergence compared to induction in isoflurane and halothane for LORR and for TC of astrocyte specific *Ndufs4(KO)*. Absolute values for emergence and induction EC_{50}s shown in smaller font in each box below the ratio. (* indicates that emergence value different than induction value, $p < 0.005$)

Methods: The SCRI IACUC approved all studies. We constructed a transgenic mouse line Pgfap-CreERT2, which conditionally expresses Cre-recombinase in GFAP-expressing cells (astrocytes). These mice were injected with 4-hydroxytamoxifen (50 ïg/g, once a day, PND33-40) to generate animals lacking Ndufs4 in astrocytes (GFAP-KO) and were subjected to behavioral tests three weeks post injections. Successful astrocytic KO was confirmed by immunohistochemistry. Cre-positive sibling mice (Ndufs4 ï„/+ or Ndufs4 lox/+) were used as controls. For the LC-specific knockout (KO), we injected adeno-associated viruses (109 pfu) encoding Cre-recombinase (WT-Cre) or inactive virus (ï„-Cre) bilaterally into the LC of Ndufs4 floxed mice, and allowed them to recover for 1-2 months. The injected mice were exposed to isoflurane or halothane and tested for the loss of righting reflex or response to a tail clamp both during induction of and emergence from anesthesia.

Results: EC50s for each VA defined by the first loss of tail flick or righting reflex were not different between the GFAP-KOs and control animals (Table 1). In contrast, EC50s for emergence from ISO and HAL for the GFAP-KO mice were markedly different from controls, at both 1 and 2 months post tamoxifen injection (Table, Figure 1). The values of hysteresis (ï„ AD, difference between EC50s for induction and emergence) were not altered by prolonged times (30 minutes) of anesthetic exposure, eliminating a pharmacokinetic effect. Preliminary results (data not shown) indicate that loss of Ndufs4 in the LC is sufficient to recapitulate the hysteresis phenotype of the GFAP-KO for both anesthetics.

Conclusion: Our conditional GFAP-KO uncovered a surprising role of astrocytes in response to VAs: recovery from the anesthetized state. Although the astrocytic KO animal has normal anesthetic sensitivity during induction, it emerges from general anesthesia at a much lower concentration than controls. The hysteresis between the induction of and emergence from anesthesia, termed neural inertia by Kelz6, is not explained by pharmacokinetics. Our study shows that astrocytes play a role in generating neural inertia, likely by supporting metabolism in glutamatergic neurons. We hypothesize that energy deficits in astrocytes disrupt Ca2+ homeostasis, thereby delaying glutamate cycling leading to inability to regain synaptic function in the presence of low concentrations of VA. Preliminary results from KO of Ndufs4 in the LC lend support to the hypothesis that the LC mediates arousal from anesthesia through modulation of astrocytes.

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NR 44 (1803)
GABA Neurons in the Rostromedial Tegmental Nucleus Modulate Arousal and Anesthetic Sensitivity in Mice

Ksenia Y. Vlasov, BA[2]; JunZhu Pei, BS[2]; Norman E. Taylor, MD, PhD[1]; Christa J. Van Dort, PhD[1]; Jennifer A. Guidera, B.A[1]; Emery N. Brown, MD, PhD[1], **Ken Solt, MD**[1]

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

Introduction: Many anesthetic drugs potentiate GABA-A receptors in the brain, but their neuroanatomic sites of action are less clear. A population of GABA neurons in the rostromedial tegmental nucleus (RMTg) was recently discovered [1]. These neurons have dense projections to the neighboring ventral tegmental area (VTA), and recent studies show that VTA dopamine neurons promote wakefulness [2] and induce emergence from isoflurane anesthesia [3]. Using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), we tested the hypothesis that RMTg GABA neurons modulate arousal and anesthetic sensitivity.

Methods: To target GABA neurons, male mice that express cre recombinase under the transcriptional control of the Vesicular GABA Transporter (VGAT-cre mice, n=4) underwent bilateral RMTg injections of viral constructs that elicit cre-dependent expression of DREADDs. A mixture of two constructs was used to induce expression of both stimulatory (Gq-coupled) human muscarinic receptor-based DREADDs (hM3Dq) and inhibitory (Gi-coupled) kappa opioid receptor-based DREADDs (KORD) [4]. hM3Dq and KORD do not respond to their native ligands, but are activated by the inert ligands clozapine-N-oxide (CNO) and salvinorin B (SalB), respectively. Two additional VGAT-cre mice received the same injections for immunohistochemical confirmation that DREADDs co-localize with the GABA-synthesizing enzymes GAD65 and GAD67 in RMTg neurons (Fig. 1). Control male VGAT-cre mice (n=4) underwent bilateral RMTg injections of viral constructs that only encode a reporter gene (mCherry). After full recovery, normal saline, CNO (1 mg/kg i.p.) or SalB (15 mg/kg i.p.) was administered, and the open field test (5 min) and accelerating rotarod (4 to 50 RPM over 5 min) were used to assess motor activity and coordination. In addition, EEG and EMG were recorded in both groups before and after CNO. To test for altered anesthetic sensitivity, mice received CNO and were placed in an anesthetizing chamber 20 min later. The sevoflurane concentration (in oxygen) was increased by 0.2% every 10 minutes until loss of righting (LOR) occurred. At least 3 days of rest were provided between experiments.

Results: In the open field test (Fig. 2) CNO greatly decreased the distance traveled in hM3Dq/KORD mice (median 0.3 cm) compared to controls (median 15.6 cm), and the difference was statistically significant (p=0.014, Mann-Whitney test). Saline and SalB had no significant effect on distance traveled. CNO significantly decreased time on the accelerating rotarod (Fig. 3) in hM3Dq/KORD mice (median 33 sec) compared to controls (median 113 sec, p=0.014), but saline and SalB had no significant effect. CNO induced slow-delta oscillations in hM3Dq/KORD mice, but not control mice (Fig. 4). After CNO, LOR occurred at a median sevoflurane dose of 1.60% in controls, and 0.87% in hM3Dq/KORD mice (Fig. 5). This difference was statistically significant (p=0.014).

Conclusion: The results of behavioral testing suggest that activation of RMTg GABA neurons decreases arousal, whereas inhibition does not appreciably increase arousal when the animal is already awake. CNO induced slow-delta oscillations similar to non-REM sleep in hM3Dq/KORD mice but not controls, suggesting that RMTg GABA neurons may be part of an endogenous sleep-promoting circuit. Activation of RMTg GABA neurons greatly increased sensitivity to sevoflurane-induced loss of righting, suggesting that these neurons may play a role in the mechanism of sevoflurane hypnosis.

continued on page 93

Oral Session II, *continued from page 92*

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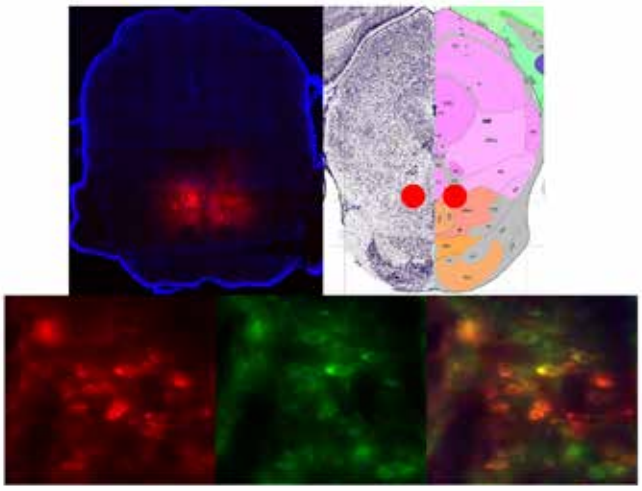

Figure 1. DREADDs are expressed in RMTg GABA neurons in VGAT-cre mice. **Top:** The presence of mCherry (red) indicates hM3Dq expression in the RMTg of VGAT-cre mice (the RMTg coordinates published by Stamatakis and Stuber[60] are indicated by red circles on the Allen brain atlas). **Bottom:** Co-localization of mCherry (red) and GAD65/67 (green) indicates hM3Dq expression in GABA neurons (merged).

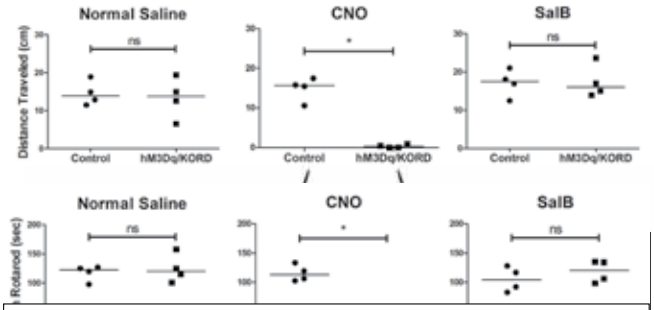

Figure 3. Rotarod results in male VGAT-cre mice. CNO (1mg/kg i.p.) had no effect on control mice, but greatly decreased the time on the rotarod in hM3Dq/KORD mice. Normal saline and SalB (15mg/kg i.p.) had no significant effects.

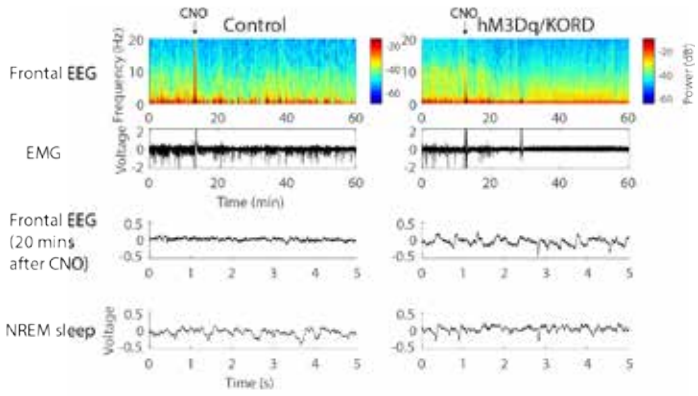

Figure 4. EEG/EMG results from individual VGAT-cre mice. **Left:** CNO did not significantly alter EEG power or EMG activity in control mice. **Right:** In hM3Dq/KORD mice, CNO increased EEG slow-delta power and decreased EMG activity within 20 minutes after injection. EEG traces show that CNO induced slow-delta oscillations (0.1-4 Hz) in hM3Dq mice but not controls. These slow-delta oscillations were similar to those observed during NREM sleep.

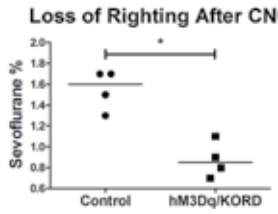

Figure 5. CNO increases sensitivity to LOR with sevoflurane in hM3Dq/KORD mice. Mice were injected with CNO and 20 min later, sevoflurane was increased by 0.2% increments every 10 minutes. The dose required to induce LOR was significantly lower in hM3Dq/KORD mice.

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Oral Presentations on Friday, May 5

SAB Oral Session III: Friday, May 5, 2017 • 8:00 am - 9:00 am

Moderators: Peter A. Goldstein, MD, and Tomoki Hashimoto, MD

Moderated Poster Discussion Session II: Friday, May 5, 2017 • 1:00 pm - 2:30 pm

	PME 42 (1349) **CX_3CR1^+ Cells in the PNS Play A Key Role in Development of Neuropathic Pain in Mice** **Jianguo Cheng, MD, PhD**[1]; LiPing Liu, MD, PhD[1]; Yan Yin, MD[1]; Fei Li, MD[1]; Zhen Hua, MD[1], PhD; *[1]Cleveland Clinic, Cleveland, OH*
	PM 53 (1440) **Corticostriatal Circuit Regulates Acute and Chronic Pain in Rodents** **Jing Wang, MD, PhD**[1]; Michelle Lee, BA[1]; Toby Manders, BA[1]; Hau Lin, BA[1]; Erik Martinez, BA[1]; Chen Su, MD[1]; Runtao Yang, BA[1] *[1]New York University School of Medicine, New York, NY*
Junior Faculty Travel Award in Perioperative Medicine	**PM 47 (1723)** **A Randomized Trial of Perioperative Gabapentin to Promote Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort** **Jennifer Hah, MD, MS**; Sean Mackey, MD, PhD; Bradley Efron, PhD; Rebecca McCue, BS; Stuart Goodman, MD, PhD; Catherine Curtin, MD; Ian Carroll, MD, MS *Stanford University, Stanford, CA* *See abstract on page 82*
	PM 50 (1750) **Dezocine for Opioid Addiction in A Rat Morphine Dependence Model** **Renyu Liu, MD, PhD**[1]; Hasan Babazada, PhD[1]; Feixiang Wu, MD, PhD[1]; Xiping Huang, PhD[2]; Weifeng Yu, MD, PhD[3] *[1]University of Pennsyvania, Philadelphia, PA, [2]University of North Carolina, Chapel Hill, NC, [3]Jiaotong University, Shanghai, Shanghai*

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Oral Presentations on Friday, May 5, *continued from page 94*

SAB Oral Session IV: Friday, May 5, 2017 • 9:15 am – 10:15 am

Moderators: Peter A. Goldstein, MD, and Tomoki Hashimoto, MD

Moderated Poster Discussion Session II: Friday, May 5, 2017 • 1:00 pm - 2:30 pm

	PS 55 (1387) **How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?** **Peter Hu, PhD**[1]; Hsiao-chi Li, PhD[1]; Shiming Yang, PhD[1]; Samuel Galvagno, MD[1]; Samuel Tisherman, MD[1]; Peter Rock, MD[1] *[1]University of Maryland Baltimore, Baltimore, MD*
Junior Faculty Travel Award in Pediatric Anesthesia	**PED 61 (1287)** **Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis** **Caleb Ing, MD, MS**[1]; Ming Sun, MS[1]; Mark Olfson, MD, MPH[1]; Charles DiMaggio, PhD, MPH, PA-C[2]; Lena Sun, MD, MPH[1]; Melanie Wall, PhD[1]; Guohua Li, MD, DrPH[1] *[1]Columbia University College of Physicians and Surgeons, New York, NY* *See abstract on page 80*
	PA 71 (1606) **Perioperative Decline in High Density Lipoprotein Particles is Associated with Increased Risk of AKI After Cardiac Surgery** **Loren Smith, MD, PhD**[1]; Derek K. Smith, DDS, PhD[1]; Alan T. Remaley, MD, PhD[2]; MacRae F. Linton, MD[1]; Frederic T. Billings, MD, Mac[1] *[1]Vanderbilt University Medical Center, Nashville, TN*

Oral Session III

PME 42 (1349)
CX_3CR1^+ Cells in the PNS Play A Key Role in Development of Neuropathic Pain in Mice

Jianguo Cheng, MD, PhD[1], LiPing Liu, MD, PhD[1]; Yan Yin, MD[1]; Fei Li, MD[1]; Zhen Hua, MD[1], PhD

[1]*Cleveland Clinic, Cleveland, OH*

Introduction: The mechanisms of neuropathic pain are complex and far from clear [(1)]. Neuroinflammation in both the central nervous system (CNS) and peripheral nervous system (PNS) has been specifically implicated [(2-4)]. Fractalkine receptor (CX3CR1) is expressed constitutively in microglia and has been used as a specific marker for microglia in the CNS [(3)]. It is a unique chemokine receptor that binds only to the chemokine, fractalkine (CX3CL1)[(5)]. We for the first time identified a unique population of CX3CR1+ cells in the PNS and investigated the role of this population of cells in the development of neuropathic pain by utilization of CX3CR1GFP knock-in mice, CX3CR1 knock-out mice, and chimeric mice with CNS or PNS CX3CR1 deficiency.

Methods: With IACUC approval, CX3CR1GFP/+ and CX3CR1GFP/GFP transgenic mice were used to induce neuropathic pain by chronic constrictive injury (CCI) of the sciatic nerve. Paw withdrawal thresholds were evaluated on post-surgical days 0, 7, 14, 21 and 28. The animals were sacrificed and perfused at these time intervals to collect samples of the sciatic nerve, DRG, and spinal cord of both sides for immunohistochemistry and flow cytometry examination of CX3CR1+ cells. We reconstituted irradiated CCR2RFP/+ or CX3CR1GFP/GFP mice with CX3CR1GFP/GFP or CCR2RFP/+ bone marrow cells to produce PNS CX3CR1 deficiency mice (CX3CR1GFP/GFP †' CCR2RFP/+) or CNS CX3CR1 deficiency mice (CCR2RFP/+ †' CX3CR1GFP/GFP) and used these mice to determine the role of CX3CR1+ cells the development of neuropathic pain. Statistical analyses were made using two-way analysis of variance (ANOVA) followed by paired comparisons with Bonferroni corrections when comparisons were made between more than 3 groups.

Results: CX3CR1 was expressed not only in microglia in the CNS but also in cells residing in the sciatic nerve and DRG in mice. The morphology of CX3CR1+ cells in the sciatic nerve and DRG was different from that of microglia in the spinal cord. These cells were positive for IBA1, a macrophage/microglia marker, and positive for CD45, a hematopoietic marker, suggesting this population of cells is a subtype of macrophages residing in the PNS. We further demonstrate that these cells were negative for NF-H (neuronal marker), myelin basic protein (MBP, marker for myelin), glutamine synthetase and Kir4.2 (markers for satellite cells), suggesting they were neither neurons nor Schwann cells, nor satellite cells. Immuno-Electronic microscopy confirmed that CX3CR1 was exclusively expressed on these cells. Interestingly, the number and morphology of CX3CR1+ cells were dramatically increased in the sciatic nerve and DRG, started from post-surgical day 3 and peaked at the day 14, in sync with hyperalgesia. Mice with CX3CR1 deficiency in both the CNS and PNS were resistant to the development of neuropathic pain. Mice with PNS CX3CR1 deficiency only (CX3CR1GFP/GFP †' CCR2RFP/+) or CNS CX3CR1 deficiency only (CCR2RFP/+ †' CX3CR1GFP/GFP) were partially resistant to the development of neuropathic pain.

Conclusion: We discovered a specific population of resident CX3CR1+ cells in the PNS (the sciatic nerve and DRG) which were morphologically different from blood CX3CR1+ cells and CNS CX3CR1+ microglia. PNS CX3CR1+ cells played a role in the development of neuropathic pain that was as important as microglia in the CNS. Further experiments will further clarify how this population of CX3CR1+ cells contribute to the initiation and/or maintenance of neuropathic pain.

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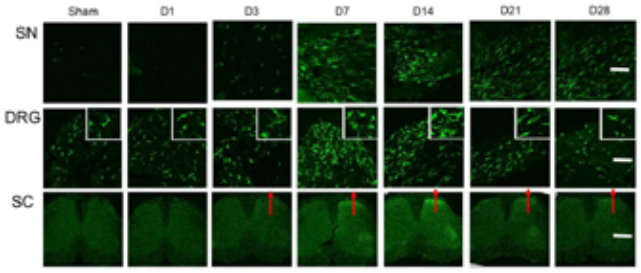
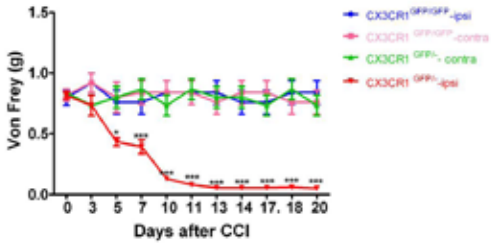
Oral Session III, *continued from page 96*

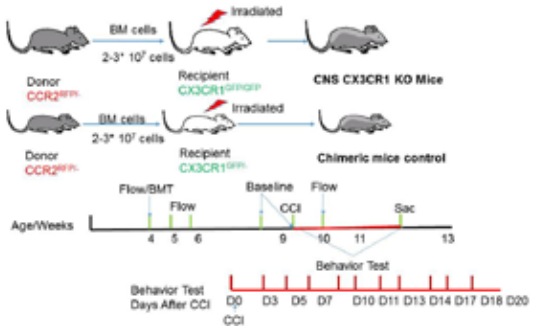
CX3CR1+ cells were dramatically increased in the sciatic nerve, DRG, and spinal cord after CCI



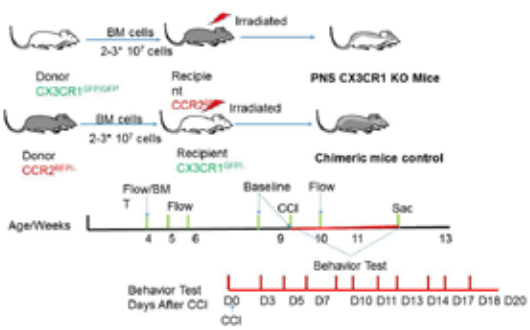
CX3CR1 KO mice were resistant to neuropathic pain



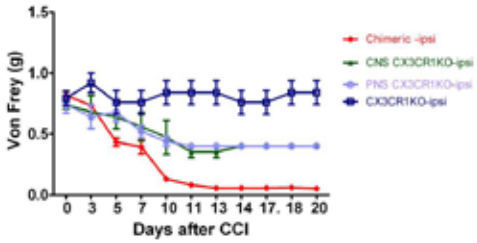
Chimeric mice - CNS CX3CR1 KO Mice



Chimeric mice: PNS CX3CR1 KO Mice



Both CNS CX3CR1 KO and PNS CX3CR1 KO mice were partially resistant to neuropathic pain



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PM 53 (1440)
Corticostriatal Circuit Regulates Acute and Chronic Pain in Rodents

Jing Wang, MD, PhD[1], Michelle Lee, BA[1]; Toby Manders, BA[1]; Hau Lin, BA[1]; Erik Martinez, BA[1]; Chen Su, MD[1]; Runtao Yang, BA[1]

[1]*New York University School of Medicine, New York, NY*

Introduction: A better understanding of the brain circuits that determine the perception and modulation of pain is crucial to the development of novel analgesics. The prefrontal cortex (PFC) is a well-known cortical region that provides top-down regulation of sensory and affective processes[1-3]. While animal and human studies have shown this region to be implicated in nociceptive regulation[4-7], the output target for the PFC in the context of acute and chronic pain remains poorly defined. The projection from the PFC to the nucleus accumbens (NAc) is an important component of the reward circuitry, and this projection has been implicated in chronic pain states[8-10]. The function of this key corticostriatal projection in pain states, however, is not known, but its understanding can significantly impact our knowledge of central pain regulation.

Methods: We used optogenetics to probe the role of the projection from PFC to NAc in pain regulation in rats. We examined both sensory and affective pain symptoms in the context of corticostriatal activation, using an acute postoperative pain model (paw incision or PI model) and a chronic neuropathic pain model (spared nerve injury or SNI model). We tested the anti-nociceptive effects of optogenetic activation of PFC neurons using mechanical allodynia and Hargreave's tests. We tested the affective symptoms of pain using conditioned place preference. Following this, we specifically targeted the projection from the PFC to the NAc using optogenetics and performed the same sensory and affective pain assays.

Results: We found that optogenetic activation of the PFC, compared with control, reduced mechanical hypersensitivity and increased latency on the Hargreave's test in both acute (n=7-10) and chronic pain models (n=8-9). Furthermore, activation of the PFC also improved affective pain symptoms as assessed by conditioned place preference (n=6 for the PI model, and n=5-7 for the SNI model). Furthermore, we showed that direct activation of prefrontal projections to the NAc core has anti-nociceptive effects in both acute (n=7) and chronic pain states (n=4-7). Finally, we showed that the activation of this PFC-NAc core projection also reduces the aversive quality of pain in both acute (n=5) and chronic pain models (n=6-7).

Conclusion: Our results indicate that the projection from the PFC to the NAc forms a novel brain circuit for the regulation of both acute and chronic pain.

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PM 50 (1750)
Dezocine for Opioid Addiction in A Rat Morphine Dependence Model

Renyu Liu, MD, PhD[1], Hasan Babazada, PhD[1]; Feixiang Wu, MD, PhD[1]; Xiping Huang, PhD[2]; Weifeng Yu, MD, PhD[3]

[1]University of Pennsyvania, Philadelphia, PA, [2]University of North Carolina, Chapel Hill, NC, [3]Jiaotong University, Shanghai , Shanghai

Introduction: The management opioid dependence remains challenging.[1] Although pharmacological replacement therapy with buprenorphine, a partial mu agonist/kappa antagonist has demonstrated some advantages over a full mu agonist methadone, it still can also cause mild to moderate dependence and precipitated withdrawal effect. [2] We have demonstrated dezocine has unique pharmacological profile without any report of addiction.[3] Here, we tested the hypothesis that dezocine, as a kappa opioid receptor (KOR) antagonist, could be an alternative medication in the management of opioid addiction and investigated mechanisms by which this agent exerts its effect using morphine dependent rat models.

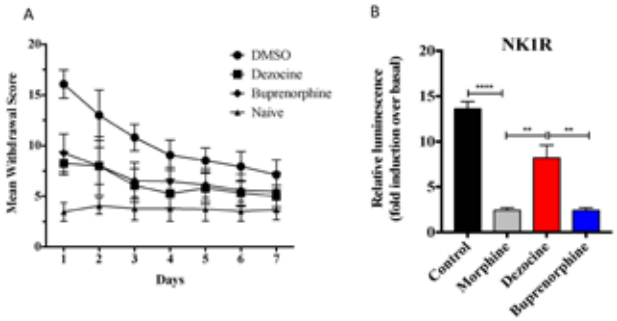

Fig 1. A. Effect of dezocine on morphine withdrawal syndrome. After the last injection of morphine, rats were injected i.p. with dezocine (1.25 mg/kg), buprenorphine (0.3 mg/kg) or 20% (v/v) DMSO. 30 min later, all rats were injected with naloxone (2 mg/kg, i.p.) and mean withdrawal score were assessed within 30 min. Data represented as mean ± SD (n=15 in each group). P<0.0001 in both Dezocine vs DMSO and Buprenorphine vs DMSO groups by Tukey's post-test after two-

Methods: The effects of dezocine on morphine withdrawal syndrome were evaluated in rat models of morphine dependence. All animal experiments were in accordance with the guidance of the NIH and approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. The pharmacological effects of dezocine on KOR are further investigated in vitro, using mammalian cells over-expressing fluorescently tagged KORs. The effect of dezocine on astrocytes activation in the nucleus accumbens (NAcc) after opioid exposure was observed by immunofluorescence. 317 GPCR targets were screened based on a G protein-independent Î²-arrestin-recruitment assay in order to reveal novel targets for dezocine, buprenorphine and morphine. Statistical analysis was carried out using two-way ANOVA followed by Tukey's multiple comparisons. P<0.05 was considered significant.

Results: The intensity of the morphine withdrawal syndrome was reduced doze-dependently in rats treated with dezocine, similar to that by buprenorphine (Fig. 1A). Chronic morphine administration through repeated subcutaneous injections induced astrocytes activation in nucleus accumbens, which was attenuated by dezocine. Dezocine also blocked the agonist-induced kappa opioid receptor internalization, one of the mechanisms involved in the development of opioid addiction. Interrogation of large library of human GPCRs via a G protein-independent Î²-arrestin-recruitment assay clearly indicated that dezocine, buprenorphine and morphine have different sets of molecular targets. It was revealed that Neurokinin 1 Receptor is potentially novel unique molecular target for dezocine that might help to explain its anti-addictive properties (Fig. 1B).

Conclusion: We demonstrated that dezocine significantly reduced morphine withdrawal syndrome in morphine-dependent rat models, indicating that dezocine as a non-addictive opioid could be an alternative medication for management of withdrawal syndrome in opioid dependence. Such pharmacological properties might relate to its unique multi-target profile as a KOR antagonist and its interaction with NK1R receptors as wells as inhibition of NAcc astrocytes activation.

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Oral Session IV

PS 55 (1387)
How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?

Peter Hu, PhD[1], Hsiao-chi Li, PhD[1]; Shiming Yang, PhD[1]; Samuel Galvagno, MD[1]; Samuel Tisherman, MD[1]; Peter Rock, MD[1]

[1]*University of Maryland Baltimore, Baltimore, MD*

Introduction: Alarm fatigue has been recognized as a critical patient safety concern in the modern hospital setting. Better characterization of alarm types and thresholds may reduce the burden of alarms and improve staff responsiveness. We tested the hypothesis that a significant reduction in the number of monitor alarms could be achieved by instituting a short delay (seconds) in activating the alarm to eliminate brief, transitory alarms, and by changing specific vital signs (VS) alarm limits based on analysis of the patient monitor alarms.

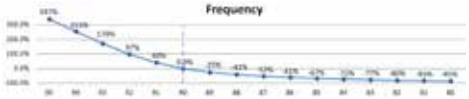

Figure 1: SpO2 LO alarm percentage changes from default (SpO2 LO ≤90%) using different alarm thresholds.

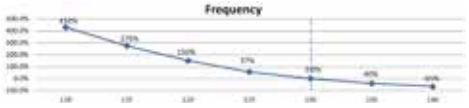

Figure 2: HR HI alarm percentage changes from default (HR HI ≥ 130 bpm) using different alarm thresholds.

Table 1: Top ten alarm events in each of four alarm classifications

Alarm (Top 10)												
Level	Category	Total N	1	2	3	4	5	6	7	8	9	10
3 (C1)	System Warning	66300 (15.5%)	SPO2 PROBE	NO ECG	CONNECT PROBE	NBP MAX TIME	SENSOR	ARRHY SUSPEND	SPO2 SENSOR	NBP FAIL	RR LEADS FAIL	NBP OVER PRES
			33.4%	23.6%	16.2%	14.7%	5.8%	4.6%	1.0%	0.4%	0.4%	0.4%
5 (C2)	Patient Advisory	245779 (57.6%)	ART S LO	PVC	CHECK ADAPTER	ART S HI	NBP S LO	ART M LO	CO2 RSP HI	NBP S HI	ART D HI	ART M HI
			25.7%	15.7%	13.6%	13.3%	6.2%	4.7%	4.2%	3.5%	3.4%	2.7%
6 (C3)	Patient Warning	98024 (23.0%)	SPO2 LO	ART DISCON N	V TACH	VT > 2	NO BREATH	FEM2 DISCON N	HR HI			
			93.4%	2.8%	1.8%	1.1%	0.9%	0.0%	0.0%			
7 (C4)	Patient Crisis	16544 (3.9%)	VT > 2	LEADS FAIL	HR HI	HR LO	BRADY	V TACH	ASYSTOLE	V BRADY	VFIB/ VTAC	
			27.1%	25.0%	14.9%	12.4%	11.8%	6.5%	1.4%	0.6%	0.3%	

Methods: We retrospectively analyzed patient VS in a 24- bed Surgical Intensive Care Unit (SICU) and collected alarm data between October 12, 2015, and February 15, 2016, from networked patient VS monitors (GE Solar) using the BedMasterEX (Excel Medical LLC, FL) system. Alarm VS name, four industry defended alarm classifications, duration, and frequency were recorded and analyzed. Most alarms were found to be brief and transitory lasting just a few seconds. Specific duration (seconds) was analyzed to achieve 25% and 50% alarm reduction. To reduce individual VS alarms, different alarm limit settings were compared with the default settings of hypoxia (SpO2 low ‰¤ 90%,) and tachycardia (heart rate: HR, high HR ‰¥ 130 bpm).

Results: There were 426,647 alarms recorded during the 4-month study period resulting in 148 alarms per bed per day in the 24 bed SICU. In the four industry pre-defined alarm classifications, the majority of the alarms were classified as 'C1: and System Warning' (66,300, 15.5%); 'C2: Patient Advisory' alarms (n = 245,779, 57.6%); 'C3: Patient Warning' (98,024, 23%). Only 3.9% were in the 'C4: Patient Crisis' alarm category. The top ten alarm events in each of the four alarm classification are listed in Table 1. In each of the above alarm classifications 25% of alarms were less than 28 seconds (C1), 4 seconds (C2), 2 seconds (C3), and 4 seconds (C4). 50% of alarms were less than 322 seconds (C1), 10 seconds (C2), 13 seconds (C3), and 12 seconds (C4). Changing from the current default alarm threshold settings of SpO2 low (‰¤90%) to SpO2 ‰¤88% (Figure1), and tachycardia (HR ‰¥ 130 bpm to HR ‰¥135 bpm could reduce alarms by 41%, and 40% (Figure 2).

Conclusion: Alarm fatigue from physiologic alarms in SICU is well recognized but a safe solution to safely reduce alarms has not been established. Our study suggests that by delaying all alarms for 4 seconds we could reduce 25% of the total alarms. By lowering alarm thresholds of SpO2 LO by 2% and increasing the tachycardiac threshold by 5 bpm could reduce an additional 40% of alarms in SICU. Further study is needed to determine what impact such changes would have upon the safety of patients being cared for in the SICU. (This study is funded by University of Maryland School of Medicine, Department of BioEngineering and Department of Anesthesiology).

References:

None

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PA 71 (1606)
Perioperative Decline in High Density Lipoprotein Particles is Associated with Increased Risk of AKI After Cardiac Surgery

Loren Smith, MD, PhD[1], Derek K. Smith, DDS, PhD[1]; Alan T. Remaley, MD, PhD[2]; MacRae F. Linton, MD[1]; Frederic T. Billings, MD, Mac[1]

[1]*Vanderbilt University Medical Center, Nashville, TN*

Introduction: Acute kidney injury (AKI) after cardiac surgery occurs in up to 30% of patients and is an independent predictor of death.[1] We previously reported that a higher preoperative high density lipoprotein (HDL) cholesterol concentration is associated with a decreased risk of AKI after cardiac surgery. HDL particle number and size better correlate with HDL's cardiovascular effects than HDL cholesterol levels,2 but the effect of HDL particle characteristics in the perioperative period has never been described. We measured HDL particle concentration and size at induction of anesthesia, at admission to the ICU following surgery, and on postoperative day two to test the hypothesis that perioperative HDL particles are associated with AKI following cardiac surgery.

Methods: After Institutional Review Board approval, we selected 75 patients who developed mild, moderate, severe, or no AKI from a recently completed, prospective trial of perioperative atorvastatin to prevent post-cardiac surgery AKI.3 Plasma samples were analyzed using the NMR Lipoprofile test, a clinical assay of HDL particle concentration and size. HDL cholesterol concentration, particle concentration, and particle size changes over time were assessed with mixed effects models adjusted for AKI risk factors. A two-component latent variable mixture model was used to assess the association between the change in HDL particle concentration from anesthetic induction to postoperative day two and the maximum serum creatinine change from baseline in the first 48 postoperative hours. Similar modeling was used to assess the association between the change in average HDL particle size and postoperative serum creatinine change.

Results: HDL cholesterol concentration did not change during the perioperative period (p=0.60, Figure 1). HDL particle concentration, however, decreased over the same period (p<0.001, Figure 2), while HDL particle size increased (p<0.001, Figure 3). A larger decrease in HDL particle concentration from induction to postoperative day two was independently associated with a greater postoperative rise in serum creatinine (p=0.02, Figure 4), while a larger increase in average HDL particle size from induction to postoperative day two was not associated with a greater postoperative serum creatinine rise (p=0.42) (Figure 5).

Conclusion: HDL particle concentrations decreased during the perioperative period while HDL particle sizes increased. HDL cholesterol concentrations did not change. A greater decrease in HDL particle concentration was independently associated with an increased risk of AKI after cardiac surgery. Further work will assess perioperative HDL protein composition and function changes, in a continued effort to identify the biological mechanism underlying the protective association between HDL and postoperative AKI.

References:

1. Perioperative Medicine, vol 1, pg 6, 2012. 2. Cardiovasc Drugs Ther, vol 29(1), pg 41, 2015. 3. JAMA, vol 315(9), pg 877, 2016.

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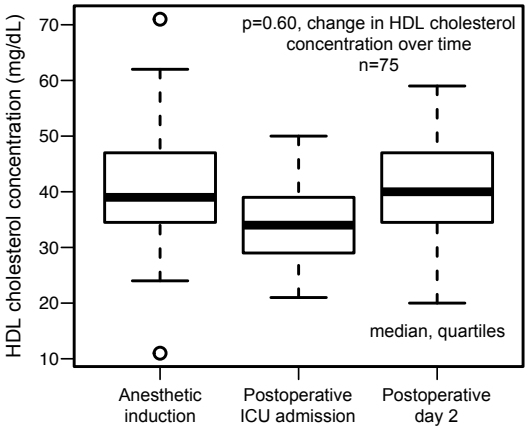

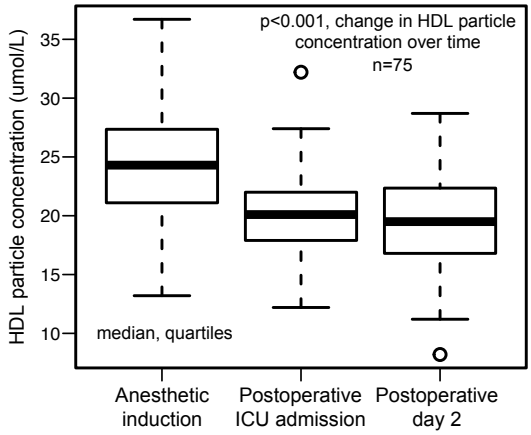

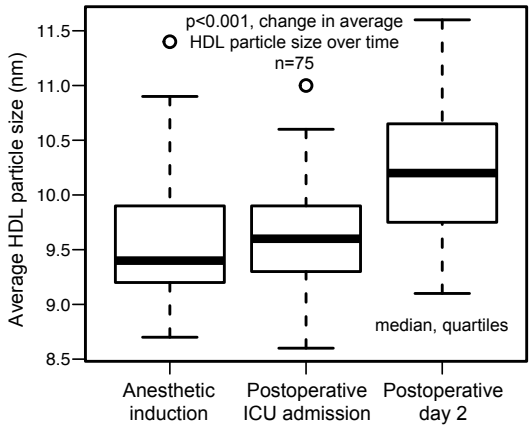

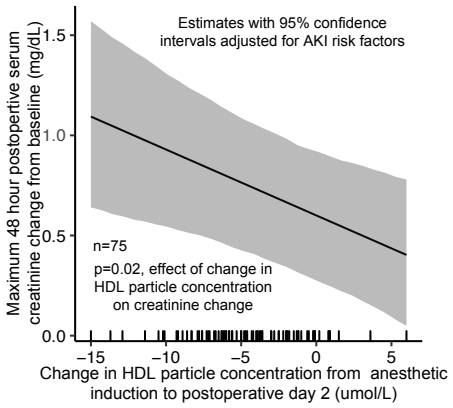

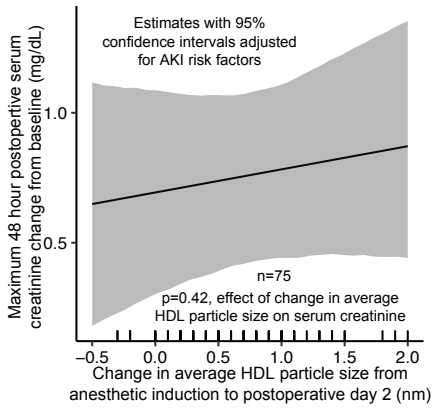

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ww4.aievolution.com/ars1701/files/content/abstracts/abs_1606/AUAFig5.pdf

Scientific Advisory Board Oral Sessions and Moderated Poster Discussion Sessions Schedule-at-a-Glance

Thursday, May 4

Scientific Advisory Board Oral Session I

9:00 am – 10:00 am

Moderated Poster Discussion Session I

10:00 am – 11:30 am

Poster Set-up: Thursday, May 4, 6:30 am - 7:30 am

Poster Removal: Friday, May 5, 6:00 pm – 7:00 pm

Scientific Advisory Board Oral Session II

11:30 am – 12:30 pm

Friday, May 5

Scientific Advisory Board Oral Session III

8:00 am – 9:00 am

Scientific Advisory Board Oral Session IV

9:15 am – 10:15 am

Moderated Poster Discussion Session II

1:00 pm – 2:30 pm

Poster Set-up: Thursday, May 4, 6:30 am – 7:30 am

Poster Removal: Friday, May 5, 6:00 pm – 7:00 pm

Scientific Advisory Board Oral Sessions and Moderated Poster Discussion Sessions General Information

Abstract Presenter

Presenters are required to attend their assigned Moderated Poster Discussion Session and Scientific Advisory Board Oral Session (SAB), if applicable. During the SAB Oral Session, presenters should give an 8-minute oral presentation. During the Moderated Poster Discussion Session, presenters should give a 3-5 minute summary of their most important findings. The poster moderator for your Moderated Poster Discussion Session will assist with facilitating the discussion.

Assigned Poster Board Identification and Location

For identification purposes, a poster board ID is assigned to all presenting authors. The assigned IDs will be affixed to each poster board in the poster room. Category Signs including day/date and session times will be placed at the end of each aisle in the poster session room. A staff member will be available to assist you with finding your poster board should you require assistance.

Poster Board ID Format and Abstract Key for Anesthesia Subspecialty Topics

The Poster Board ID format is the following:

Poster Board Anesthesia Subspecialty Topic Abbreviation, Poster Board #, (Abstract #).

Example: AM 1 (230). See the Abstract Category Key for Anesthesia Subspecialty Topics below.

Abstracts Category Key for Anesthesia Subspecialty Topics

AM	Airway Management
AMB	Ambulatory Anesthesia
AP	Anesthetic Pharmacoloy
BLD	Blood Management
CA	Cardiovascular Anesthesiology
CC	Critical Care
EEP	Education, Economics and Policy
GA	Geriatric Anesthesia
GH	Global Health
L	Liver
NR	Neuroscience in Anesthesiology and Perioperative Medicine
O	Obesity
OB	Obstetric Anesthesiology
PME	Pain Mechanisms
PM	Pain Medicine
PS	Patient Safety
PED	Pediatric Anesthesiology
PA	Perioperative Anesthesia
RA	Regional Anesthesia
RES	Respiration
SM	Sleep Medicine
TCSEM	Technology, Computing and Simulation, Equipment Monitoring
T	Trauma
TRSL / BS	Translational /Bench Science

General Information, *continued from page 104*

Scientific Advisory Board (SAB) Oral Session and Moderated Poster Discussion Session, Setup and Breakdown Times

The following are the times for setup, presentation and breakdown:

Presentation Date	Presentation Name	Presentation Times	Poster Setup Time**	Poster Removal Time**
Thursday, May 4	SAB Oral I* SAB Oral II	9:00 am – 10:00 am 11:30 am – 12:30 pm	For Thursday: Thursday, May 4 6:30 am - 7:30 am	For Thursday: Thursday, May 4 6:00 pm - 7:00 pm
	MPDS I**	10:00 am – 11:30 am		
Friday, May 5	SAB Oral III SAB Oral IV	8:00 am – 9:00 am 9:15 am – 10:15 am	For Friday, Friday, May 5 6:30 am - 7:30 am	For Friday: Friday, May 5 6:00 pm - 7:00 pm
	MPDS II	1:00 pm – 2:30 pm		

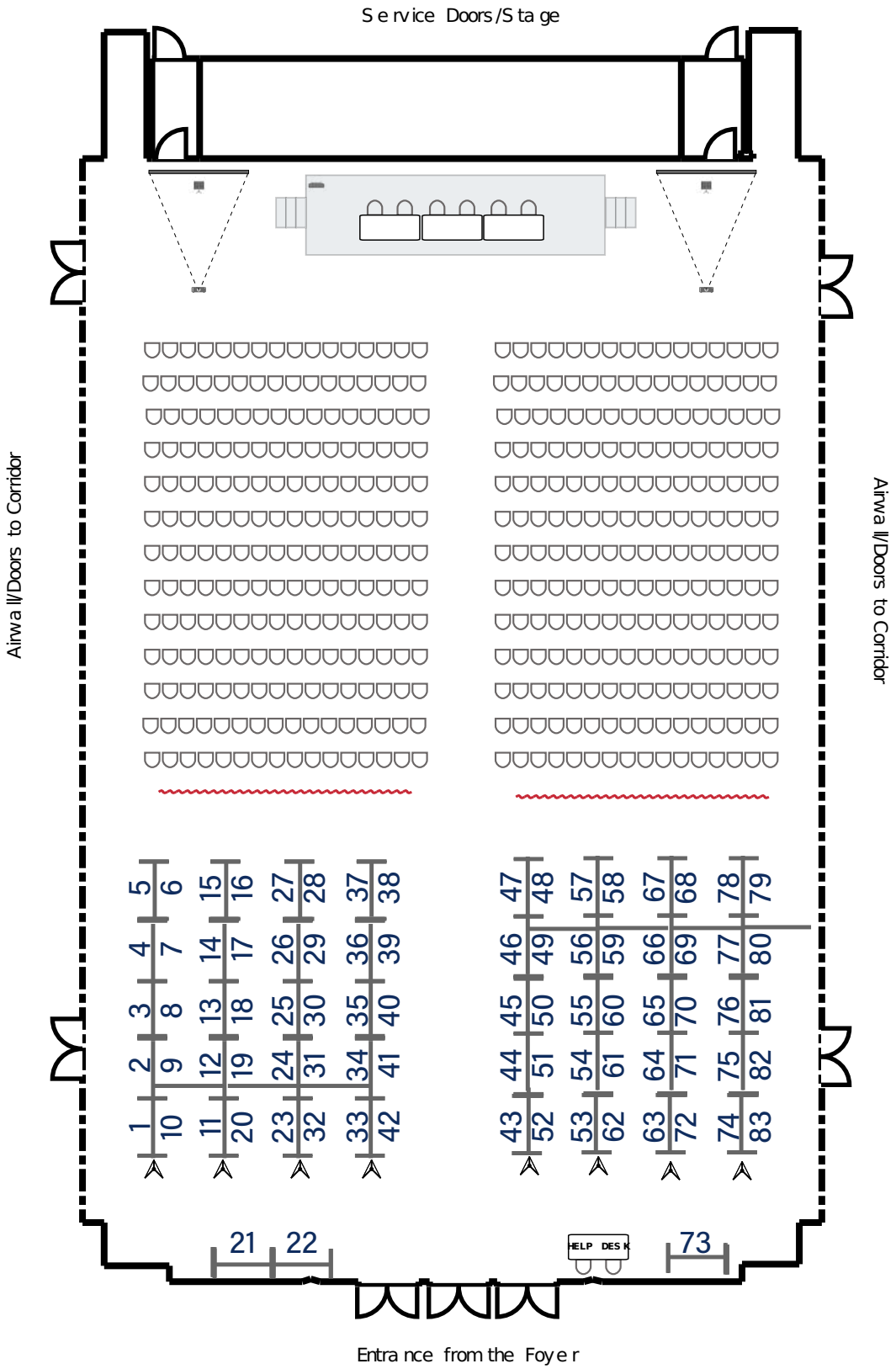
You are responsible for removing all material from the poster boards during the time interval listed above. There is no storage available for posters and any materials remaining will be discarded.

**SAB stands for Scientific Advisory Board*
**MPDS stands for Moderated Poster Discussion Session*

Dedicated Scientific Advisory Board Oral Session and Moderated Poster Discussion Session Rooms

Scientific Advisory Board (SAB) Oral Session Room Location: *Independence A, Independence Level*

Moderated Poster Discussion Session Room Location: *Independence A, Independence Level*



Moderated Poster Discussion Sessions

Thursday, May 4, 2017 • 10:00 am - 11:30 am

Category	Poster Board Number
Anesthetic Pharmacology	1 – 10
Pain Mechanisms	11
Cardiovascular Anesthesiology	12 – 16
Critical Care	17 – 18, 20 – 22
Economics, Education and Policy	23 – 28
Geriatric Anesthesia	29 – 30
Pediatric Anesthesiology	31 – 35
Liver	36
Global Health	37
Respiration	38 – 41
Neuroscience in Anesthesiology and Perioperative Medicine	42 – 52
Pain Medicine	53 – 55
Regional Anesthesia	56 – 57, 59
Perioperative Anesthesia	61 – 65
Translational / Bench Science	66 – 74
Trauma	75 – 77
Critical Care	78
Technology, Computing and Simulation, Equipment Monitoring	79

Poster Presentation Schedule – Thursday, May 4

Thursday, May 4, 2017 • 10:00 am – 11:30 am

Anesthetic Pharmacology: Group 1

Moderator: Randall Schell, MD, MACM, University of Kentucky, Lexington, Kentucky

AP 1 (1431)
A Comparative Efficacy Trial of Intravenous vs. Oral Acetaminophen in Sinus Surgery

Ravi Bhoja, MD[1]; Matthew Ryan, MD[1]; Kevin Klein, MD[1]; Bradley Marple, MD[1]; Abu Minhajuddin, PhD[1]; David McDonagh, MD[1]

[1]UT Southwestern Medical Center, Dallas, TX

AP 2 (2077)
Mapping the Orientation and Site of Neurosteroid Binding in GLIC, a Pentameri Ligand-Gated Ion Channel

Wayland W. Cheng, MD, PhD[1]; Zi-wei Chen, PhD[1]; Melissa Budelier, BSc[1]; Douglas F. Covey, PhD[1]; Gustav Akk, PhD[1]; Alex Evers, MD[1]

[1]Washington University School of Medicine at St. Louis, Saint Louis, MO

AP 3 (1510)
Isoflurane Modulates Activation and Inactivation Gating of the Prokaryotic Na+ Channel NaChBac

Kevin Gingrich, MD[1]; Rheanna Sands, PhD[2]; Tamar Macharadze, PhD[3]; Karl Herold, MD, PhD[2]; Hugh Hemmings, MD, PhD[2]

[1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Weill Cornell Medical College, New York, NY

AP 4 (1952)
H-bond Propensity, Molecular Volume and Ring Ï€-Electrons/Planarity Differentially Determine if Propofol-Like Molecules are Inverse Agonists of HCN1 Channel Opening or Competitive Antagonists Thereof

Rebecca L. Joyce, BS[1]; Nicole P. Beyer, BA[1]; Georgia Vasilopoulos[1]; Adam C. Hall, PhD[2]; Roderic G. Eckenhoff, MD[3]; Peter Goldstein, MD[1]; E Gareth R Tibbs[1]

[1]Weill Cornell Medicine, New York, NY, [2]Smith College, Northampton, MA; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

AP 5 (2061)
Development and Validation of Pharmacokinetic Model for Propofol in Mice

Brenna P. Shortal, BS[1]; Sarah Reitz, BS; Max Kelz, MD, PhD[2]; Andrew McKinstry-Wu, MD[2]; Quing C. Meng, PhD[2]; Alex Proekt, MD, PhD[2]

[1]University of Pennsylvania, Pennsylvania, PA, [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Anesthetic Pharmacology and Pain Mechanisms: Group 2

Moderators: Paul S. Garcia, MD, Emory University/VAMC Atlanta, Decatur, Georgia; and Peter A. Goldstein, MD, Weill Cornell Medical College New York-Presbyterian Hospital, New York, New York

AP 6 (1180)
Propofol Potently Impedes Processive Kinesin Motion via an Allosteric Binding Site

Kellie Woll, PhD[1]; Brandon Bensel, BS[2]; Susan Gilbert, PhD[2]; Roderic Eckenhoff, MD[3];

[1]University of Pennsylvania, Philadelphia, PA, [2]Rensselaer Polytechnic Institute, Troy, NY, [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

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Poster Presentation Schedule, *continued from page 108*

Anesthetic Pharmacology and Pain Mechanisms: Group 2, *continued*

AP 7 (1108)
Molecular Mechanism of Stimulation of the Metabolism of Anesthetics by Cyt P450 2B4

Lucy Waskell, MD, PhD[1]; Naw May Pearl, PhD[1]; Jarett Wilcoxen, PhD[2]; Sangchoul Im, MD, PhD[1]; Ryan Kunz, PhD[3]; R. Britt, PhD[2]; Stephen Ragsdale, PhD[1]

[1]University of Michigan, Ann Arbor, MI

AP 8 (1956)
Norbuprenorphine First in Man Pharmacology 3. Clinical Effects and Pharmacodynamics

Evan Kharasch, MD, PhD[1]; Alicia Flaker[1]; Kristi Kraus, RN[1]; Jane Blood, RN[1]

[1]Washington University School of Medicine in St. Louis, St Louis, MO, [2]Columbia University, New York, NY, [3]Weill Cornell Medical College, New York, NY

AP 9 (1949)
Norbuprenorphine First in Man Pharmacology 2. Arterial and Venous Pharmacokinetics

Thomas K. Henthorn, MD[1]; Evan Kharasch, MD[1], PhD, Alicia Flaker[1]; Kristi Kraus, RN[1]; Jane Blood, RN[1]

[1]Washington University School of Medicine in St. Louis, St Louis, MO

AP 10 (1942)
Norbuprenorphine First in Man Pharmacology 1. Dose Escalation Evaluation

Evan Kharasch, MD, PhD[1]; Alicia Flaker[1]; Kristi Kraus, RN[1]; Jane Blood, RN[1]

[1]Washington University School of Medicine in St. Louis, St Louis, MO, [2]Emory University School of Medicine, Atlanta, GA, Stanford University, Stanford, CA, [3]Weill Cornell Medical College, New York, NY

PME 11 (2146)
Low Dose Isoflurane Selectively Suppresses Withdrawal to Thermal A-δ Nociceptor Stimulation Compared to C-Fiber Stimulation in Rat: Behavioral And Transcriptomic Analysisn

Stephen Raithel[1]; Michael Iadarola[2]; Andrew Mannes[2]

[1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, [2]National Institutes of Health, Clinical Center, Bethesda, MD

Cardiovascular Anesthesiology: Group 3

Moderators: Tomoki Hashimoto, MD, University of California, San Francisco, San Francisco, California; and Matthias Riess, MD, Vanderbilt University Medical Center, Nashville, Tennessee

CA 12 (1213)
Bayesian Network Analysis of Systolic Anterior Motion

Koichi Akiyama, MD[1]; Maki Ishii, MD[1]; Keiichi Itatani, MD, PhD[1]; Mao Kinoshita, MD, PhD[1]; Masaru Shimizu, MD, PhD[1]; Hideya Kato, MD[1]; Teiji Sawa, MD, PhD[1]

[1]Kyoto Prefectural University of Medicine, Kyoto City, Kyoto Prefecture, Japan

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continued on page 110

Poster Presentation Schedule, *continued from page 109*

Cardiovascular Anesthesiology: Group 3, *continued*

CA 13 (1160)
3-Oxoglutarate is a Novel Marker of Ischemia in Humans

Nathan Clendenen, MD[1]; Kirk Hansen, PhD[1]; Angelo D'Alessandro, PhD[1]; Nathaen Weitzel, MD[1]

[1]*University of Colorado, Denver, CO*

CA 14 (1290)
Cardiac-Specific Human Resistin Overexpression Impairs Contractility in Mice

Wei Dong Gao, MD, PhD[1]; Wei Yang, MD, PhD[2]; John T. Skinner, MS[1]; Qing Lin, MD, PhD[1]; Chunling Fan, PhD[1]; Kazuyo Yamaji-Kegan, PhD[1]; Roger A. Johns, MD, PhD[1]

[1]*Johns Hopkins University School of Medicine, Baltimore, MD*

CA 15 (1656)
Association of Testosterone Replacement Therapy (TRT) and the Incidence of Perioperative Major Adverse Cardiac Events (MACE) in Men undergoing Non-Cardiac Surgery

Daniel Ramos, MD[1]; Jing You, MS[1]; Sandeep Khanna, MD[1]; Kamal Maheshwari, MD, MPH[1]; Carlos Trombetta, MD[1]; Maged Y. Argalious, MD, MSc, MBA, MEd[1]

[1]*Cleveland Clinic, Cleveland, OH*

CA 16 (1250)
Proceduralist-Directed, Nurse-Administered Dexmedetomidine Sedation for PSVT Ablation

Andrew Slupe, MD, PhD[1]; Jessica Minnier, PhD[2]; Merritt Raitt, MD[3]; Ignatius Zarraga, MD[3]; Karen MacMurdy, MD[3]; Peter Jessel, MD[3]

[1]*Oregon Health and Science University, Portland, OR,* [2]*OHSU-PSU School of Public Health, Portland, OR,* [3]*VA Portland Health Care System, Portland, OR*

Critical Care: Group 4

Moderators: May Pian-Smith, MD, Massachusetts General Hospital, Boston, Massachusetts; and Edward Sherwood, MD, PhD, Vanderbilt University School of Medicine, Nashville, Tennessee

CC 17 (1621)
A 4-Year Review of Eclampsia Managed in the Intensive Care Unit: Lesson Learnt

Ajibola Uthman Otegbeye, MBBS, DA[1]; Olusola Idowu, MBBS, FWACS

[1]*University College Hospital, Ibadan, FM*

CC 18 (1099)
Epidemic Propagation of Pseudomonas Aruginosa ST357 Clones Harboring exoU Gene

Atsushi Kainuma, MD[1]; Kyoko Momiyama[2]; Koichi Akiyama, MD[1]; Yoshifumi Naito, MD[1]; Mao Kinoshita, MD, PhD[1]; Hideya Kato, MD[1]; Teiji Sawa, MD, PhD[1]

[1]*Kyoto Prefectural University of Medicine, Kyoto City, Kyoto Prefecture,* [2]*Kyoto Pharmaceutical University, Kyoto City, Japan*

continued on page 111

Poster Presentation Schedule, *continued from page 110*

Critical Care: Group 4, *continued*

CC 20 (1407)
Comprehension of Critical Care Issues by Proxies of Patients Undergoing Major Surgery

Stephen Cassidy, BFA[1]; Gebhard Wagener, MD[1]

[1]*Columbia University, New York, NY*

CC 21 (1687)
Increased Intraoperative Crystalloid Administration for Esophagectomy Decreases Unplanned ICU Admissions in a Single Center Study

Jeffrey Paul Cardinale, MD, PhD[1]; Morgan Smith, MBBS[1]; Phillip Boysen, MD[2]; Bobby Nossaman, MD[3]

[1]*Ochsner Medical Center, New Orleans, LA,* [2]*Ochsner Clinic Foundation, New Orleans , LA,* [3]*Emory University Hospital, Atlanta, GA*

CC 22 (1036)
Independent Risk Factors for Anesthesia Related Postoperative Respiratory Failure in a Rural Tertiary Academic Medical Center

Manuel C. Vallejo, MD, DMD[1]; Ahmed Attaallah, MD, PhD[1]; Norman D. Ferrari, MD[1]

[1]*West Virginia University, Morgantown, WV*

Education, Economics and Policy: Group 5

Moderators: George Gallos, MD, Columbia University, New York, New York; and Manuel Pardo, MD, University of California, San Francisco, San Francisco, California

EEP 23 (1525)
A Pilot Study To Assess the Feasibility of a Smartphone Application for Asynchronous Workplace Based Learning

Leslie L. Fowler, MD[2]; **Jesse Ehrenfeld, MD**[2]; Matthew D. McEvoy, MD[1]

[1]*Vanderbilt University Medical Center, Nashville, TN,* [2]*Vanderbilt University School of Medicine, Nashville, TN*

EEP 24 (1979)
Predicting Novice Success at Patient Intubation by Capturing Laryngoscopy Motion in Manikins

Randolph H. Hastings, MD, PhD[1]; Dale Glaser, PhD[2]; Nathan J. Delson, PhD[3]

[1]*VA San Diego Healthcare System, San DIego, CA,* [2]*University of San Diego, San Diego, CA,* [3]*UC San Diego, La Jolla, CA*

EEP 25 (1351)
Impact of Public Reporting of 30-day Mortality on Timing of Death after CABG Surgery

May Hua, MD, MSc[1]; Damon Scales, MD, PhD[2]; Ruxandra Pinto, PhD[3]; Vivek Moitra, MD[1]; Hannah Wunsch, MD, MSc[3];

[1]*Columbia University, New York, NY,* [2]*University of Toronto, Toronto, Ontario,* [3]*Sunnybrook Health Sciences Centre, Toronto, Ontario*

continued on page 112

Poster Presentation Schedule, *continued from page 111*

Education, Economics and Policy: Group 5, *continued*

EEP 26 (1490)
Generative Retrieval Improves Learning and Retention of Cardiac Anatomy Using Transesophageal Echocardiography

Julie L. Huffmeyer, MD[1]; Amanda Kleiman, MD[1]; Katherine Forkin, MD[1]; Allison Bechtel, MD[1]; Stephen R. Collins, MD[1]; Jennie Z. Ma, PhD[1], Edward Nemergut, MD[1]

[1]*University of Virginia, Charlottesville, VA*

EEP 27 (1634)
Trends in Specialty Selection Among US Medical Students from 2006-2016. How Does Anesthesiology Compare?

Corey Spiro, MD[1]; Brandon Minzer, MD, EdM, MA[1]; Hao Deng, MD[1]; Ersne Eromo, MD, MBA[1]

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

EEP 28 (1081)
Global Overview of Anesthesiology Certification and Practice — a Survey Study

Makiko Tani, MD, PhD[1]; Jan D. Smith, MBChB, FRCP, DTM&H, FACP[1]; Tetsuro Sakai, MD, PhD[1]

[1]*University of Pittsburgh Medical Center, Pittsburgh, PA*

Geriatric Anesthesia and Pediatric Anesthesia: Group 6

Moderators: Matthew McEvoy, MD, Vanderbilt University Medical Center, Nashville, Tennessee; and Christina Pabelick, MD, Mayo Clinic, Rochester, Minnesota

GA 29 (1599)
Persistent Pain Is Associated with Accelerated Memory Decline and Dementia in a Longitudinal Cohort of Elders

Elizabeth L. Whitlock, MD, MSc[1]; L. G. Diaz-Ramirez, MS[1]; M. M. Glymour, ScD, MS[1]; W. J. Boscardin, PhD[1]; Kenneth E. Covinsky, MD[1]; Alexander K. Smith, MD, MPH[1]

[1]*University of California, San Francisco, San Francisco, CA*

GA 30 (1728)
Subjective and Objective Memory Function after Cardiac Surgery or Cardiac Catheterization: A Population-Based Cohort Study

Elizabeth L. Whitlock, MD, MSc[1]; L. G. Diaz-Ramirez, MS[1]; M. M. Glymour, ScD, MS[1]; W. J. Boscardin, PhD[1]; Michael Avidan, MBBCh[2]; Kenneth E. Covinsky, MD[1]; Alexander K. Smith, MD, MPH[1]

[1]*University of California, San Francisco, San Francisco, CA*

PED 31 (2107)
Quantitative MRI Study Evaluating Prolonged Sedation on the Brain Growth in Infants Younger than 6 Months

David M. Gilman, MD Candidate[1]; Hannah W. Kilcoyne, BS Candidate[1]; Sophie L. Wilcox, PhD[1]; Russell W. Jennings, MD[1]; Patricia E. Grant, MD[1]; **Dusica M. Bajic, MD, PhD**[1]

[1]*Boston Children's Hospital, Boston, MA*

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Geriatric Anesthesia and Pediatric Anesthesia: Group 6, *continued*

PED 32 (2212)
Long-Term, Persistent Deficits in Neurotransmission Following Multiple Exposures to Anesthesia in Infant Non-Human Primates

Verginia Cuzon Carlson, PhD[1]; Gregory A. Dissen, PhD[2]; Lauren D. Martin, DVM[3]; Ansgar Brambrink, MD, PhD[3];

[1]Oregon Health & Science University, Beaverton, OR, [2]Oregon National Primate Research Center, Beaverton, OR, [3]Colubmia University Medical Center, New York

PED 33 (1756)
An Objective Measure of Neuraxial Block Onset and Offset

Alyssa Rachel Padover, MD[1]; Robert S. Greenberg, MD[1]; Jessica A. George, MD[1]; Wayne I. Sternberger, PhD[1]

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

PED 34 (2174)
Hemostasis Management in a Pediatric Patient with Hermansky-Pudlak Syndrome

Mary Rhee, MD[1]; Roberto Blanco, MD[1]; **Benjamin Kloesel, MD**[1]

[1]University of Minnesota, Minneapolis, MN

PED 35 (2081)
Anesthetic Management of Combined Renal-Liver Transplant in a Pediatric Patient with Primary Hyperoxaluria

Zachary Wichner, DO[1]; Benjamin Kloesel, MD[1]

[1]University of Minnesota, Minneapolis, MN

Liver, Global Health and Respiration: Group 7

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

L 36 (1524)
IL-33 Critically Modulates Foxp3+Treg Responses in A Mouse Model of Drug-Induced Hepatitis

Maeva Nyandjo, BS[1]; Merylin Cottagiri, MHS[2]; **Dolores B. Njoku, MD**[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

GH 37 (2014)
Monitoring Pediatric Perioperative Anesthesia Care and Mortality Rates in a Sample of Kenyan Hospitals: Initial Results from over 5,000 Cases

Bantayehu Sileshi, MD[1]; Savannah Hurt, MD[1]; Mark Newton, MD[2]; Warren S. Sandberg, MD, PhD[1]; Matthew D. McEvoy, MD[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Kijabe AIC Hospital, Kijabe, Kijabe

RES 38 (1459)
Incidence of Respiratory Depression Following Inpatient Surgery

Rami Ben-Joseph, PhD[1]; Angela Meier, MD, PhD[2]; Francine Chingcuanco, MHS[1]; Weiyi Ni, PhD[1]; Victoria Divino, BS[3]; Mitch DeKoven, MHSA[3]; Ronald Gordon, MD, PhD[2]

[1]Millennium Health, San Diego, CA, [2]University of California, San Diego, San Diego, CA

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Liver, Global Health and Respiration: Group 7, *continued*

RES 39 (2063)
Minimizing Parenchymal Strain Heterogeneity During Oscillatory Ventilation

David Kaczka, MD, PhD[1], Jacob Herrmann, MS[1]

[1] University of Iowa, Iowa City, IA

Junior Faculty Research Award Winner

RES 40 (1386)
Photo-Relaxation: Light Mediated Airway Smooth Muscle Relaxation

Peter Yim, MD[1]; Daniel Berkowitz, MD[2]; George Gallos, MD[3]; Charles Emala, MD[1]

[1]Columbia University, New York, NY, [2]Johns Hopkins University, Baltimore, MD, [3]Columbia University, New York, NY

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RES 41 (1503)
AMPK Activators Increase Survival after Bromine Inhalation

Ting Zhou, MD[1]; Mingyuan Jian, MD, PhD[1]; Paul Wolkowicz, PhD[1]; Yilan Liu[1]; Sadis Matalon, PhD[1]; Judy Creighton, PhD[1];

[1]University of Alabama at Birmingham, Birmingham, AL

Neuroscience in Anesthesiology and Perioperative Medicine: Group 8

Moderator: Thomas Floyd, MD, Stony Brook University, Stony Brook, New York

NR 42 (1408)
Isoflurane Exposure During Brain Development Activates the mTOR Pathway

Jing Xu, MD[1]; Michael Xu, BS[1]; Danye Jiang, BS[1]; Eunchai Kang, PhD[1]; Cyrus Mintz, MD, PhD[1]

[1]Johns Hopkins School of Medicine, Baltimore, MD

NR 43 (1033)
Awake Craniotomy: Comparison of Monitored Anesthesia Care Versus Asleep Awake Asleep

Punita Tripathi, MD[1]; Chikezie I. Eseonu, MD[1]; Oscar Garcia, MPH1[3]; Karim ReFaey, MD[2]; Amballur D. John, MD[3]; Alfredo Quinones-Hinojosa, MD[2]

[1]Johns Hopkins University, Baltimore , MD, [2]Mayo Clinic, Jacksonville, Fl, Jacksonville, FL

NR 44 (1803)
GABA Neurons in the Rostromedial Tegmental Nucleus Modulate Arousal and Anesthetic Sensitivity in Mice

Ksenia Vlasov, BA[2]; JunZhu Pei, BS[2]; Norman E. Taylor, MD, PhD[1]; Christa J. Van Dort, PhD[1]; Jennifer A. Guidera, B.A[1]; Emery N. Brown, MD, PhD[1]; **Ken Solt, MD**[1]

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

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Neuroscience in Anesthesiology and Perioperative Medicine: Group 8, *continued*

NR 45 (1339)
Propofol-Induced Decrease in Spectral Complexity

Robert D. Sanders, BSc, PhD, MBBS, FRCA[1]; Jamie Sleigh, MBChD MD[2]; Matthieu Darracq, MSc[1]; Melanie Boly, MD, PhD[1]

[1]*University of Wisconsin, Madison, Madison, WI*

NR 46 (1735)
Astrocyte-Specific Knockout of A Mitochondrial Protein in Mice Increases Neural Inertia

Renjini Ramadasan Nair, PhD[1]; Jessica Hui, BS[1]; Philip Morgan, MD[2]; Margaret Sedensky, MD[3]

[1]*Seattle Children's Research Institute, Seattle, WA,* [2]*University of Washington, Seattle, WA,* [3]*University of Washington, Seattle , WA*

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NR 47 (1758)
Ketamine Reduces Post-Traumatic Brain Injury Neurogenesis and Improves Outcomes in Mice

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

[1]*OHSU, Portland, OR,* [2]*StonyBrook University, New York, NY*

Neuroscience in Anesthesiology and Perioperative Medicine: Group 9

Moderator: Jeffrey Sall, PhD, MD, University of California San Francisco, San Francisco, California

Resident Travel Award Winner

NR 48 (1310)
Sensitivity to Volatile Anesthetics Predicts Postoperative Delirium

Bradley A. Fritz, MD[1]; Hannah Maybrier, BS[1]; Michael S. Avidan, MBBCh[1]

[1]*Washington University School of Medicine at St. Louis, St. Louis, MO*

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NR 49 (1795)
Innate Immunity is Required for Neuronal Regeneration After Cerebral Ischemia

Ines P. Koerner, MD, PhD[1]; Rumie Wakasaki, MD, PhD[1]; Eric Schnell, MD, PhD[1]

[1]*OHSU, Portland, OR*

Margaret Wood Resident Research Award Winner

NR 50 (1707)
Weak EEG α-Power During General Anesthesia as a Marker of Delirium in the PACU

Matthias Kreuzer, PhD[1]; September Hesse, PhD[1]; Darren Hight, BPhEd[2]; Jamie Sleigh, MBChD MD[2]; Paul S. Garcia, MD, PhD[1]

[1]*Emory University/VAMC Atlanta, Decatur, GA,* [2]*Waikato Hospital, Hamilton, AK*

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Neuroscience in Anesthesiology and Perioperative Medicine: Group 9, *continued*

NR 51 (1640)
Ubiquitin-Proteasome Associated Mechanisms of Sevoflurane-Induced Cognitive Impairment in Young Mice

Han Lu, MD, PhD[1]; Yuanlin Dong, MD[2]; Yiying Zhang, MD[3]; Buwei Yu, MD, PhD[4]; Zhongcong Xie, MD, PhD[3]

[1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital and Harvard Medical School, Boston, MA, [4]Columbia University New York Presbyterian Hospital, New York, NY

NR 52 (1632)
The Influence of Catastrophizing, Anxiety and Depression On Opioid Consumption, Postoperative Pain and Quality of Recovery after Adult Spine Surgery

Bhiken Naik, MBBCh[1]; Lauren K. Dunn, MD, PhD[1]; Marcel Durieux, MD, PhD[1]; Siny Tsang, PhD[2]; Edward Nemergut, MD[1]

[1]University of Virginia Health System, Charlottesville, VA

Pain Medicine and Regional Anesthesia: Group 10

Moderators: Lucy L. Chen, MD, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts; and Jianguo Cheng, MD, PhD, Cleveland Clinic, Cleveland, Ohio

PM 53 (1439)
AMPAkines as Novel Analgesics in Rat Pain Models

Jing Wang, MD, PhD[1]; Chen Su, MD[1]; Hau Lin, BA[1]; Runtao Yang, BA[1]; Kevin Liu, BA[1]

[1]New York University School of Medicine, New York, NY

PM 54 (1664)
Widespread Pain Three Months after Traumatic Injury: Preliminary Results

Elisabeth Powelson, MS MD[1]; Vivian Lyons, MPH[1]; Millie Boyd, BS[1]; William Henderson-Drager, BS[1]; Michele Curatolo, MD, PhD[1]; Monica Vavilala, MD[1]

[1]University of Washington, Seattle, WA

PM 55 (1563)
Intraoperative Esmolol Decreases Intraoperative Opioid Use, PACU Opioid Use, and PACU Pain Scores: A Systematic Review, Meta-Analysis, and Meta-Regression

Anthony (Tony) Anderson, PhD, MD[1]; Amanda M. Gelineau, MD[1]; Michael R. King, MD[2]; Karim Ladha, MD[3]; Sara M. Burns, MS[1]; Timothy Houle, PhD[1]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [3]Toronto General Hospital, Toronto, OH

RA 56 (1126)
Comparison of Ultrasound Guided Paravertebral Block with Serratus Plane Block for MRM

Kapil Gupta, MBBS, DA, DNB[1]; Vincent Chan, MD, FRCPC, FRCA[1]

[1]Toronto Western Hospital, Toronto, Ontario, Canada

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Pain Medicine and Regional Anesthesia: Group 10, *continued*

RA 57 (1714)
RCT of US-Paravertebral vs US-Proximal Intercostal Block in Mastectomy Patients

Kristin Schreiber, MD, PhD[1]; Avery Williams-Vafai, MD[1]; Atif Chowdhury, MD[1]; David Ende, MD[1]; Jose Zeballos, MD[1]; David Janfaza, MD[1]; Kamen Vlassakov, MD[1]

[1]*Brigham and Women's Hospital, Boston, MA*

RA 59 (2243)
Ultrasound Guided Single Injection Quadratus Lumborum Block for Postoperative Pain Control in Patients Undergoing Total Hip Arthroplasty

Ayesha Hameed, MD[1]; Ezra Kassin, MD[1]; Lucas Bejar, MD[1]; Oonagh Dowling, PhD[2]

[1]*Northwell Health System, New Hyde Park, NY,* [2]*Hofstra Northwell School of Medicine, New Hyde Park, NY*

Perioperative Anesthesia: Group 11

Moderator: Holger K. Eltzschig, MD, PhD, The University of Texas Health Science Center at Houston, Houston, Texas

PA 61 (2078)
Enhanced Recovery After Surgery (ERAS) – An Assessment Six Months After Discharge

Thomas J. Deiss, BS[1]; Ankit Sarin, MD[1]; Ramana Naidu, MD[1]; **Lee-Lynn Chen, MD**[1]

[1]*University of California, San Francisco, San Francisco, CA*

PA 62 (2153)
A Comparison of the Responses and Utility of the Capuzzo Likert-Based and Modified Bauer/Brice Perioperative Satisfaction Scales

Scott Segal, MD[1]; Timothy Harwood, MD[1]

[1]*Wake Forest University Health Sciences, Winston-Salem, NC*

PA 63 (1977)
Blood Gas Analyzer Glucose Measurement Accuracy

Yafen Liang, MD[1]; Jonathan Wanderer, MD[1]; James Nichols, PhD[1]; David Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE[2];

[1]*Vanderbilt University Medical Center, Nashville, TN,* [2]*Mills-Peninsula Health Services, San Mateo, CA*

PA 64 (2222)
Effect of Using the Taperguard Endotracheal Tube on the Prevention of Postoperative Ventilator Associated Pneumonia

Ross Martini, MD[1]; Cobin Soelberg, MD JD[1]; Praveen Tekkali, BS[1]; N. David Yanez, PhD[1]; Miriam Treggiari, MD, PhD[1]; Michael Aziz, MD[1]

[1]*Oregon Health and Science University, Portland, OR*

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Poster Presentation Schedule, *continued from page 117*

Perioperative Anesthesia: Group 11, *continued*

PA 65 (1953)
Utility of Scoring Tools and Type of Surgery in Predicting Complications and 30-day Readmission in a Urology Perioperative Surgical Home

J. Matthias Walz, MD[1]; Jaclyn K. Longtine, BA[1]; Dane Netherton, PhD[2]; Arlene A. Ash, PhD[2]; Khaldoun Faris, MD[3]; Mitchell Sokoloff, MD[3]; Shubjeet Kaur, MD[3]

[1]University of Massachusetts Medical School, Worcester, MA, [3]UMass Memorial Medical Center, Worcester, MA

Translational / Bench Science: Group 12

Moderator: Wei Chao, MD, PhD, FAHA, University of Maryland School of Medicine, Baltimore, Maryland

Junior Faculty Research Award Winner

TRSL/BS 66 (1985)
Implication of LDL Receptors in the Development of Pulmonary Hypertension

Soban Umar, MD, PhD; Mylene Vaillancourt, MSc; Christine Cunningham, BSc; Shayan Moazeni, BSc; Gregoire Ruffenach, PhD; Aman Mahajan, MD, PhD; Mansoureh Eghbali, PhD

University of California Los Angeles, Los Angeles, CA

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TRSL/BS 67 (1447)
Post-Injury Neurogenesis Drives Aberrant Hippocampal Circuit Function in Mice

Eric Schnell, MD, PhD[1]; William D. Hendricks, BA[2]; Laura E. Villasana, PhD[3]; Austin Peters, MD[3]; Gary L. Westbrook, MD[2]

[1]VA Portland / OHSU, Portland, OR, [2]Vollum Institute, Portland, OR, [3]OHSU, Portland, OR

TRSL/BS 68 (1783)
Spinal Cord Stimulation Reduces Ventricular Arrhythmias During Acute Ischemia Through Attenuation of Regional Myocardial Excitability in a Porcine Model

Kimberly Howard-Quijano, MD, MS[1]; Tatsuo Takamiya, MD[1]; Erica Dale, PhD[1]; Jasmine Kipke, BS[1]; Yukiko Kubo, MD[1]; Tristan Grogan, MS[1]; Aman Mahajan, MD, PhD[1]

[1]University of California at Los Angeles, Los Angeles, CA

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TRSL/BS 69 (1402)
Ketamine Resistance in Mice with Neuronal Type-Specific Knock Out of a Mitochondrial Protein

Charles W. Carspecken, MD, MSc, MBA[1]; Margaret Sedensky, MD[1]; Franck Kalume , PhD[2]; Philip Morgan, MD[1]

[1]University of Washington, Seattle Children's Research Institute, Seattle, WA, [2]Seattle Children's Research Institute, Seattle, WA

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Poster Presentation Schedule, *continued from page 118*

Translational / Bench Science: Group 12, *continued*

TRSL/BS 70 (1338)
Bitter Taste Receptors in Airway Smooth Muscle Cells of a Cystic Fibrosis Mouse Model

Nicholas M. Dalesio, MD[1]; Seakwoo Lee, PhD[1]; Steven An, PhD[2]; Charles W. Emala, MD[3]; Pamela L. Zeitlin, MD[4]; Daniel Berkowitz, MD[1]

[1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins School of Public Health, Baltimore, MD, [3]Columbia University, New York, NY, [4]National Jewish Health, Denver, CO

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Translational / Bench Science, Trauma, Critical Care, and Technology, Computing and Simulation, Equipment Monitoring: Group 13

Moderators: Warren Sandberg, MD, PhD, Vanderbilt University, Nashville, Tennessee

TRSL/BS 71 (1255)
Attenuation of Airway Contraction In Vivo in Mice by Inhalation of Gelsolin Peptide

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

[1]Columbia University, New York, NY

TRSL/BS 72 (1331)
Sterile Lung Inflammation Augments Bacterial Clearance in Mice via NLRP3 Inflammasome

Arun Prakash, MD, PhD[1]; Xiaoli Tian, PhD[1]; Judith Hellman, MD[1]

[1]UCSF, San Francisco, CA

TRSL/BS 73 (1109)
Identification of a New Pulmonary Spinal Sympathetic Afferent Reflex in Rodents

Hanjun Wang, MD[1]; Irving H. Zucker, PhD[1]; Zhiqiu Xia, MD[1]; Julia Shanks, PhD[1]; George J. Rozanski, PhD[1]; Andrew J. Patterson, MD, PhD[1]; Steven J. Lisco, MD[1]

[1]University of Nebraska Medical Center, Omaha, NE

TRSL/BS 74 (1332)
A Novel GABA-A Receptor α-Subunit-Selective Ligand Relaxes Mouse and Human Airway Smooth Muscle

Gene Thomas Yocum, MD[1]; Peter Yim, MD[1]; Yi Zhang, MD[1]; Jose F. Perez-Zoghbi, PhD[1]; Alexander Arnold, PhD[2]; James Cool, PhD[2]; Charles W. Emala, MD[1]

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

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Translational / Bench Science, Trauma, Critical Care, and Technology, Computing and Simulation, Equipment Monitoring: Group 13, *continued*

T 75 (1933)
Down-Regulation of Angiopoietin-1 Mediates Neuronal Cell Death Following Experimental Traumatic Brain Injury in Mice

Bogdan Stoica, MD[1]; Boris Sabirzhanov, PhD[1]; Tarryn Aubrecht, PhD[1]; Rebecca Henry, PhD[1]; Alan Faden, MD[1]

[1]*University of Maryland School of Medicine, Baltimore, MD*

T 76 (1277)
Alcohol-Impaired Driving in US Counties, 2002-2012

Jacob Sunshine, MD, MS[1]; Laura Dwyer-Lindgren, PhD[2]; Alan Chen, BS[2]; Sam Sharar, MD[1]; Ali Mokdad, PhD[2]

[1]*University of Washington, Seattle, WA,* [2]*Institute for Health Metrics and Evaluation*

T 77 (1770)
Neuropathology and Behavioral Deficits in a Rat Model of Brain Injury to Occupants of Vehicles Targeted by Land Mines: Mitigation by Shock-Absorbing Hull Designs

Flaubert Tchantchou, PhD[1]; Ulrich Leiste, PhD[2]; Adam Puche, PhD[1]; William Fourney, PhD[2]; Gary Fiskum, PhD[1]

[1]*University of Maryland School of Medicine, Baltimore, MD,* [2]*University of Maryland College Park, College Park, MD*

CC 78 (1713)
Testing a Novel Manual Communication System for Mechanically Ventilated ICU Patients

Miriam A. Goldberg, M.Eng[1]; Leigh R. Hochberg, MD, PhD[2]; Dawn Carpenter, NP[1]; Johnny Isenberger, MSN[1]; Stephen Heard, MD[1]; J. Matthias Walz, MD[1]

[1]*University of Massachusetts Medical School, Worcester, MA,* [2]*Brown University, Providence, RI*

TCSEM 79 (1719)
Principles of Augmentative & Alternative Communication System Design in the ICU Setting

Miriam A. Goldberg, M.Eng[1]; Leigh R. Hochberg[2], Dawn Carpenter[1], Johnny Isenberger[1], Stephen Heard[1], J. Matthias Walz[1]

[1]*University of Massachusetts Medical School, Worcester, MA,* [2]*Brown University, Providence, RI*

Poster Presentations

AP 1 (1431)
A Comparative Efficacy Trial of Intravenous vs. Oral Acetaminophen in Sinus Surgery

Ravi Bhoja, MD[1], Matthew Ryan, MD[1]; Kevin Klein, MD[1]; Bradley Marple, MD[1]; Abu Minhajuddin, PhD[1]; David McDonagh, MD[1]

[1]*UT Southwestern Medical Center, Dallas, TX*

Introduction: Acetaminophen is recommended as a part of a balanced peri-operative multimodal analgesic approach and is available in oral (PO) and intravenous (IV) formulations[1]. The comparative clinical efficacy of preoperative PO versus intraoperative IV administration remains an open question in functional endoscopic sinus surgery (FESS). IV acetaminophen has higher bioavailability, avoids first-pass hepatic metabolism, and generates higher serum and CSF levels than PO acetaminophen[2,3]. However, such divergent pharmacokinetics may not always lead to clinically significant differences in analgesic effect[4]. Furthermore, preoperative PO administration may provide additional benefits since it is given 'preemptively' with regards to surgical stress[5]. The current study was designed to compare the clinical efficacy of PO vs. IV acetaminophen in patients undergoing FESS. Based on the pharmacokinetic data, our primary hypothesis was that patients receiving IV acetaminophen would have less post-operative pain than those receiving PO.

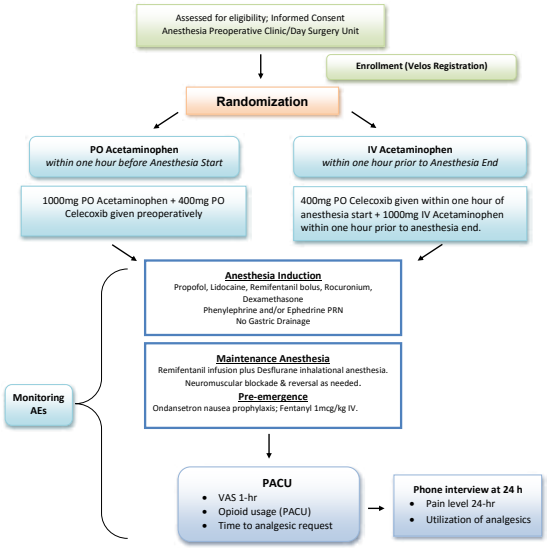

Figure 1. Study design for the comparative efficacy of PO vs. IV acetaminophen

Methods: This was a prospective randomized clinical trial conducted at a single large academic medical center, and the protocol was approved by the institutional IRB. Adult patients undergoing FESS were randomized into two groups: one receiving PO acetaminophen before anesthetic induction and one receiving IV acetaminophen intraoperatively prior to emergence. All patients underwent a standardized general anesthetic protocol and all received preoperative PO celecoxib (Fig. 1). The primary endpoint was the visual analog scale pain score (VAS, 0-100mm) obtained 1-hour post-operatively. Secondary outcome measures included VAS scores at 24-hours post-operatively and opioid usage following surgery. A 15mm change in the VAS was deemed clinically significant requiring a calculated 45 patients per group to provide 80% power (1-Î²) at a 0.05 level of significance (Î±)5. To allow for up to 20% loss to follow-up due to the given ambulatory patient population, 110 patients were enrolled. Statistical analysis was performed using the Wilcoxon test (SAS version 9.3, SAS Inc., Cary, NC).

Results: Nine patients were excluded from the 110 enrolled patients (1 lost to follow up; 4 did not receive acetaminophen; 4 did not receive celecoxib). Fifty patients were randomized to the IV group, and 51 to the PO group. VAS median and interquartile ranges were determined for the PO and IV groups at 1-hour and 24-hour postoperative time points. The median VAS scores were similar in the two groups and at both time points (Figs. 2 and 3). There was no significant difference between PO and IV groups in regards to: total opioid use in the PACU (p=.402), time to first analgesic request in the PACU (p=.237), and 24-hour opioid use (p=.184).

Conclusion: This is the first comparative efficacy trial of oral vs. IV acetaminophen in FESS. Overall, intraoperative IV acetaminophen offers no apparent analgesic advantage over preoperative PO acetaminophen in sinus surgery patients.

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ww4.aievolution.com/ars1701/files/content/abstracts/abs_1431/Figure1.pdf

AP 2 (2077)
Mapping the Orientation and Site of Neurosteroid Binding in GLIC, a Pentameri Ligand-Gated Ion Channel

Wayland W. Cheng, MD, PhD[1], Zi-wei Chen, PhD[1]; Melissa Budelier, BSc[1]; Douglas Covey, PhD[1]; Gustav Akk, PhD[1]; Alex Evers, MD[1]

[1]*Washington University, Saint Louis, MO*

Introduction: Neurosteroids are endogenous brain sterols that modulate pentameric ligand gated ion channels (pLGICs), and exogenously administered neurosteroid analogues are potent general anesthetics. Knowledge of the stoichiometry, orientation and sites of neurosteroid binding to pLGICs is essential for understanding the mechanism of neurosteroid action and structure-based drug design. We used a series of neurosteroid photolabeling reagents with the photo-reactive moiety in different positions of the sterol backbone to map the orientation and site of neurosteroid binding in the pH-gated Gleobacter ligand gated ion channel, GLIC. Neurosteroid-photolabeled GLIC was characterized using top-down mass spectrometry (MS), a technique that analyzes intact proteins and permits determination of the efficiency and stoichiometry of photolabeling.

Methods: Purified GLIC was photolabeled with 100 Î¼M of (3Î±,ï¡ï€¬5Î±ï¡)-3-hydroxypregnane neurosteroid reagents with a diazirine in positions 6, 12, 15, and 20 (5Î±ï¡-6-AziP, 5Î±ï¡-12-AziP, 5Î±ï¡-15-AziP, and 5Î±ï¡-20-AziP). Photolabeled GLIC samples were analyzed with top-down MS by direct injection in an Elite LTQ mass spectrometer. Raw spectra were deconvoluted to the 'zero charge' state to identify unlabeled and labeled GLIC features, and analyzed to determine the efficiency and stoichiometry of photolabeling. To localize the sites of photolabeling, photolabeled protein was fragmented with higher energy collisional dissociation (HCD) and fragment ions analyzed in an Orbitrap mass analyzer. Photolabeled GLIC was also digested in-solution with trypsin and digests analyzed by LC-MS/MS. Neurosteroid analogue modulation of GLIC function was assessed by two-electrode voltage-clamp of Xenopus oocytes injected with GLIC cRNA. Oocytes were harvested from frogs with ASC approval.

Results: The photolabeling efficiency of 5Î±ï¡-6-AziP (38%) for GLIC was markedly higher than 5Î±ï¡-12-AziP, 5Î±ï¡-15-AziP, and 5Î±ï¡-20-AziP (photolabeling efficiencies of 12%, 7%, and 12%, respectively). These reagents were found to be equally photo-reactive, based on their ability to non-specifically photolabel the peptide, YGGFLRF, with similar efficiency. Also, currents from GLIC elicited by pH 5.5 were inhibited by 5Î±ï¡-6-AziP, 5Î±ï¡-12-AziP, and 5Î±ï¡-15-AziP with comparable potency (estimated IC 50s of 44 Î¼M, 16 Î¼M, and 39 Î¼M, respectively), suggesting that the lower photolabeling efficiencies in 5Î±ï¡-12-AziP and 5Î±ï¡-15-AziP compared to 5Î±ï¡-6-AziP are not due to lower binding affinities. 5Î±ï¡-20-AziP was a weak inhibitor of GLIC (estimated IC 50> 100 ïÎ¼M). Top-down analysis of GLIC photolabeled with 5Î±ï¡-6-AziP showed a stoichiometry of two photolabeled residues per subunit. Top-down fragmentation and MS/MS analysis of tryptic digests localized both photolabeled residues to a site in the C-terminal end of transmembrane domain 3 (TM3).

Conclusion: Neurosteroids inhibit GLIC channel activity, and bind GLIC in a specific orientation with the 6-position of the neurosteroid in closest proximity to the photolabeled site. This site is located in the intracellular side of TM3 analogous to a site previously identified in the Î²ï¢3 homomeric GABAA receptor [(1)]..

References:

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Poster Presentations, *continued from page 122*

AP 3 (1510)
Isoflurane Modulates Activation and Inactivation Gating of the Prokaryotic Na+ Channel NaChBac

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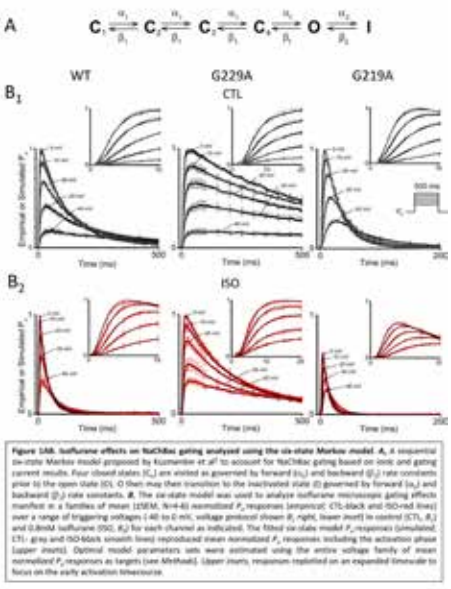
Introduction: Voltage-gated Na+ channels (Nav) have emerged as important presynaptic targets for volatile anesthetic (VA) effects on synaptic transmission. VAs alter macroscopic activation and inactivation of the prokaryotic Na+ channel NaChBac, which is useful as a structural and functional model of mammalian Nav. A recent study proposes that the ether VA sevoflurane inhibits NaChBac through open channel block.[1] However, detailed biophysical mechanisms by which ether VAs modulate Nav function remain unclear. We studied the effects of the common ether VA isoflurane on NaChBac function by analyzing macroscopic Na+ currents (INa) in wild-type (WT) and mutated NaChBac with impaired (G229A) or enhanced (G219A) inactivation.



Methods: Wild-type (WT) NaChBac cDNA (Bacillus halodurans) was modified by introducing two known point mutations in the S6 helix: G219A accelerates and G229A slows inactivation, respectively.[2] cDNA clones were confirmed by sequencing and were expressed heterologously in HEK293T cells. INas were measured by whole-cell patch-clamp electrophysiology. We collected INa families over a range of triggering voltages (ˆ'40 to 0 mV) for each channel in the absence and presence of isoflurane. Activation and steady-state inactivation curves were determined. We analyzed microscopic channel gating using a recognized six-state Markov model3(Fig. 1A), which includes parameters describing the voltage dependence of gating (z1 and z2 are the valences of activation and inactivation transitions; x1 and x2 are fraction of the electric field where the energy barrier peak is located for inactivation and inactivation respectively). Currents were adjusted for driving force resulting in responses reflecting channel open probability (Po), which were normalized to the peak of the 0 mV response in control (or in isoflurane if it was greater) to yield families of normalized Po responses. Model differential equations were solved using MATLAB v7.5 (The MathWorks, Natick, MA) and model parameters were estimated using the Levenberg–Marquardt method to solve iteratively for an optimal fit to a family of mean normalized Po responses.

Results: Isoflurane accelerated activation and inactivation, and shifted conductance and steady-state inactivation curves in the hyperpolarizing direction for WT and G219A. The six-state Markov model reproduced gating for all three channels in the absence or presence of isoflurane (Fig. 1B), thereby supporting model application. Isoflurane increased forward activation (Î±1), and inactivation (Î±2) rate constants at 0 mV associated with estimated chemical free energy changes of ~-0.2 and ~-0.7 kcal/mol, respectively (Fig. 1C). Activation was voltage-dependent (z1 ‰ˆ 2e0, x1 ‰ˆ 0.3), inactivation showed little voltage dependence, and isoflurane had little effect on either. Forward inactivation rate constants were more than 20-fold greater than backward rate constants for control and isoflurane.

Conclusion: These results indicate that isoflurane modulates NaChBac gating primarily by increasing forward activation and inactivation rate constants, which supports accumulating evidence for multiple sites of anesthetic interaction with the channel.

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Poster Presentations, *continued from page 123*

AP 4 (1952)

H-Bond Propensity, Molecular Volume and Ring Ï€-Electrons/Planarity Differentially Determine if Propofol-Like Molecules are Inverse A of HCN1 Channel Opening or Competitive Antagonists Thereof

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Introduction: Inhibition of HCN1 is anti-hyperalgesic in multiple animal models of neuropathic pain[1]. Propofol and the non-anesthetic 2,6-di-tert-butylphenol (26DTBP) potently and robustly inhibit gating of HCN1 channels by stabilizing closed state(s) via an interaction with the membrane-embedded channel core[2,3]. Here, we systematically examine the functional importance of each of the structural motifs of propofol and 26DTBP and demonstrate that the HCN1 alkylphenol site is a druggable target. These findings open the way to generate a novel class of non-opioid therapeutics.

Methods: Prior to two-electrode voltage clamp, Xenopus oocytes expressing HCN1 channels were incubated for 20 min in a standard frog Ringer solution containing DMSO alone (0.2% v/v) or vehicle plus ligand. Tail current amplitudes were fit with the Boltzmann function. Drug-induced shifts in the mid-point of gating (Î"V1/2) were fit with the Hill function to determine EC 50 or with a series of equations derived from a highly-constrained 6 parameter, 45-state model (Fig 1).

Results: Four key characteristics that define alkylphenols and alkylhexanols (hydrophobicity, molecular volume, hydrogen bond propensity, and ring saturation/planarity) all influence the interaction between the ligands and the HCN1 channel (Figs 2-4). With optimal alkyl groups (apparently iso-propyl or tert-butyl) in the 2,6 position, conversion of the 1-position -OH to an -SH, -NCO or -F results in progressive loss of potency with no obvious diminution of efficacy (Figs 2,3). Increasing the size of the 2,6-alkyl groups serves to increase both hydrophobicity and molecular volume. While it is difficult to experimentally separate these properties, it is possible to consider this post hoc. A plot of the effective EC 50 (aqueous EC 50 multiplied by the calculated accumulation ratio) versus molecular volume (Fig 4) reveals a dependence on molecular volume consistent with a 'cut-off' phenomena. There are indications that the cut-off effect is associated with reduced efficacy when the side chains are smaller than optimal. Saturation of the ring with the concomitant loss of planarity and Ï€ electrons decreases efficacy; again, this occurs in a 2,6 side chain-dependent manner. In the background of di-iso-propyl, the cyclohexanol is a partial inverse agonist while in the background of di-tert-butyl the cyclohexanol exhibits no inverse agonist activity at all (Figs 3,4). Critically, 2,6-di-iso-propyl cyclohexanol is not additive with sub-maximal 26DTBP (not shown) while 2,6-di-tert-butyl cyclohexanol suppresses 26DTBP inverse agonism (Fig 5). Fits of a gating model wherein the cyclohexanol derivatives are represented as having lost some or all of the coupling energy with no diminution of initial binding energy well describes the observed data.

Conclusion: These findings suggest an H-bond acceptor at position 1 contributes to initial binding energy but not coupling energy while ring planarity and/or Ï€ electrons contribute to coupling energy but are not the sole determinant – molecular geometry and/or van der Waal interactions based on the 2,6-side chains likely also contribute. These findings suggest a higher potency analogue with drug-like properties can be developed, particularly as the HCN1 crystal structure is now available4. Such a molecule could point the way to an opioid-free treatment for neuropathic pain.

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Poster Presentations, *continued from page 124*

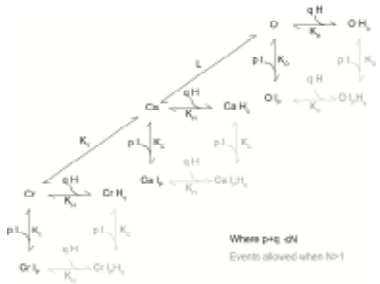

Figure 1: Alkylphenol interaction with HCN1 channel activation modeled as coupling of inverse agonists and competitive antagonists.

Cr, Ca and O represent the closed-resting, closed-activated and open states; Kv and L the equilibrium constants describing activation and opening; I and H an inverse agonist and a competitive antagonist thereof where p and q represent the number of binding events of I and H. For simplicity, only activation and opening transitions between unliganded states are shown but all Cr-Ca and Ca-O transitions are permissible. With N=1 the model contains 9 states, when N=4 there are 15 states per plane, 45 states in total. Importantly, three simple assumptions reduces the number of free parameters to 3 irrespective of N. Where A = (1+[I]Ko) / (1+[I]Kc) and B = (1+[I]Ko+[H]Kh) / (1+[I]Kc+[H]Kh), equations 1 and 2 describe $\Delta V_{1/2}$ in the presence of I alone or I plus H. Ko is defined as Kc/F where F is the fold loss of affinity upon channel opening.

1. $\Delta V_{1/2}$ (I) = $25.4/Z * \{Ln[1+L*A^N] - Ln[1+L]\}$
2. $\Delta V_{1/2}$ (I-H) = $25.4/Z * \{Ln[1+L*B^N] - Ln[1+L]\}$

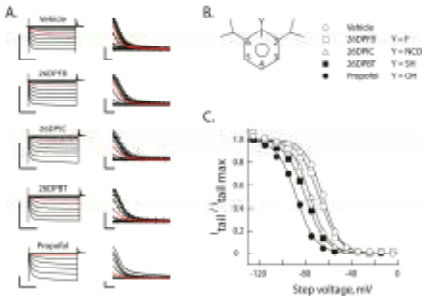

Figure 2: Hydrogen bond functionality at position 1 is important for alkylbenzene inhibition of HCN1 gating.

- **A.** Representative recordings of HCN1 following incubation for 20 min in the absence or presence of 10 μM of the indicated reagent. All recordings were obtained on the same day from a single batch of oocytes. Scale bars are 2 μA and 1s (left) and 200 nA and 50 ms (right).
- **B.** Schematic representation of 2,6-di-*iso*-propylbenzenes. Substitutions at the one position as per the legend describe molecules reported in A and C.
- **C.** Normalized steady-state activation curves constructed from the records shown in A. The smooth lines are fits of the Boltzmann function. Symbols represent molecules as described in B.

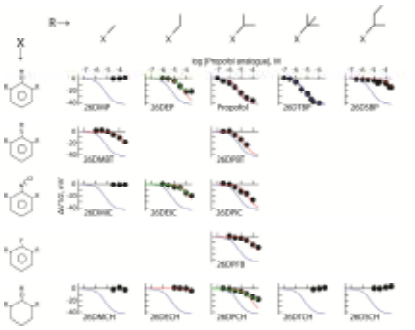

Figure 3: HCN1 inhibition by propofol derivatives reveals hydrogen bond potential, alkyl side chain identity and the presence or absence of Pi electrons (and/or ring planarity) all contribute to the coupling between the ligand(s) and the channel.

Panels show the shift in the $V_{1/2}$ as a function of concentration of each of the indicated ligands. The blue lines are the fit of the Hill equation to 26DTBP. The red lines are the 26DTBP fit adjusted by eye to the observed data, in each case only the EC_{50} was changed. Where present, the green lines are fits of the Hill function to those data sets that appeared to display partial behavior as inverse agonists. All data are mean ± SEM with 6 or more determinations per point.

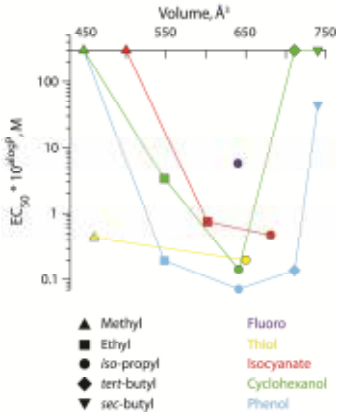

Figure 4: Inverse agonist potency of propofol analogues as a function of molecular volume.

The corrected EC_{50} (aqueous EC_{50} determined from manually adjusted Hill curves in Figure 3 multiplied by the calculated accumulation ratio) plotted as a function of the calculated molecular volume. For ligands where no inflection was observable in the concentration response curve, the corrected EC_{50} was set equal to 300M.

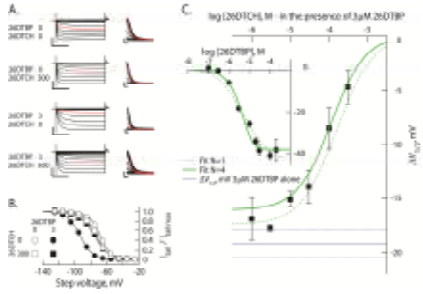

Figure 5: 26DTCH acts as a competitive antagonist of 26DTBP .

- **A.** Representative TEVC records from cells expressing HCN1 following incubation in the indicated concentrations (μM) of 26DTBP and 26DTCH. Recordings were obtained on the same day with cells from a single donor frog. Scale bars are 2.5μA and 1s (left) and 200nA and 50ms (right).
- B. Normalized steady-state activation curves constructed from the records shown in A. The smooth lines are fits of the Boltzmann function.
- C. $\Delta V_{1/2}$ as a function of concentration of 26DTCH in the presence of 3μM 26DTBP. The $\Delta V_{1/2}$ elicited by 3μM 26DTBP is indicated by the solid blue line, dashed blue lines represent the SEM around this measure. Data in the inset are reproduced from Figure 3. Solid green lines are from simultaneous fits of the model to both data sets with $K_H=K_O$, N=4, the dashed green lines are fits of the model with $K_H=K_O$, N=1. At N=1 the model is poorly determined, at N=4 F=18 ± 7, L=67 ± 9, Kc=$2.2x10^5$ ± $2.5x10^4$. Fitting with $K_H=K_C$ did not yield reasonable fits and was not robust, it readily resulted in failure of the algorithm.

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Poster Presentations, *continued from page 125*

AP 5 (2061)
Development and Validation of Pharmacokinetic Model for Propofol in Mice

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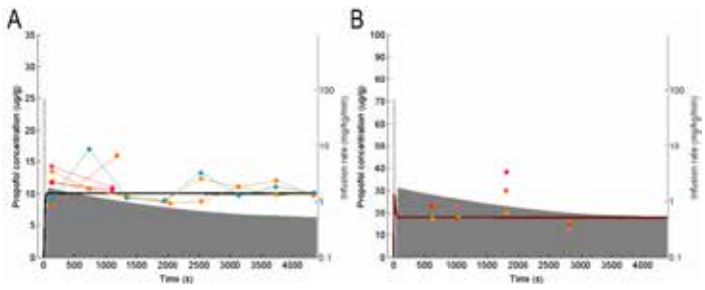
Introduction: Despite the fact that the molecular mechanisms of anesthetic action are becoming elucidated, little is known about the processes through which anesthetics disrupt neural activity and lead to a state of unconsciousness. In order to investigate these processes, it is essential to have tight control over anesthetic pharmacology in an animal model that can be readily used in neurophysiological investigations. Therefore, we developed a pharmacokinetic model for propofol in mice and demonstrated that our model can be used to maintain a fixed brain propofol concentration.

Methods: Repeated measurements of brain and blood propofol concentration were performed in adult male C57BL/6 mice. A three compartment pharmacokinetic model was used to fit these data using an iterative process. MATLAB-based software was written to deliver a target-controlled infusion aimed at maintaining a fixed brain propofol concentration was developed and implemented by interfacing the software with a syringe pump. Validity of the target controlled infusion was confirmed with measurements of brain propofol concentrations.

Results: With an infusion based upon our pharmacokinetic model, we were able to rapidly attain and maintain a targeted brain propofol concentration. When targeted concentration was 10 Î¼g/g, measured brain concentration was 10.9 ± 2.1 Î¼g/g ($p > 0.05$), and, throughout the hour-long infusion, the measured brain concentration was maintained at the targeted concentration (median 11.38 Î¼g/g over first 20 minutes vs. 10.66 Î¼g/g after 40 minutes, $p=0.28$). Additionally, the slope of the linear fit to the measurements was indistinguishable from zero.



PK model used to attain and maintain a fixed brain propofol concentration. All of our data were fit together to produce a final set of pharmacokinetic rate constants. Shown here are the data collected from the set of experiments done using these rate constants which give rise to an accurate target controlled infusion model for predicting propofol concentration in the mouse brain. The model targets 10 µg/kg in brain tissue. (A) Brain data. Connected points are the concentrations measured in the brain samples collected from a single subject. (B) Blood data. Points that are the same color were collected from the same subject, and the points are not connected because there are only two per subject. The shaded gray area shows the infusion rate across time and is plotted on a log scale shown on the right y-axis. Heavy black (A) and red (B) lines show the concentration predicted by this final set of rate constants for the brain and blood, respectively. For the brain data, the slope of the measured data was calculated as $-3x10^{-4}$ ($\mu g \cdot g^{-1} \cdot s^{-1}$) with a 95% confidence interval of [$-9x10^{-4}$, $2x10^{-4}$]. Therefore, a slope of zero is within the 95% confidence interval, and we cannot detect any significant time-dependent variance in propofol concentration.

Conclusion: Our contribution here is the creation and validation of pharmacokinetic model for propofol in mice. Mice are commonly used in studies of anesthetic action, and a wide array of genetic tools for interrogating and manipulating neural activity exist for mice. The ability to reliably fix brain anesthetic concentration at a desired level, as we have accomplished here, will allow for future studies of the processes through which anesthetics alter brain activity.

References:

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AP 6 (1180)
Propofol Potently Impedes Processive Kinesin Motion via an Allosteric Binding Site

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Introduction: Previous work has suggested involvement of the cytoskeleton and intracellular trafficking machinery in anesthetic action, but evidence for direct, target-specific effects has been modest. Neglected has been a potential contribution from interactions with the molecular motors, multi-subunit proteins that are responsible for attaching and transporting cargos along microtubules (MT) via processive 'stepping'. We hypothesize that processive kinesins bind anesthetics like propofol, weakening interactions with Î²-tubulin, resulting in detachment from the MT, thereby impeding anterograde cargo delivery in the CNS. Cargos of this motor family include mitochondria, GABAA receptors, neurotransmitter receptors, and synaptic vesicle precursors.

Methods: We employed three approaches to evaluate this hypothesis. 1) Single molecule TIRF microscopy assays to assay movement along MT for dimeric KIF-3 (A/B, A/A, or A/C) with and without various concentrations of propofol, aziPm (1) and of fropofol (2). 2) Photolabeling experiments with aziPm of dimeric kinesin (KIF-3A/C; A/B) alone, MT ·KIF3 complexes without nucleotide, and MT ·KIF3 complexes with nucleotide (AMPPNP), which traps kinesins onto the MT. 3) Fluorescent mitochondrial movement assays in cultured MDCK epithelial cells with and without 10 µM propofol.

Results: In approach 1), propofol and aziPm significantly shortened kinesin run-length (increased detachment) (EC50s of ~0.1 µM) with no effect on velocity. Fropofol had no effect at any concentration. In approach 2), significantly greater photoincorporation of 3H-aziPm into KIF-3A/B or A/C was observed in the presence of MTs + AMPPNP. Detected with mass spectrometry, several adducted residues defined two distinct binding sites on KIF-3B or C, both allosteric to the nucleotide site and to the interface with Î²-tubulin. No photomodifications were found on KIF-3A. Finally, fluorescence organelle tracking revealed more detached mitochondria and greater perinuclear distribution in the presence of propofol.

Conclusion: Our results demonstrate specific, conformationally sensitive propofol binding sites on dimeric KIF-3 that likely underlie reduced anterograde delivery of cargos via weakened interactions with Î²-tubulin. Kinesin subunit specificity suggested by approach 2) was verified by a complete lack of propofol effect on KIF-3A/A processivity using approach 1) methods. The kinesin-2 family is ideally positioned to have far reaching consequences on cellular/neuronal function, and the lack of effects of the nonanesthetic molecule fropofol render it a plausible functional direct target of propofol.

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Poster Presentations, *continued from page 127*

AP 7 (1108)
Molecular Mechanism of Stimulation of the Metabolism of Anesthetics by Cyt P450 2B4

Lucy Waskell, MD, PhD[1], Naw May Pearl, PhD[1]; Jarett Wilcoxen, PhD[2]; Sangchoul Im, MD, PhD[1]; Ryan Kunz, PhD[3]; R. D. Britt, PhD[2]; Stephen Ragsdale, PhD[1]

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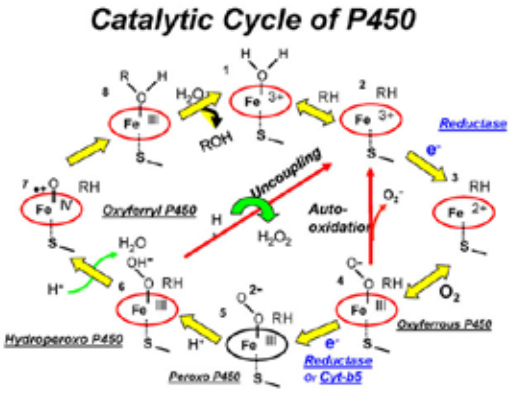
Introduction: Approximately 20 microsomal human cytochromes P450 (cyt P450) are major determinants of the efficacy, duration of action, and toxicity of the majority of drugs used by anesthesiologists. Early studies demonstrated that the metabolism of volatile anesthetics by cyt P450 2B4 was markedly stimulated by cytochrome b5 (cyt b5).[1] Meanwhile, other investigators had observed that cyt b5 could either stimulate, inhibit, or have no effect on the metabolism of a variety of drugs, hormones, and vitamins depending on the cyt P450 and the particular substrate. In an effort to elucidate the puzzling molecular mechanism of the stimulatory effect of cyt b5 on anesthetic metabolism by cyt P450 2B4, we previously demonstrated that under single turnover reaction conditions, cyt b5 enhances the rate of catalysis by up to ~100-fold compared to cyt P450 reductase.[2] Examination of the cyt P450 catalytic cycle (Fig 1) shows that acceptance by cyt P450 of the second electron, which can be delivered either by cyt b5 or cyt P450, triggers an irreversible cascade of events, including delivery of 2 protons (H+), ultimately resulting in product formation. The demonstration that a process occurring after delivery of the second electron was enhanced by cyt b5 but not cyt P450 reductase prompted the hypothesis that cyt b5 stimulated metabolism of substrates by enhancing delivery of a proton to the unstable ferric heme hydroperoxo intermediate of cyt P450 (Fe+3OOHË‰, Fig 1). In this work we employ single-turnover, rapid freeze-quench EPR (electron paramagnetic resonance) experiments to demonstrate that the rate of proton delivery to the heme hydroperoxo cyt P450 intermediate is faster in the presence of cyt b5 than cyt P450 reductase. More rapid proton delivery causes more rapid substrate metabolism.



Methods: The full-length membrane-binding forms of cyt P450 2B4, cyt b5, and cyt P450 reductase were expressed in E. coli and purified. A complex of ferrous cyt P450 2B4 with either ferrous cyt b5 or 2 electron reduced cyt P450 reductase in buffer was quickly mixed with an O2-containing buffer to initiate catalysis. At designated times after the start of the reaction the reaction mixture was swiftly frozen at -140 °C and subsequently interrogated by EPR.

Results: The EPR spectra (Fig 2) of reactions quenched at various times after starting the reaction of the cyt P450-cyt P450 reductase complex with O2, demonstrate formation of a low-spin ferric heme hydroperoxo intermediate signal as hypothesized. In contrast, in a similar experiment with a cyt P450-cyt b5 complex a hydroperoxo intermediate could not be observed (Fig 3). Our inability to detect a cyt P450 ferric heme hydroperoxo intermediate when catalysis occurs in the presence of cyt b5 was interpreted to indicate that protonation and product formation occurred very rapidly before it was possible to quench the reaction. Discussion: The ability to detect an unstable cyt P450 ferric hydroperoxo intermediate that was generated under ambient conditions elucidates the molecular mechanism of action of cyt b5 in anesthetic and drug metabolism and helps explain many of the puzzling results of anesthetic drug metabolism studies that have been performed by a variety of investigators.

Conclusion: Cyt b5 stimulates catalysis by cyt P450 2B4 by increasing the rate of protonation of the ferric hydroperoxo heme intermediate (Fe+3 OO)Ë‰ which results in faster product formation and decreased formation of the side products superoxide and hydrogen peroxide.

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Poster Presentations, *continued from page 128*

AP 8 (1956)
Norbuprenorphine First in Man Pharmacology 3. Clinical Effects and Pharmacodynamics

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Introduction: Buprenorphine, a long-duration opioid used for treating pain and opiate addiction, has complex pharmacology. It is a partial μ agonist, Î´ and Îº antagonist, and nociceptin receptor agonist. It has ceiling effects for analgesia and respiratory depression. Buprenorphine is extensively metabolized in humans, primarily to norbuprenorphine; both buprenorphine and norbuprenorphine undergo glucuronidation. Metabolite exposure exceeds that of buprenorphine. Norbuprenorphine is a potent, high-affinity μ, Î´ and Îº opioid agonist. In rodents, buprenorphine dealkylation to norbuprenorphine is a bioactivation pathway, causing anti-nociception and respiratory depression and .norbuprenorphine was 10x more potent than buprenorphine. Buprenorphine- and norbuprenorphine-glucuronides are also pharmacologically active. Mechanisms of buprenorphine pharmacology in humans remain undefined. We conducted a series of first-in-man studies to evaluate the clinical pharmacology of norbuprenorphine (NorBup).

Methods: This was an IRB-approved, single-center, open label, study in 12 healthy volunteers, to evaluate the pharmacokinetics of NorBup, a primary metabolite of buprenorphine. Healthy volunteers 18-50 yr were eligible. Subjects received a 1 hr infusion of NorBup (0.3 mg). Arterial (radial) and venous plasma was sampled for 13 hr and 96 hr, respectively. Pupil diameter, respiratory rate, end-expired CO2, and subjective self-assessment of drug effect were recorded. Response to thermal stimulus (Peltier thermode analgesia), was assessed using the methods of limits (maximal tolerated temperature) and ramp and hold mmethod (VAS pain rating to a predetermined temperature).

Results: NorBup caused mild miosis; maximum pupil diameter change was 1.3 ± 0.8 mm. NorBup caused minimal respiratory depression; respiratory rate decreased from 16 ± 1 to 14 ± 3 and end-expired CO2 increased from 39 ± 2 to 41 ± 2. NorBup was slightly anti-analgesic. Maximum tolerated temperature decreased from 49 ± 1 to 48 ± 1 °C. VAS pain ratings to a preset temperature increased to 113 ± 13% of baseline. Drug effects were negligible after 24 hr. Graphs of effect (miosis) vs concentration showed hysteresis.

Conclusion: NorBup, the primary metabolite of buprenorphine, is pharmacologically active in man. NorBup effects however are atypical for an opioid: miosis and respiratory depression yet anti-analgesic (hyperalgesia). NorBup may contribute to the pharmacologic effects of buprenorphine. Multiple metabolites, with differing receptor binding profiles, and different pharmacologic effects, demonstrate the complexity of buprenorphine pharmacology.

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AP 9 (1949)
Norbuprenorphine First in Man Pharmacology 2. Arterial and Venous Pharmacokinetics

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Introduction: Buprenorphine, a long-duration opioid for treating pain and opiate addiction, has complex pharmacology. It is a partial μ agonist, Î´ and Îº antagonist, and nociceptin receptor agonist, with ceiling effects for analgesia and respiratory depression. Buprenorphine is extensively metabolized, primarily to norbuprenorphine; both buprenorphine and norbuprenorphine undergo glucuronidation. Metabolite exposure exceeds that of buprenorphine. Norbuprenorphine (NorBup) is a potent, high-affinity μ, Î´ and Îº opioid agonist. In rodents, buprenorphine dealkylation to NorBup is a bioactivation pathway. NorBup was 10x more potent than buprenorphine. Buprenorphine and norbuprenorphine glucuronides are also pharmacologically active. Mechanisms of buprenorphine pharmacology in humans remain undefined. We conducted a series of first-in-man studies to evaluate the clinical pharmacology of NorBup.

Methods: This IRB-approved, single-center, open label, first-in-man study evaluated NorBup pharmacokinetics (PK) in 12 healthy volunteers (18-50 yr eligible). Subjects received a 1 hr infusion of NorBup (0.3 mg). Arterial (radial) and venous plasma was sampled for 13 hr and 96 hr, respectively. Urine was collected for 96 hr. NorBup and NorBup-glucuronide were quantified by LCMSMS. Population PK modeling was performed with Phoenix 64 NMLE 7.0 using the FOCE ELS algorithm (Certara). Model parameters were assumed to be log-normally distributed across the population. Independent PK models for arterial (NorBup & NorBup-glucuronide) and venous (NorBup & NorBup-glucuronide) were tested against a minimal, comprehensive model that linked arterial and venous drug/metabolite concentrations, using recirculatory model principles, and a metabolic tanks-in-series pathway. Criteria for accepting the linked model were improvement of -2LL of at least 3.84 and reduction in AIC (Chi squared, $p<0.05$). Urine drug and metabolite concentrations were incorporated in the respective models as cumulative drug or metabolite collected at each collection time point.

Results: NorBup arterial concentrations were 2x venous concentrations during the infusion, and similar thereafter with venous systematically higher. The A-V difference was well modeled with a linked 3-compartment base model and a recirculatory mixing component having a typical cardiac output (tvCO) of 6.52 L/min. NorBup to the glucuronide tvCl was 342 ml/min and renal tvCl of NorBup-glucuronide was 125 ml/min, based on urine collection. Non-renal clearance accounted for 91% of NorBup and 71% of NorBup-glucuronide clearances.

Conclusion: Large A-V differences during infusion and small inverse A-V differences afterwards were described by a novel 3-compartment model with an additional frontend, recirculatory component. NorBup was largely metabolized by glucuronidation, but only 30% of NorBup-glucuronide was accounted for in urine by GFR, suggesting that entero-hepatic recirculation may affect late phase NorBup kinetics.

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Poster Presentations, *continued from page 130*

AP 10 (1942)
Norbuprenorphine First in Man Pharmacology 1. Dose Escalation Evaluation

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Introduction: Buprenorphine, a long-duration opioid used for treating pain and opiate addiction, has complex pharmacology. It is a partial μ agonist, Î´ and Îº antagonist, and nociceptin receptor agonist. It has ceiling effects for analgesia and respiratory depression. Buprenorphine is extensively metabolized in humans, primarily to norbuprenorphine; both buprenorphine and norbuprenorphine undergo glucuronidation. Metabolite exposure exceeds that of buprenorphine. Norbuprenorphine is a potent, high-affinity μ, Î´ and Îº opioid agonist. In rodents, buprenorphine dealkylation to norbuprenorphine is a bioactivation pathway, causing anti-nociception and respiratory depression and .norbuprenorphine was 10x more potent than buprenorphine. Buprenorphine- and norbuprenorphine-glucuronides are also pharmacologically active. Mechanisms of buprenorphine pharmacology in humans remain undefined. We conducted a series of first-in-man studies to evaluate the clinical pharmacology of norbuprenorphine (NorBup).

Methods: This was an IRB-approved, single-center, open label, dose-escalation, first-in man pilot in healthy volunteers, to evaluate dose-dependent pharmacokinetics and clinical effects of NorBup, a primary metabolite of buprenorphine. Healthy volunteers 18-50 yr were eligible. Subjects received a 1 hr infusion of NorBup (0.005-1 mg). Plasma was sampled for up to 13 hr, and urine collected for 24hr. Pupil diameter, respiratory rate, end-expired CO2, and subjective self-assessment of drug effect were recorded. NorBup and NorBup-glucuronide were quantified by LCMS.

Results: Plasma concentrations were readily quantifiable even at the lowest dose (5 μg). NorBup-glucuronide exceeded NorBup concentrations after the infusion. NorBup and NorBup-glucuronide AUCs were proportional to dose (r2>0.9) throughout the entire dose range. NorBup Cmax/Dose, AUC/D, clearance, Vz, and half-life were 5.8 ± 1.8 ng/ml/mg, 18 ± 4 ng-hr/ml/mg, 12 ± 4 ml/kg/min, 4.6 ± 1.2 L/kg, and 5 ± 2 hr (n=19). NorBup-glucuronide Cmax/Dose, AUC/D, Tmax, and half-life were 2.1 ± 0.8 ng/ml/mg, 26 ± 12 ng-hr/ml/mg, 3 ± 1 hr, and 7 ± 3 hr. In urine, NorBup and NorBup-glucuronide excretion were proportional to dose (r2>0.8) throughout the entire dose range. Urine NorBup and NorBup-glucuronide excretion were 3 ± 2% and 12 ± 4% of the dose, respectively, over the first 24 hr. Formation clearances were 0.3 ± 0.1 and 1.3 ± 0.5 ml/kg/min, respectively. Fractional excretion was constant over the dose range. Small changes in miosis, respiratory rate, and end-expired CO2 were observed at high NorBup doses. There were no side effects or adverse events.

Conclusion: NorBup was well-tolerated. NorBup demonstrates linear (dose-independent) pharmacokinetics. NorBup is rapidly glucuronidated, and NorBup-glucuride is formation-rate limited. NorBup doses were identified that afford NorBup plasma concentrations observed after buprenorphine administration, to guide further studies.

References:

1. Anesthesiology 2011;115:1251-60
2. Journal of Pharmacology and Experimental Therapeutics 2012;343:53-61

PME 11 (2146)

Low Dose Isoflurane Selectively Suppresses Withdrawal to Thermal A-δ Nociceptor Stimulation Compared to C-fiber Stimulation in Rat: Behavioral and Transcriptomic Analysis

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Introduction: The peripheral nervous system expresses many potential targets of anesthetics. Paradoxically, some peripheral C-fiber nociceptors have increased firing while exposed to volatile anesthesia, raising concern over how exposure to volatile anesthetics might contribute to both the peripheral pain signal and subsequent central sensitization(1). The present study investigated isoflurane suppression of withdrawal from A-δ specific thermal stimulation and C-fiber specific thermal stimulation. We tested the hypothesis that differences in nociceptor responsiveness of A-δ and C-fibers to volatile anesthetics may be attributable to differences in their expression of anesthetic targets.

Methods: Male Sprague-Dawley rats (n=10) were tested with brief pulse (100 ms) and continuous infrared diode laser to assess A-δ and C-fiber thermal nociception, respectively. Animals were stimulated on hind-paws and ears under increasing levels of isoflurane (Awake, 1%, 1.5%, 2%). Withdrawal response and withdrawal latency to thermal stimulation were compared via ANOVA with post-hoc testing procedures for multiple comparisons. Literature was reviewed for targets of anesthesia and gene expression was analyzed in rat dorsal root ganglia (n=8) and compared to central nervous system expression levels using RNA-sequencing. Single-cell RNA-seq data was used to compare expression levels of anesthetic targets between A-δ and C-fiber nociceptors to determine meaningful targets (publicly available data of mouse dorsal root ganglion cells from reference 2). Thermo-nociceptive cells were selected for expression of TRPV1 (transient receptor potential cation channel subfamily V); expression of neurofilament heavy chain distinguished A-δ from C-fiber nociceptors.

Results: Increasing doses of inhaled isoflurane (Awake, 1%, 1.5%, 2%) led to successive suppression of paw withdrawal to pulsed laser stimulation over a wide range of stimulus intensities (A-δ assay, $p<0.05$ for linear trend). However, paw withdrawal to continuous laser stimulation (C-fiber assay) was not suppressed by 1% or 1.5% isoflurane. These results were of greater magnitude in the paw than in the ear. There was biologically meaningful expression of many anesthetic molecular targets in the rat dorsal root ganglion ($p<0.05$ for non-zero expression). Single-cell differential expression showed multiple genes with potential anesthetic relevance with significant differential expression in A-δ neurons, with no such targets differentially found in C-fiber neurons.

Conclusion: There are multiple potential targets of anesthesia preferentially expressed by A-δ nociceptors, which suggests a mechanism for the selective suppression of withdrawal to A-δ stimulation seen in isoflurane administration. Further experimental manipulation of peripheral targets of anesthesia that are preferentially found on A-δ nociceptors will help elucidate to what degree volatile anesthetics selectively suppress subpopulations of peripheral nociceptors.

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Poster Presentations, *continued from page 134*

CA 12 (1213)
Bayesian Network Analysis of SysAolic Anterior Motion

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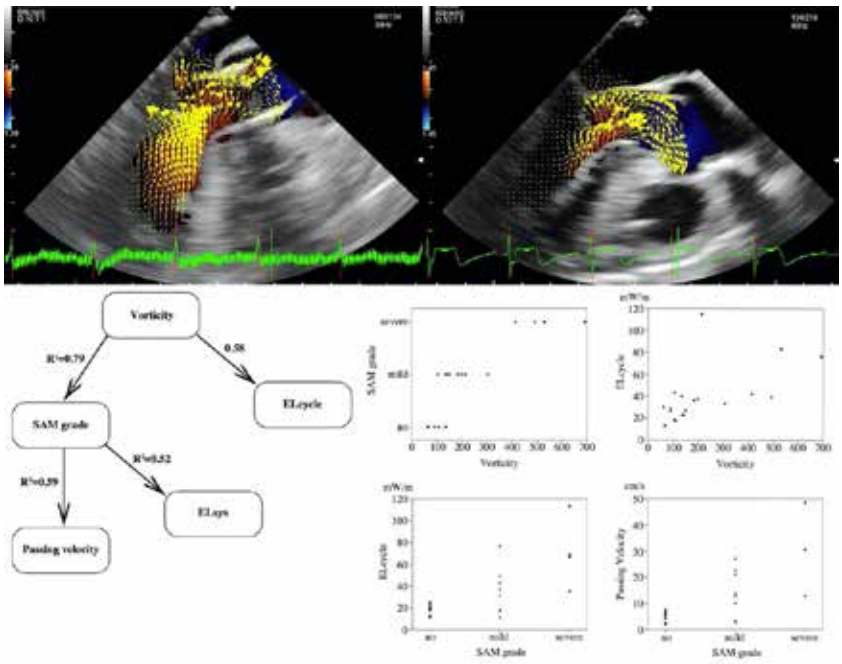
Introduction: Venturi effect had been once supposed to be the cause of Systolic Anterior Motion (SAM). However, drag force has been considered to be the main cause of SAM lately[1]. We investigated the causal relationships between SAM and measured parameters by echocardiography using Vector Flow Mapping (VFM).



Methods: Intraoperative transesophageal echocardiographic movies of SAM were analyzed using VFM. Four Severe SAM cases in which left ventricular outflow tract obstruction (LVOTO) and mitral regurgitation were observed, eight mild SAM cases in which systolic anterior motion of mitral leaflet was observed without LVOTO, and eight no SAM cases of normal cardiac function were enrolled. Coaptation length, AL/PL, C-Sept, Aortomitral angle, LVDd, LVDs were measured from transesophageal echocardiographic images. Furthermore, intraventricular blood flow, intraventricular energy loss averaged per one cardiac cycle (ELcycle), intraventricular energy loss averaged of systolic phase (ELsys), vorticity during mid-systole, velocity at tip of mitral leaflet (Passing velocity) were analyzed using VFM. Intraventricular blood flow was visually analyzed and other parameters were statistically analyzed using Bayesian network.

Results: Drag force was identified in all SAM cases. Bayesian network showed that vorticity was the causal factor of SAM and ELcycle, and that SAM was the causal factor of passing velocity and ELsys.

Conclusion: We could confirm that drag force and vorticity caused SAM and SAM caused ejection flow velocity.

References:

1. J Am Coll Cardiol, 36, 1344-54, 2000

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CA 13 (1160)
3-Oxoglutarate is a Novel Marker of Ischemia in Humans

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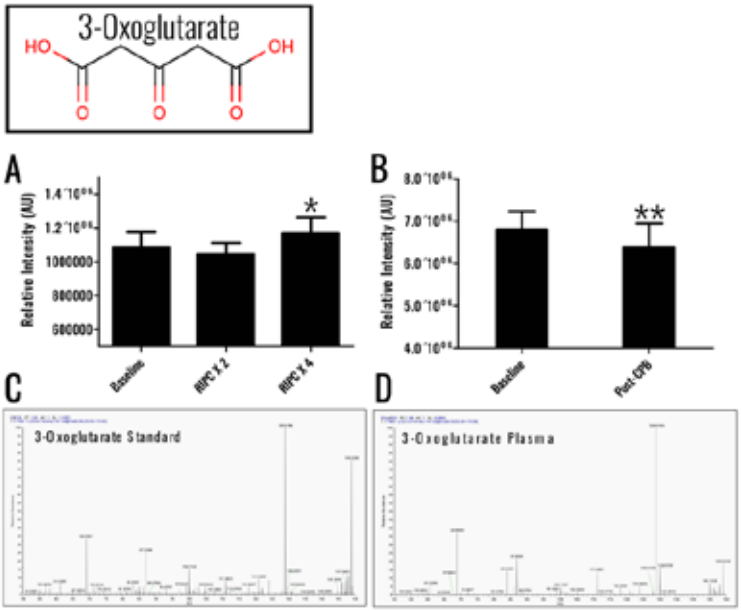
Introduction: Hypoxia results in inhibition of prolyl hydoxylases (PHD) leading to hypoxia inducible factor 1 alpha (HIF1a) signaling with subsequent changes in gene transcription (1). This hypoxic inhibition of PHD leads to accumulation of a-ketoglutarate which serves as a circulating signal of local hypoxia that is converted to kynurenine and kynurenic acid in the liver when oxygen is unavailable to induce remote ischemic cardioprotection (RIPC) (2). Since RIPC induces cardioprotection through a mechanism that is not completely understood, we performed untargeted metabolomic screening of healthy volunteers undergoing RIPC. This screening identified 3-oxoglutarate as a novel marker of ischemia in humans.



Methods: 4 healthy subjects were recruited for the study and written informed consent was obtained. Each participating was subjected to 4 cycles of vascular occlusion of 5 minutes each. Blood samples were collected into 3.2% citrate. Plasma was prepared by centrifugation and stored at -80 C until analysis. Metabolomics analyses were performed as previously reported (3,4) and untargeted data analysis identified 3-oxoglutarate as increasing in response to RIPC. 3-oxoglutarate was identified by matching retention time and MS/MS fragmentation to a commercially available standard. 3-oxoglutarate was then measured in a separate cohort of patients undergoing cardiac surgery (n=23) and in a porcine model of shock and targeted organ ischemia (n=5). Statistical analysis was performed with a paired t test with $p < 0.05$ considered significant.

Results: 3-Oxoglutarate increased significantly after 4 cycle of RIPC in healthy volunteers (Fig 1A) and decreased from baseline following cardiac surgery (Fig 1B). Comparison of the MS/MS fragmentation pattern of 3-oxoglutarate standard and the metabolite of interest in plasma confirmed 3-oxoglutarate as the biomarker of interest (Fig 1C,D). In a porcine model, 3-oxoglutarate levels did not change in response to 60 minutes of experimental shock (mean arterial pressure 25 mmHg, Fig 2A). Clamping of the vascular supply to the spleen, liver, small bowel, and kidneys to induce ischemia followed by reperfusion led to changes in the level of 3-oxoglutarate present (Fig 2B).

Conclusion: 3-oxoglutarate is a novel marker of ischemia in humans that warrants further study.

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CA 14 (1290)
Cardiac-Specific Human Resistin Overexpression Impairs Contractility in Mice

Wei Dong Gao, MD, PhD[1], Wei Yang, MD, PhD[2]; John Skinner, MS[1]; Qing Lin, MD, PhD[1]; Chunling Fan, PhD[1]; Kazuyo Yamaji-Kegan, PhD[1]; Roger Johns, MD, PhD[1]

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Introduction: Right ventricular dysfunction (RVD) has been reorganized as the strongest predictor of mortality in patients with pulmonary hypertension. Although elevated pulmonary vascular resistance is well known to play a critical role in the progression of right heart dysfunction, pressure overload-independent factors may also be implicated in the transition from adaptive RV compensation to failure. Recently, accumulating evidence suggested that resistin, a member of resistin-like molecule (RELM) family, has been involved in the pathology of various cardiovascular diseases, including heart failure. Therefore, we hypothesize that resistin may play a role in the process of excitation-contraction coupling and impairs intrinsic right ventricular contractility.

Methods: 1. Transgenic mouse model of human resistin over-expression. This is a double transgenic mouse model, which has two genes: tetracycline-controlled transactivator (tTA) and human resistin, such that only mice with both positive tTA and human resistin gene will express human resistin in the heart. 2. Animal Studies. Both wild-type and transgenic mice were anesthetized with isoflurane 1-3% for echocardiography studies. The cardiac effect of isoflurane was minimized by maintaining baseline heart rate 3. Trabecular muscles. Twitch force and intracellular Ca2+ concentration ([Ca2+]i) measurement. Trabecular muscle from the right heart were dissected and mounted onto the experimental setup (Illustration on right), and superfused with K-H solution at a rate of ~10 ml/min, and stimulated at 0.5 Hz. Force was measured by a force transducer and [Ca2+]i was measured using fura-2. The muscles underwent isometric contractions with the resting muscle length set such that resting force was 15% of total force development (i.e., optimal muscle length 4. Immunohistological Studies. Heart tissue samples were incubated with fluorescent antibody against myosin, fluorescent stains for nuclei and cell membrane connect tissue. Immunoflurescent and fluorescent images of stained tissue sections were analyzed and compared between transgenic and wild-type hearts.

Results: 1. Human resistin is specifically overexpressed in hearts from myosin heavy chain humanize mice as. Genotyping by PCR analysis of genomic DNA shows amplification of a 363 bp product encoding the myc-RENT epitope region of the transgene indicates that an animal carries the myc-RENT transgene. A 535 bp product was specifically amplified from animals carrying the tTA transgene using previously described primers. Immunoflurescence images show expression of hRETN within myocytes (Figure 1). 2. The hRETN overexpressed heart has increased myocyte size, enlarged heart chambers and decreased function as evaluated by echocardiography (P,0.05, n=7-10). (Figures 2 and 3) 3. The hRETN overexpressed muscles exhibited blunted force development with decreased intracellular Ca2+ transients in comparison with non-TG controls as stimulation frequency increased (P<0.01, n=3). (Figure 4) 4. At a molecular level, resistin-overexpression cardiac tissue exhibited increased phosphorylation of Akt but decreased phosphorylation of protein kinase A (PKA), both of which are involved in the regulation of Ca2+ channels and phosphorylation of myofilaments. (Figure 5).

Conclusion: Our findings implicate that increased hRETN May directly depress cardiac force development thus promoting the development of heart failure, especially right heart failure in pulmonary hypertension.

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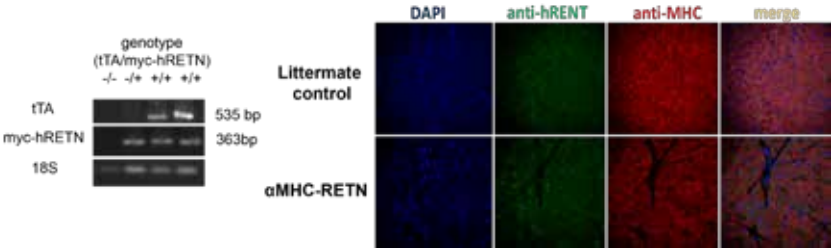
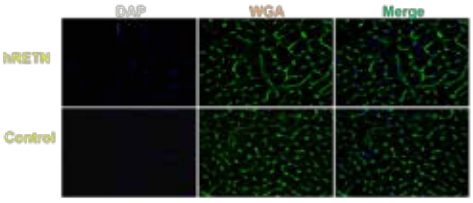
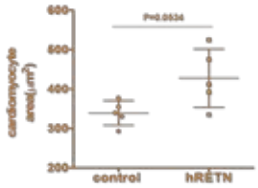
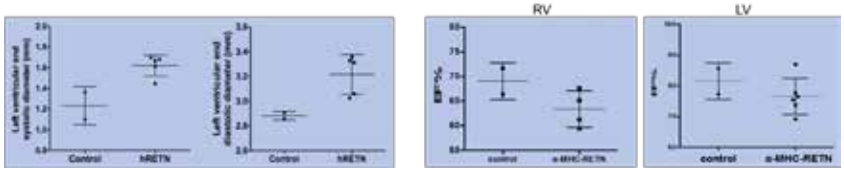
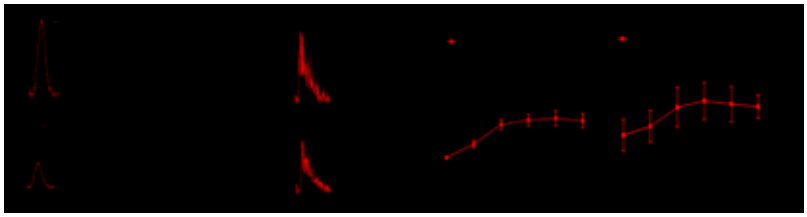
Poster Presentations, *continued from page 135*

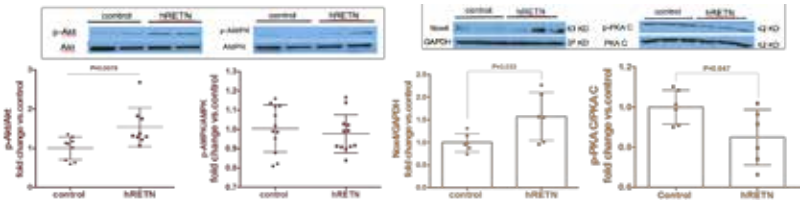












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CA 15 (1656)
Association of Testosterone Replacement Therapy (TRT) and the Incidence of Perioperative Major Adverse Cardiac Events (MACE) in Men Undergoing Non-Cardiac Surgery

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Introduction: Testosterone replacement therapy (TRT) has been dramatically increasing in recent years to treat age related decline in serum testosterone and to treat reduced physical function and decreased extremity strength in healthy older men with low serum testosterone levels. There has been a 65% increase in the sale of testosterone supplements from 2009-2013. Data on the effect of testosterone on cardiovascular outcomes are conflicting. Several observational trials [(1,2)] have reported increased cardiovascular risk in patients taking TRT, which prompted the FDA to require label changes for all prescription testosterone products to reflect a possible increased risk of MI, CVA, and thrombotic complications. In contrast, a randomized trial of testosterone therapy reported no increase in cardiovascular events [(3)]. Risk of perioperative major adverse cardiac events (MACE) in patients on TRT undergoing non-cardiac surgery remains unknown. This prompted our evaluation of identifying the impact of TRT on the incidence of MACE in men undergoing non-cardiac surgery.

Methods: This propensity score matched retrospective single center cohort trial included 5,545 males, 40 years of age and older, classified as ASA I – IV patients, who underwent non-cardiac surgery between May 2005 and December 2015 at the Cleveland Clinic main campus. The primary exposure of interest was routine preoperative testosterone use. The primary outcome was a composite of in-hospital mortality and postoperative major adverse events. We matched patients who received TRT and those who did not (non TRT) using propensity score matching and exact matching. The matched patients were compared on the composite of in-hospital mortality and postoperative major adverse events, using a generalized estimating equation model, in which we estimated the average log-odds ratio 'treatment (TRT) effect' across the components of the outcome composite.

Results: 49,273 patients met inclusion and exclusion criteria, including 955 TRT patients. Based on demographics, baseline characteristics, and surgical factors, we successfully matched 947 TRT patients (99% of 955 TRT patients) with 4,598 non-TRT patients. The incidence of in-hospital mortality was 1.3% in the TRT group and 1.1% in the non-TRT group, giving an odds ratio of 1.17 (95% CI: 0.51, 2.68) (TRT vs. non-TRT), P = 0.63. The incidence of MI was 0.2% in the TRT group and 0.6% in the non-TRT group, again giving a non-significant odds ratio of 0.34 (95% CI: 0.05, 2.28), P = 0.15. Similarly, no significant difference was found in stroke (TRT vs. non-TRT: 2% vs. 2.1%), PE (0.5% vs. 0.7%), or DVT (2.0% vs. 1.7%) (Table 1). The average relative effect across the five components of the composite was 0.81 (95% CI: 0.53, 1.25) for TRT vs. non-TRT (P = 0.33), adjusting for preoperative creatinine.

Conclusion: The use of preoperative TRT is not associated with an increased incidence of a composite of in-hospital mortality and major adverse cardiac events. To our knowledge, this is the first study investigating the association of preoperative TRT and the incidence of perioperative MACE and in-hospital mortality.

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3. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. 95: 639-50. 2010

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Table 1:

Comparison between propensity score matched TRT and non-TRT patients on the composite of in-hospital major morbidities and mortality				
Outcome	**TRT N = 947**	**Non-TRT N = 4,598**	**OR* (95% CI) ^**	**P^**
In hospital mortality	1.3%	1.1%	1.17 (0.51, 2.68)	0.63
Myocardial infarction	0.2%	0.6%	0.34 (0.05, 2.28)	0.15
Stroke	2.0%	2.1%	0.96 (0.50, 1.84)	0.87
Pulmonary embolism	0.5%	0.7%	0.76 (0.22, 2.62)	0.56
Deep vein thrombosis	2.0%	1.7%	1.20 (0.62, 2.34)	0.48
Average relative effect			**0.81 (0.53, 1.25)**	**0.33**

TRT = Testosterone replacement therapy

* The ratio of the odds of the outcome occurring in the TRT patients versus non-TRT patients

^ CIs adjusted for multiple testing by Bonferroni correction. Correspondingly, P value of < 0.05 was considered significant for the average relative effect across all the components of the composite. P values of < 0.01 were considered significant for individual component.

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CA 16 (1250)
Proceduralist-Directed, Nurse-Administered Dexmedetomidine Sedation for PSVT Ablation

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Introduction: Dexmedetomidine (Dex) is an attractive agent for procedural sedation due to its unique pharmacodynamic profile, specifically affording predictable sedation without concurrent respiratory depression. However, Dex has previously been reported to prevent or terminate arrhythmias. The purpose of this study was to investigate paroxysmal supraventricular tachycardia (PSVT) inducibility and safety of proceduralist-directed, nurse-administered (PDNA) Dex for sedation during electrophysiology studies (EPS) and ablation.

Methods: We performed a retrospective review of 163 consecutive patients referred for PSVT ablation that received Dex as the primary sedative. This cohort was compared to 163 consecutive control patients who received fentanyl and midazolam for sedation. PSVT inducibility was assessed prior to ablation and was defined as a sustained arrhythmia or non-sustained rhythm that enabled a diagnosis and target for ablation.

Results: The arrhythmia profiles of the Dex and control cohorts were very similar. The overall incidence of a 'negative' EPS in which arrhythmia was not induced was 24% in the Dex group and 26% in the control group (p=0.7). Unintended deep sedation was significantly less with Dex (4.3% vs. 27%, p=<0.0001). However, Dex use was associated with a higher incidence of intraprocedure hypotension.

Conclusion: PDNA Dex sedation during EPS is not associated with a reduction in PSVT inducibility. The therapeutic utility of Dex during EPS arises from the predictable sedation Dex affords, but this may be mitigated by an increased incidence of intraprocedure hypotension.

References:

None

CC 17 (1621)
A 4-Year Review of Eclampsia Managed in the Intensive Care Unit: Lesson Learnt

Ajibola Uthman Otegbeye, M.B.B.S, DA[1], Olusola K. Idowu, MBBS, FWACS[2]

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Introduction: Eclampsia is a clinical condition seen in obstetrics. It is diagnosed when women with pre-eclampsia develop fits. Its an obstetric emergency seen in 1.7/1000 births in our part of the world. Mortality is quite high accounting for 25% of maternal mortality. This is a retrospective criteria based clinical audit which evaluated women admitted into the ICU with eclampsia. The objective is to identify causes of mortality and evaluate the outcome of the ICU interventions.

Methods: Patients admitted into the ICU over April 2011-April 2014 were evaluated using their case notes and treatment charts. Variables studied include bio-data, type of eclampsia, antenatal booking status, glasgow coma scale on admission. Interventions like use of mannitol, transfusion, mechanical ventilation were also analysed. Outcome is either death or discharged. The variables were analysed to see if they have a relationship with outcome. SPSS version 20 was used for analysis. Chi-square was used to determine prognosis and pvalue less than 0.05 was significant.

Results: A total of 83 patients were admitted. Mean age is 31.5 years. 59 (71.1%) had antepartum eclaampsia, 24 (28.9%) had postpartum eclampsia. 53 (63.9%) were discharged to the ward while 30 (36.1%) died. It was commoner in the unbooked patients(79.5%) and in the age group 26-35 (51.8%). Admitting GCS was 3-7 in 20 (26.7%), 8-12 in 28 (37.3%) and 13 -15 in 37 (22.5%). They all had magnessium sulphate. The use of mannitol, mechanical ventilation, blood transfusion were all found to have an influence on the outcome. Autopsy showed intra-cerebral hemorrhage as a leading cause of death.

Conclusion: This study shows the trend of Eclampsia in Nigerian women. It shows there's high mortality despite specialized care. Mortality was higher in the unbooked population. Centers are advised to draw a protocol to determine ICU admission and optimise care. Research should continue into reducing mortality.

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CC 18 (1099)
Epidemic Propagation of Pseudomonas Aeruginosa ST357 Clones Harboring exoU Gene

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Introduction: Pseudomonas aeruginosa (P. aeruginosa), a gram-negative bacillus, is widespread in the environment, and is a common cause of urinary infections, ventilator-associated pneumonia, and surgical site infections. The aim of this study was to characterize the genetic diversity of multidrug resistant (MDR, defined as resistance to ‰§ 3 antimicrobial agents) P. aeruginosa strains isolated at the university hospital of Kyoto, Japan.

Methods: We investigated MDR P. aeruginosa isolates collected prospectively from 2005 to 2013. Antimicrobial resistance was tested using the disk diffusion method, as recommended by the CLSI, and MDR P. aeruginosa isolates were selected. The genotyping of type …¢ secretory virulence (exoS and exoU) was conducted by PCR, and genetic diversity was examined using the multi-locus sequence typing (MLST) technique developed by Curran et al.

Results: Twenty-one P. aeruginosa strains were isolated from urine (14), sputum (2), skin (3), blood (1), and a catheter tips (1). A total of 21 multilocus sequence types (ST) were identified. Twenty isolates were exoS-/exoU+; the ST of 19 of these isolates was ST357 and one was ST235. The 19 ST357 isolates were ciprofloxacin and levofloxacin resistant; two isolates were ceftazidime resistant, one of which also exhibited piperacillin, imipenem/cilastatin, and meropenem resistance. One isolate ST512 was exoS+/ exoU-.

Conclusion: This study demonstrates the widespread prevalence of ST357 exoS-/exoU+ strains in our hospital over eight years. These ST357 isolates contain several different antibiotic resistance determinants. Further research is required to identify the causes of the pandemic and the underlying resistance mechanisms in order to control hospital infection.

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Poster Presentations, *continued from page 141*

CC 20 (1407)
Comprehension of Critical Care Issues by Proxies of Patients Undergoing Major Surgery

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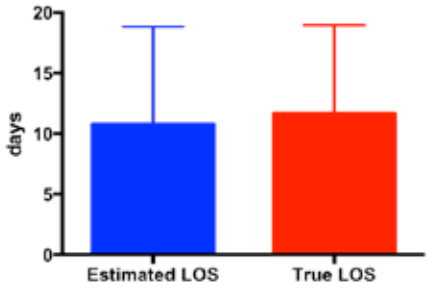
Introduction: Previous studies suggested that patient representatives in medical ICUs have very poor comprehension of the diagnoses, treatment, or prognosis of the patient they represent [(1)]. Information needs of proxies for patients in medical ICUs are consistently not being met especially with regard to treatments and complications [(2)]. There is however little information about the level of understanding healthcare proxies have when potentially representing patients undergoing major surgery where ICU treatment is common. The aim of this study is to determine the understanding of medical interventions by these potential patient surrogates and identify areas of concern and lack of knowledge.

Methods: This is a prospective, observation, single center questionnaire study. After IRB approval and informed consent were obtained, 20 healthcare proxies of patients undergoing major surgery were given a questionnaire prior to surgery and then again 2 and 5 days post-op if they remained in the ICU for that time. The questionnaire contained visual analogue scales, Likert-scales, objective knowledge assessments, and several open-ended questions to assess knowledge of the patient's diagnosis, illness duration, surgery, and afflicted organs. We additionally asked for an estimation of the length of stay, expected discharge location, and type of ICU interventions to be expected (sedation, mechanical ventilation, blood pressure medication, etc). Estimated and true length-of-stay were compared using paired t-test.

Results: All 20 patients whose proxies were enrolled were transferred to a surgical ICU post-op. 16/20 procedures were open cardiac. Most proxies understood the patient's surgery and diagnosis (19/20 and 18/20 respectively), and all could identify the primary organ involved in the patient's pathology. However, they underestimated the hospital length of stay (Figure: 10.7 +/- 8.6 versus 12.3 +/- 7.5 days, p< 0.05) and were frequently unable to identify necessary ICU interventions (Table). It was additionally found that 16 of 20 patients used the Internet to obtain information, and all of these proxies found the information from the Internet helpful to very helpful (6-10 on a scale of 1-10, mean 8.1).



Conclusion: Our data suggests that healthcare proxies of patients undergoing major surgery with expected post-op ICU admission were well informed about the patient's surgery and diagnosis. This may not be surprising considering the many discussions that occur during preparation for surgery. Many of these proxies additionally turned to the internet to satisfy their information needs, and they generally found this helpful. However, it remains unclear whether this is transferred into objective knowledge. We found that proxies tended to underestimate hospital length of stay, though this gap was not significant. It was however notable that many proxies were unable to predict routine treatment modalities the patients in our cohort were anticipated to undergo. All patients could be expected to remain on sedative medications, mechanical ventilation and pressors at some point during their ICU stay. Though not all received these interventions (eg. extubated in the OR), fewer numbers of proxies identified these as possibilities than the numbers of patients that actually experienced the intervention. It remains unknown whether this gap correlate to degrees of stress of dissatisfaction on the part of the proxy.

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CC 21 (1687)
Increased Intraoperative Crystalloid Administration for Esophagectomy Decreases Unplanned ICU Admissions in a Single Center Study

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Introduction: The high risk of perioperative morbidity and mortality following esophageal resection is well known.[1] The debate between restrictive versus liberal intraoperative crystalloid fluid administration for esophagectomy and the effect on postoperative complications remains in contention.[1-3] Striking the correct balance with fluid administration between adequate tissue perfusion and adverse outcomes is an important component of anesthetic management for this patient population.[2] The present investigation aims to highlight the role of intraoperative fluid management in decreasing unplanned ICU admissions and subsequent length of stay following esophagectomy.

Methods: Following IRB approval, data were extracted from the medical records of 99 consecutive patients in a single care center undergoing esophageal resection surgery to analyze the association of intraoperative crystalloid administration on the incidence of unplanned surgical ICU (SICU) admission, SICU duration of stay, and on the incidence on long-term assisted care (LTAC) admissions. Data were summarized as counts (%), means with standard deviation (SD), or medians [25-75% interquartile range: IQR], and analyzed with Wilcoxon rank sum test with robust fit set for statistical significance ($p<0.01$) to reduce the incidence of false discovery rates. A decision tree with 5-fold internal cross-validation was generated for predictor variables with LogWorth values ‰¥2.0 to indicate statistical significance when <0.01. Misclassification rates were utilized to calculate the proportion of observations allocated to the incorrect group.

Results: Patients who received <6L crystalloid fluid intraoperatively (n=57), 20 (35%) patients required unplanned SICU admission. In patients who received >6L of intraoperative crystalloid, no patients experienced an unplanned SICU admission (G2=86, LogWorth=2.9). Duration of postoperative length of SICU stay was also examined, and in patients who received <5.3L of intraoperative crystalloid, SICU length of stay was 10 SD 13.4 days. In contrast, in patients who received >5.3L of intraoperative crystalloid, SICU length of stay was 3 SD 3.5 days (LogWorth=1.5). Finally, the role intraoperative crystalloid administration on the incidence of long-term assisted care (LTAC) placement was examined, and 8 patients (14%) required LTAC placement, all of whom received less than 5L of intraoperative crystalloid with a misclassification rate of 8% ($p=0.2679$).

Conclusion: Intraoperative fluid administration for esophageal resection surgery is an important component contributing to postoperative complications. These data suggest a more liberalized approach to crystalloid management decreases unplanned SICU admissions, SICU length of stay and LTAC placement.

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CC 22 (1036)

Independent Risk Factors for Anesthesia Related Postoperative Respiratory Failure in a Rural Tertiary Academic Medical Center

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Introduction: Unplanned tracheal reintubation and prolonged intubation after surgery results in significant postoperative complications including longer mechanical ventilation duration, tracheostomy, increased pulmonary complications, longer Intensive Care Unit (ICU) stay and hospitalization duration, higher costs, and increased mortality. [1,2] The purpose of this study is to identify risk factors for postoperative respiratory failure in a rural tertiary care academic medical center.

Methods: A retrospective time-matched, case-control, cohort analysis of patient specific, preoperative specific, and operative specific reintubation risk factors from September 2010 through December 2013 at a rural academic tertiary care operating room medical center of 98 patients with anesthesia related postoperative respiratory failure compared to a control group of 4,055 patients. Data was analyzed using t-test or ANOVA, Mann-Whitney or Kruskal Wallis, Chi-square or Fisher exact test where appropriate. Multivariate analysis was performed using logistic regression. Results are reported in odds ratios with 95% confidence intervals. A P value < 0.05 was considered significant.

Results: The overall incidence of anesthesia related postoperative respiratory failure was 2.4%. Independent risk factors for anesthesia related postoperative respiratory failure are age 61.6 ± 14.3 years (95% CI: 58.8-64.5) vs. 54.0 ± 17.4 years (95% CI: 53.5-54.6, P < 0.001), in-patient status 97.9% vs. 65.4% (OR 25.1, 95% CI: 6.2-102.1, P < 0.001), preoperative diagnosis of hypertension 69.8% vs. 52.0% (OR 2.1, 95% CI: 1.4-3.3, P < 0.001), COPD 30.9% vs. 10.6% (OR 3.8, 95% CI: 2.4-5.9, P < 0.001), elective procedure 97.9% vs. 82.7% (OR 10.0, 95% CI: 2.5-40.5, P < 0.001), surgical duration > 2 hours 90.7% vs. 38.7% (OR 15.5, 95% CI: 7.8-30.9, P < 0.001) and ASA physical status ‰¥ 3 [78.1% vs. 57.6% (OR 2.6, 95% CI: 1.6-4.3, P < 0.001)], Tables 1 and 2. Multivariate regression analysis of significant variables found patient age (P = 0.014), body mass index (BMI, P < 0.001), surgical duration (P < 0.001), elective case (P < 0.001), in-patient status, and the preoperative diagnosis of COPD (P < 0.001) to be significant risk factors for postoperative respiratory failure.

Table 1. Patient-specific and pre-operative-specific risk factors.

	PRF (n=98)	95% CI	Control (n=4055)	95% CI	*P* value	Odds Ratio (OR)
Patient Specific						
Age (years)	61.6 ± 14.3	(58.8-64.5)	54.0 ± 17.4	(53.5-54.6)	0.001	-
BMI (kg/m2)	32.2 ± 9.4	(30.3-34.1)	30.8 ± 9.5	(30.5-31.1)	0.14	-
Gender (%)					0.58	0.9 (0.6-1.3)
Women	59.2%		56.4%			-
Men	40.8%		43.6%			-
In-patient Status (%)	97.9%		65.4%		< 0.001	25.1 (6.2-102.1)
Pre-Operative Specific						
Smoker (%)	29.9%		43.3%		0.6	0.9 (0.6-1.4)
Hypertension (%)	69.8%		52.0%		< 0.001	2.1 (1.4-3.3)
Cardiovascular Disease (%)	46.4%		3.2%		< 0.001	26.5 (17.2-41.1)
COPD (%)	30.9%		10.6%		< 0.001	3.8 (2.4-5.9)
Diabetes Mellitus (%)	17.7%		20.4%		0.51	0.8 (0.5-1.4)
Abnormal LFTs (%)	15.1%		21.7%		0.13	0.6 (0.4-1.1)
Anemia (%)	19.0%		37.2%		0.003	0.5 (0.3-0.8)
Acute Respiratory Infection (%)	8.4%		3.6%		0.02	2.5 (1.2-5.2)

Legend: PRF = Postoperative Respiratory Failure, data are mean ± SD with 95% CI, or median with range in parenthesis, or proportion and OR with 95% CI, LFTs = liver function tests

Conclusion: Independent risk factors for anesthesia related postoperative respiratory failure include older age, in-patient status, hypertension, COPD, elective procedure, surgical duration > 2 hours, and ASA physical status ‰¥ 3.

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EEP 23 (1525)
A Pilot Study to Assess the Feasibility of a Smartphone Application for Asynchronous Workplace-Based Learning

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Introduction: Anesthesiologists are expected to demonstrate ongoing life-long learning and proficiency in medical knowledge and clinical competency. MOCA Minute™, an essential component of MOCA 2.0, is a continuous longitudinal assessment tool that allows diplomats to demonstrate their aptitude in clinical reasoning while acquiring new medical knowledge[1]. Providing asynchronous, work based learning in a similar method as the MOCA Minute „¢ may better prepare our residents for practice after graduation. This type of spaced education method has the potential to improve acquisition of clinical knowledge, long-term retention, and performance on standardized specialty examinations (i.e. in-training exam and anesthesia knowledge test) for anesthesiology residents.[2-3] The primary goal of this pilot study was to assess the feasibility of a smartphone application to provide asynchronous workplace based learning using the concept of spaced education to anesthesiology residents.

Methods: Vanderbilt University Institutional Review Board deemed our study exempt. QuizTime, a smartphone app developed by Vanderbilt University School of Medicine, was designed to promote asynchronous learning and assessment of knowledge acquisition. A group of faculty members created questions based upon the ITE key words in which our residents had the lowest scores. For a four-week period, daily questions were sent via QuizTime to 68 anesthesiology residents. (Figure 1) During the study, user response data were collected and displayed within the application dashboard. (Figure 2) At the end of the implementation phase, residents completed a survey, via REDCap4, assessing the functionality of QuizTime as well as their perception of the usability within a residency training program environment.

Results: The implementation of QuizTime mobile application was well received by residents. Results show approximately 88% of respondents opened the daily questions. However, 23% opened but did not answer the questions. (Table 1) Post implementation survey revealed 81% of residents were comfortable navigating the application. While 97% believe it could be used to educate residents within their specialty, 66% believed it could be used to educate residents outside of their specialty about topics concerning their specialty. Sixty-six percent of residents reported they would revise current practice behavior to incorporate what they learned during the educational activity.

Conclusion: Quiztime, a mobile application, has the capability of providing anesthesia specific questions via text message to our residents. This innovative educational technology provided an asynchronous, work based style learning format similar to the MOCA Minute „¢. Our study showed residents believed this technology could be used to educate within their residency as well as outside of their specialty. This educational modality has the potential to drive learning based on content knowledge gaps identified through in training exams or anesthesia knowledge tests. Furthermore, the knowledge gained may ultimately translate into practice improvement in the clinical arena. Additionally, the application has the capacity to improve the delivery and quality of patient care. Further directions will include a study about knowledge gained and its application in clinical practice.

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Figure 1: QuizTime mobile interface

Figure 2: QuizTime Question Dashboard

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EEP 24 (1979)
Predicting Novice Success at Patient Intubation by Capturing Laryngoscopy Motion in Manikins

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Introduction: Laryngoscopy complications are common for novice operators and the likelihood is inversely related to experience(1). People vary in the rate at which they master psychomotor skills and as much as two years of anesthesia experience may be necessary for trainees to be confident of intubation success when patient factors or environmental conditions are unfavorable(2). Thus, a method to discern a trainee's skill with direct laryngoscopy would be useful for following progress. Skill in simulator tasks predicts performance at laparoscopic cholecystectomy(3). Similarly, motion analysis of simulated laryngoscopy might predict clinical intubation performance. The goal of this observational study was to determine if trainee motion during laryngoscopy on a manikin would predict the trainee's success at patient intubation.

Methods: Movement patterns were tracked for 3 anesthesiology attendings wielding a Macintosh 3 laryngoscope on a Medical Plastics airway trainer. Motion was measured by a miniBird position sensor mounted on the laryngoscope handle (4). Trajectories from 18 laryngoscopies were combined to establish the space used by experts for laryngoscopy on that airway model (Fig. 1). On day 1 of residency, 12 beginning anesthesiology residents performed the same laryngoscopy test and their movements were compared for conformity to the expert space (Fig. 2). Residents were then assessed in the operating room over the next 4 weeks for success at patient laryngoscopy and intubation. Multilevel modeling was used to analyze the relationship of manikin test metrics to the patient outcomes.

Results: Resident laryngoscopies conformed to the expert space over an average 74 ± 6% (SE) of the trajectory length, compared to 100% for attendings ($P < 0.01$). Residents frequently deviated from experts near the end of the procedure and were commonly too deep (Fig. 3). Resident conformity was greatest in the first third of the trajectory and progressively increased toward the end of laryngoscopy (Fig. 4). Residents attempted intubation on 117 patients in their first month. Individual residents succeeded at intubation in 36 to 100% (82 ± 5%) of patients and laryngoscopy failure rates/patient ranged from 0.2 to 1.1 (0.40 ± 0.02). % conformity on the manikin was a significant predictor of intubation outcomes in patients (see Table). For each percentage point increment in expert space conformity, a resident's odds of patient intubation success increased by 3.3% (95% confidence interval 0.7-5.9%), and the rate of failed laryngoscopy attempts decreased by 1.8% (0.4-3.1%).

Conclusion: Laryngoscopy motion in manikins may predict which trainees can complete a patient intubation successfully with few failed laryngoscopy attempts. Such a test could help determine resident readiness for unsupervised clinical assignments and identify individuals needing additional training. Finally, a test that predicts trainee outcomes with patients could be a useful tool in conducting research on laryngoscopy training.

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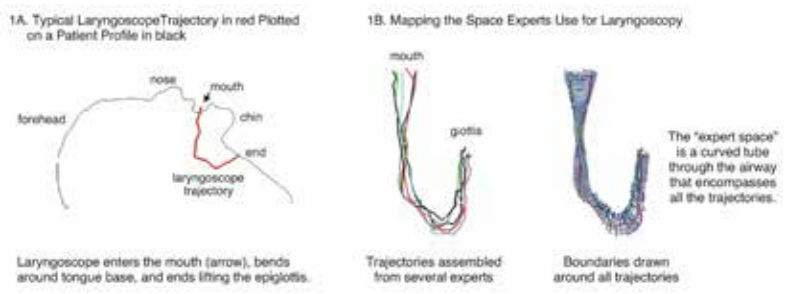
continued on page 151

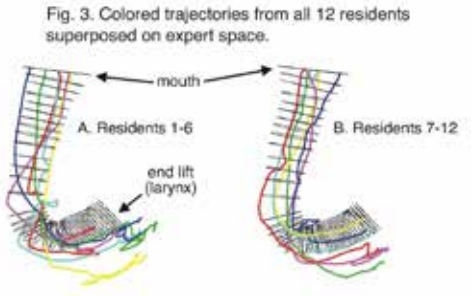
Poster Presentations, *continued from page 147*

Table. Full Model Parameter Estimates from Logistic Multilevel Modeling with HLM 7.01

		Intubation Success, Odds Ratio			
		Estimate	SE	p-value	OR
Level 1 (patient covariates)					
	Intercept (β_{0i})	1.774	0.304	< .001	5.895
	Pt Factors (β_1)	-0.394	0.406	0.334	0.675
	Pt Order (β_2)	0.047	0.083	0.571	1.048
Level 2 (subject covariates)			Intubation	Success	Rate
	Prev Exper (γ_{01})	0.799	0.425	0.097	2.224
Manikin test	Path Length (γ_{02})	0.147	0.100	0.178	1.159
Manikin test	Pct Conform (γ_{03})	0.032	0.013	0.040	1.033
		Number of Failed Laryngoscopies, Incident Rate Ratio			
		Estimate	SE	p-value	IRR
Level 1 (patient covariates)					
	Intercept (β_{0i})	-1.131	0.184	< .001	0.323
	Pt Factors (β_1)	0.346	0.226	0.129	1.414
	Pt Order (β_2)	0.002	0.047	0.968	1.002
Level 2 (subject covariates)					
	Prev Exper (γ_{01})	-0.396	0.237	0.134	0.673
Manikin test	Path Length (γ_{02})	-0.143	0.065	0.059	0.867
Manikin test	Pct Conform (γ_{03})	-0.018	0.007	0.045	0.982

Level 1: ηij = β0j + β1j*(Patient Factorsij) + β2j*(Patient Orderij)
Level 2: β0j = γ00 + γ01*(Previous Experiencej) + γ02*(Path Lengthj) + γ03*(Pct Conformityj) + u0j





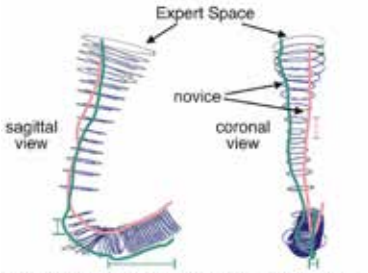


Fig. 2. Novice trajectories in color on two views of the expert space. Bars mark where novices deviate from the expert space. % conformity is the trajectory fraction inside the expert space.

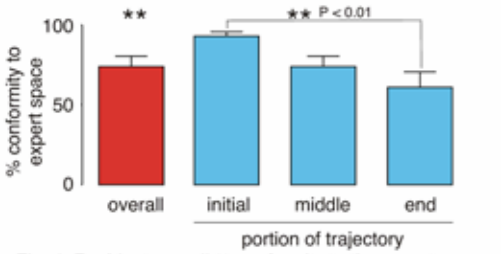


Fig. 4. Resident overall % conformity to the expert space was significantly less than 100%. Conformity was higher initially and decreased in the last third of the procedure.

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https://ww4.aievolution.com/ars1701/files/content/abstracts/abs_1979/Table.pdf

EEP 25 (1351)
Impact of Public Reporting of 30-Day Mortality on Timing of Death after CABG Surgery

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Introduction: Recent reports have raised concerns that public reporting of 30-day mortality after cardiac surgery may delay decisions to withdraw life-sustaining therapies in anticipation of death for some patients. We sought to examine whether mortality after coronary artery bypass graft (CABG) surgery significantly increases after day 30 in Massachusetts (MA), a state that reports 30-day mortality. We used New York (NY) as a comparator state, which reports combined 30-day and all in-hospital mortality, irrespective of time since surgery.

Methods: Design: Retrospective cohort study of patients who underwent CABG surgery in hospitals in MA and NY, 2008-2013. Setting: All hospitals in MA and NY that performed CABG surgery. Patients: All patients who underwent CABG surgery. Main Outcomes & Measures: We calculated the empiric daily hazard of in-hospital death, without censoring on hospital discharge. We used joinpoint regression to identify significant changes in the daily hazard over time.

Results: In MA and NY, 24,864 and 63,323 patients underwent CABG respectively. In-hospital mortality was low, with 524 deaths (2.1%) in MA and 1,398 (2.2%) in NY. Joinpoint regression did not identify a change in the daily hazard of in-hospital death at day 30, or at any point after day 30, in either state; significant joinpoints were identified on day 10 (95% confidence interval 7-15) for MA and days 2 (2-3) and 12 (8-15) for NY.

Conclusion: In MA, a state with a long history of publicly reporting cardiac surgery outcomes at day 30, we found no evidence of increased mortality occurring immediately after day 30 for CABG patients. These findings suggest that delays in withdrawal of life-sustaining therapy do not routinely occur as an unintended consequence of public reporting.

References:

None

Poster Presentations, *continued from page 149*

EEP 26 (1490)
Generative Retrieval Improves Learning and Retention of Cardiac Anatomy Using Transesophageal Echocardiography

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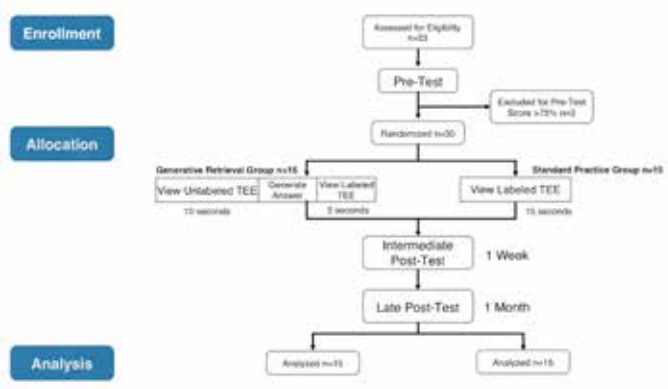
Introduction: Transesophageal echocardiography (TEE) is a valuable monitor for patients undergoing both cardiac and non-cardiac surgery as it allows for rapid evaluation of cardiovascular compromise in the perioperative period. It is challenging for anesthesiology residents and medical students rotating in anesthesiology to learn to use and interpret TEE in the busy clinical environment. A core, critical component of learning to use and interpret TEE imaging, is a strong grasp of normal cardiovascular ultrasound anatomy. Generative retrieval, a novel technique in which there is an attempt to retrieve (and produce) an answer from memory, has demonstrated efficacy as a learning and memory enhancement technique but is relatively unexplored in medical education.



Methods: Participants were randomized to learning TEE cardiac anatomy in a Generative Retrieval (GR) group and Standard Practice (SP) group. GR participants were required to verbally assign an identity to each unlabeled cardiac anatomical structure within 10 seconds of the TEE video appearing on the screen. After 10 seconds, a correctly labeled TEE video clip was shown to the GR participant for 5 more seconds. SP group participants viewed the same TEE video clips as GR group but there was no requirement for SP group participants to identify or generate an answer; for the SP group, each TEE video image was labeled with the correctly identified anatomical structure for the entire 15 second period. All participants were tested for intermediate (1 week) and late (1 month) retention of normal TEE cardiovascular anatomy. Improvement of intermediate and late retention of TEE cardiovascular anatomy was evaluated using a linear mixed effects model with random intercepts and random slopes.

Results: Fifteen fourth-year medical students and 15 post-graduate year (PGY) 1 and 2 anesthesiology residents without prior training in cardiac anesthesia or TEE viewed normal cardiac anatomy using TEE video clips (Figure 1). There was no statistically significant difference in baseline exam score between group GR (49% ± 11) and group SP (50% ± 12), with mean difference (95% CI) -1.1% (-9.5, 7.3%). At one week following the educational intervention, group GR performed significantly better than group SP (90% ± 5 vs. 82% ± 11, respectively), with mean difference (95% CI) 8.1% (1.9, 14.2%); p=0.012. This significant increase in exam scores persisted one month later in the late posttest session (group GR: 83% ± 12; group SP: 72% ± 12), with mean difference (95% CI) 10.2% (1.3 to 19.1%); p=0.026 (Figure 2). The mixed effects analysis showed significant improvements in TEE cardiovascular anatomy over time, at the rate of 5.9% and 3.5% per week for GR and SP groups respectively (p = 0.0003), and GR group improved marginally faster than SP (p = 0.065).

Conclusion: Medical students and anesthesiology residents inexperienced in the use of TEE showed both improved learning and retention of basic cardiac ultrasound anatomy with the incorporation of generative retrieval into the educational experience.

References:

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EEP 27 (1634)
Trends in Specialty Selection Among U.S. Medical Students from 2006-2016. How Does Anesthesiology Compare?

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Introduction: In the United States, more than 18,000 graduating medical students participate annually in the National Resident Matching Program (NRMP) to match into a training program of their chosen specialty.[1] Understanding historical and current directions of medical specialties may have important implications for shaping the future workforce of a given medical field.[2] While there is significant data tracking residency applications and match outcomes, analyses of recent trends in U.S. medical student specialty choice are limited. In this study, we describe the trends in specialty selection and compare the trajectories of anesthesiology against similar specialties. We hypothesize that the number of applicants relative to available positions for matching into anesthesiology is not only decreasing, but there is a growing disparity in comparison to other fields.

Methods: From the NRMP data from 2006-2016, we retrospectively analyzed medical specialty choice amongst U.S. medical school seniors. Specialties were selected for comparison to anesthesiology if they shared at least one of the following: (1) provides acute care [emergency medicine (EM)], (2) has minimal exposure during medical school [otolaryngology (ENT), orthopedic surgery], or (3) has the perception of controllable lifestyle [dermatology, radiology].[3] The primary outcome used to compare the trends was the ratio of applicants to total number of available positions for a given specialty. We performed a linear regression using specialty, year, and relationship between year and specialty in which anesthesiology served as the reference group. Regression coefficients with 95% confidence intervals and p-values were determined.

Results: Between 2006 and 2016, there were a combined total of 53,857 applicants for 60,893 positions for the included specialties, which represented 29.7% and 20.4% of the total number of NRMP applicants and positions, respectively. Different trends were observed in the total number of applicants and positions for each specialty (Figure 1). Table 1 depicts the ratio of applicants to positions. When compared to EM (95%CI 0.01-0.04,p<0.001), ENT (95%CI 0.01-0.04, p=0.001), and orthopedic surgery (95%CI 0.002-0.005,p<0.001), the divergence between applicants and available positions was statistically significant. Both dermatology (95%CI -0.01-0.02,p=0.216) and radiology (95%CI -0.02-0.01,p=0.201) did not reach statistical significance (Table 2).

Conclusion: Our results suggest that there is a growing disproportion between the number of U.S. medical students applying into anesthesiology and positions available. There exist significant differences in this trend between anesthesiology and other fields (i.e. EM, ENT, and orthopedic surgery). Specialties historically defined by the literature as those with controllable lifestyles (i.e. dermatology, radiology) failed to reach statistical significance. This increasing discrepancy in recruitment into the specialty may have important implications for the ability of anesthesiology to meet the increasing demand for quality care. Future investigation is needed to identify potentially modifiable factors to increase medical student interest in the specialty.

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2. Rivo, M., Satcher D. JAMA. 1993;270(9):1074-8.
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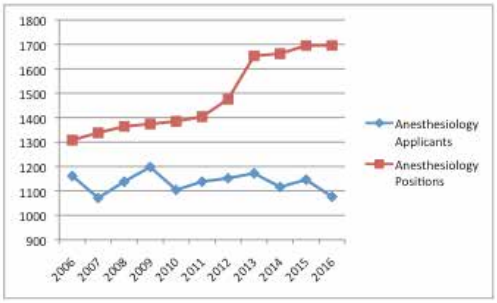

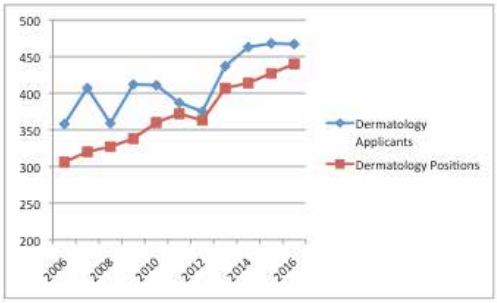

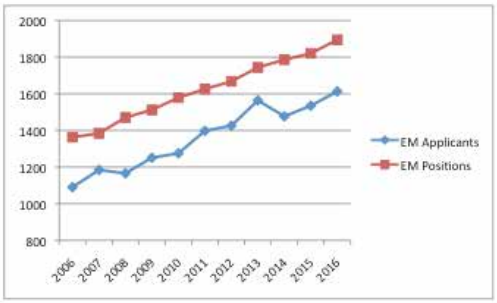

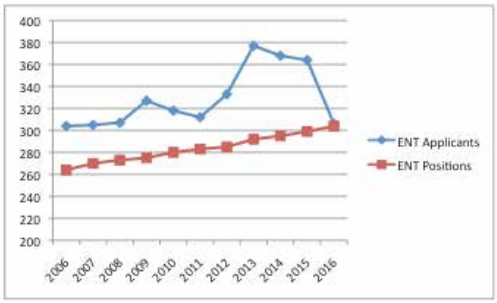

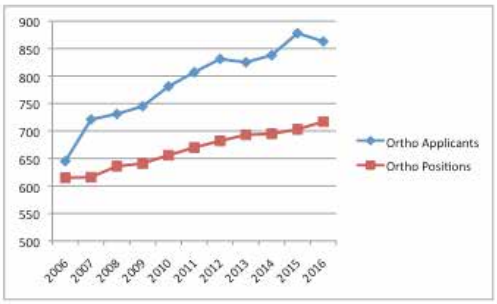

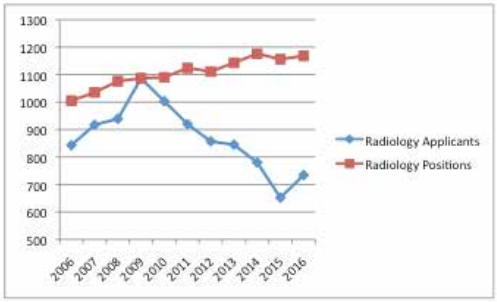

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EEP 28 (1081)
Global Overview of Anesthesiology Certification and Practice – A Survey Study

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Introduction: International collaboration among anesthesiologists necessitates mutual understanding of the educational backgrounds of each collaborator's country. However, a comprehensive description of worldwide training and certification systems has not yet been published. We aimed to describe anesthesiologists' training and certification processes in anesthesia societies in the world.

Methods: An electronic survey consisting of a 25-item questionnaire on anesthesia training and practice was sent by e-mail to 126 anesthesia societies that belong to the World Federation of Societies of Anaesthesiologists (WFSA). We sent reminders to non-responding societies two and three months later initial request. In addition, we contacted personal acquaintances to get responses regarding their societies. We referred to a WFSA website to obtain the numbers of members of each anesthesia society. To perform an economic analysis, we obtained data on each country's gross domestic product (GDP) and total population from government publications. The data received were tabulated and comparatively analyzed in three categories that included specific questions on the following factors: certification process (certification, examination by society, residency, subspecialty training requirements, and non-operative training requirements), recertification process (recertification, continuing medical education program), and non-anesthesiologist anesthesia care providers.

Results: We contacted 122 anesthesia societies except for four societies whose contact information was invalid. Twenty-six representatives for each society and eight personal acquaintances replied to the survey. The overall response rate was 27.9% (34/122 societies). Nations of 16 societies were members of Organization for Economic Co-operation and Development (OECD), while nations of the 18 other societies were not. The results are shown in Table 1. Twenty-eight societies except 6 societies including Estonia, Iceland, Micronesia, Rwanda, Venezuela, and Sweden had their certification process and their society's examination for the certification. All societies except Micronesia had residency programs. Out of the 28 societies with certification systems, 12 required both specific subspecialty training and non-operative training; 15 required one of the two, and China did not require either. Fourteen societies had recertification systems; five of those 14 societies had continuing medical education programs. Non-anesthesiologist healthcare professionals were reported to provide anesthesia care in 13 societies. Neither GDP per capita nor number of anesthesia society members per capita were associated with development of certification and recertification processes or the existence of non-anesthesiologist anesthesia care providers.

Conclusion: Anesthesia certification and recertification processes and backgrounds of anesthesia care providers widely varied among WFSA responders. Economic development and number of anesthesiologists had no relationship with the development of certification programs and availability of non-anesthesiologists care providers.

References:

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2. ACGME Program Requirements for Graduate Medical Education in Anesthesiology. https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/040_anesthesiology_2016.pdf (Last accessed on January 28. 2017)

continued on page 154

Table 1 Economic backgrounds and anesthesiology practice in responding societies

Society	GDP	Nominal GDP	Society member	Member per population	Certification	Examination	Residency	Sub-specialty training	Non-operative training	Recertification	CME program	Non anesthesiologist
USA	17940	58	32009	104	Y	Y	Y	Y	Y	Y	Y	Y
NZ	172	41	509	120	Y	Y	Y	Y	Y	Y	Y	N
Ukraine	91	2	112	2	Y	Y	Y	Y	Y	Y	Y	N
Latvia	27	13	330	154	Y	Y	Y	N	Y	Y	Y	N
Moldova	8	2	114	32	Y	Y	Y	N	Y	Y	Y	N
Korea	1417	28	2500	49	Y	Y	Y	Y	Y	Y	N	Y
Slovenia	39	19	200	97	Y	Y	Y	Y	Y	Y	N	N
Mongolia	12	4	80	26	Y	Y	Y	Y	Y	Y	N	N
Japan	4124	32	7118	56	Y	Y	Y	Y	N	Y	N	Y
HK	309	42	350	48	Y	Y	Y	Y	N	Y	N	N
Israel	296	35	340	40	Y	Y	Y	N	Y	Y	N	N
Nigeria	481	3	6241	34	Y	Y	Y	N	Y	Y	N	Y
Brazil	1885	9	11346	55	Y	Y	Y	N	Y	Y	N	Y
China	10982	8	12016	9	Y	Y	Y	N	N	Y	N	N
Bangladesh	157	1	100	1	Y	Y	Y	Y	Y	N	N	N
Myanmar	57	1	380	7	Y	Y	Y	Y	Y	N	N	Y
Turkey	8561	109	2536	32	Y	Y	Y	Y	N	N	N	Y
Finland	300	55	1151	210	Y	Y	Y	N	Y	N	N	N
France	2421	36	2500	38	Y	Y	Y	N	Y	N	N	Y
Australia	1223	51	2250	94	Y	Y	Y	Y	Y	N	N	N
Czech	182	17	950	90	Y	Y	Y	Y	Y	N	N	N
Slovak	87	16	400	74	Y	Y	Y	Y	Y	N	N	N
Singapore	293	53	234	42	Y	Y	Y	Y	Y	N	N	N
Malta	10	23	78	181	Y	Y	Y	N	Y	N	N	N
S. Africa	313	6	1072	20	Y	Y	Y	N	Y	N	N	Y
Nepal	21	1	243	9	Y	Y	Y	N	Y	N	N	N
Lao	12	2	60	9	Y	Y	Y	N	Y	N	N	Y
India	2007	2	2178	2	Y	Y	Y	N	Y	N	N	N
Sweden	493	50	1600	162	N	N	Y	N	N	N	N	Y
Iceland	19	59	50	152	N	N	Y	N	N	N	N	N
Estonia	21	16	212	162	N	N	Y	N	N	N	N	N
Rwanda	8	1	19	2	N	N	Y	N	N	N	N	Y
Venezuela	374	13	1260	43	N	N	Y	N	N	N	N	N
Micronesia	0	3	7	70	N	N	N	N	N	N	N	Y

GDPs are shown as per US $10 billion. Nominal GDPs are shown as per thousand. Numbers of society members were calculated as per one million population.
GDP: gross domestic product, CME: continuing medical education, NZ: New Zealand, HK: Hong Kong, S. Africa: South Africa

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Poster Presentations, *continued from page 154*

GA 29 (1599)
Persistent Pain is Associated With Accelerated Memory Decline and Dementia in a Longitudinal Cohort of Elders

Elizabeth L. Whitlock, MD, MSc[1], L. G. Diaz-Ramirez, MS[1]; M. M. Glymour, ScD, MS[1]; W. J. Boscardin, PhD[1]; Kenneth E. Covinsky, MD[1]; Alexander K. Smith, MD, MPH[1]

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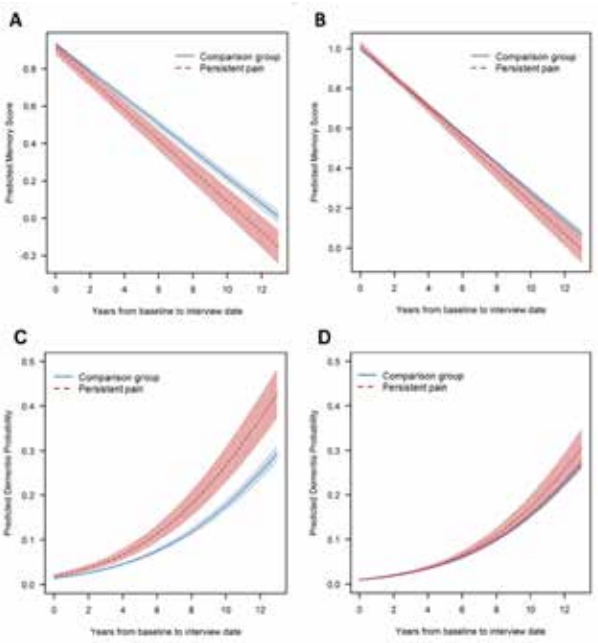
Introduction: Chronic pain is common among the elderly and is associated with poor performance on neuropsychiatric testing, particularly in the domains of memory and attention. It is unknown whether this reflects accelerated cognitive decline during later life. Using data from the Health and Retirement Study (HRS), a population-based longitudinal study of elders with data ascertainment by biennial interview, we modeled the association between persistent pain at cohort inception and measures of memory and dementia probability over the following 12 years.

Methods: We studied HRS participants who were at least 62 in 2000 and answered pain and cognition questions by self-report in both 1998 and 2000. Elders who reported being often troubled with moderate or severe pain in both the 1998 and 2000 HRS interviews were considered to have 'persistent pain.' Composite memory score and dementia probability were estimated by combining HRS cognitive test results and/or proxy ratings of participant's cognition according to published methodology[1]; cognitive measures were tracked until death/dropout or the 2012 interview. Linear mixed effects models, accounting for demographic and comorbidity covariates fixed at the 2000 interview and allowing random slope and intercept for each participant, were used to estimate the impact of persistent pain on the slope of the population-level memory score and dementia probability trajectories, applying sampling weights to represent the 2000 US population age 62+. To quantify the possible impact of persistent pain on functional independence, we combined our primary results with information on the association between memory and dependence in ability to manage medications and finances.



Results: Participants with proxy response in 1998 or 2000 (n=1292), and those who did not complete pain or cognition testing (n=701), were excluded; 10,065 participants made up the final cohort, of whom 10.9% reported persistent pain. The pain group reported pain at 69% of subsequent interviews, suggesting this approximates a chronic pain phenotype (Table 1). After covariate adjustment, persistent pain was associated with 9.2% (95% CI 2.8-15.0%) faster memory decline compared with controls (Figure 1A-B). After 10 years, the memory score decrement translated to a 15.9% higher relative risk of inability to manage medications and 11.8% higher relative risk of inability to manage finances independently. Adjusted dementia probability increased 7.7% faster (95% CI 0.5-14.2%) for those with persistent pain (Figure 1C-D).

Conclusion: Persistent pain, which may reflect chronic pain, is associated with accelerated memory decline and development of dementia. Care providers should be aware of this association, which may help identify patients at higher risk for current and incident cognitive impairment.

References:

1. Alzheimer Disease and Associated Disorders 2013, 27(3):207-212

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GA 30 (1728)
Subjective and Objective Memory Function after Cardiac Surgery or Cardiac Catheterization: A Population-Based Cohort Study

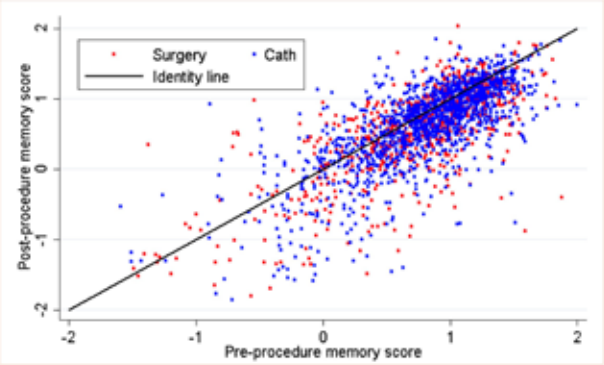
Elizabeth L. Whitlock, MD, MSc[1], L. G. Diaz-Ramirez, MS[1]; M. M. Glymour, ScD, MS[1]; W. J. Boscardin, PhD[1]; Michael Avidan, MBBCh[2]; Kenneth E. Covinsky, MD[1]; Alexander K. Smith, MD, MPH[1]

[1]University of California, San Francisco, San Francisco, CA, [2]Washington University School of Medicine, St. Louis, MO

Introduction: Some studies suggest postoperative cognitive dysfunction disproportionately affects patients undergoing cardiac surgery. However, few studies use an appropriate nonsurgical control group, and cognitive evaluations are performed in a periprocedural research context, with results potentially affected by anxiety or acute health considerations. Studying postprocedural cognitive change in a longitudinal population-based dataset, with cognitive evaluations performed without regard to procedural status, may therefore be informative.

Methods: Community-dwelling elders 62 and older enrolled in the population-based Health and Retirement Study (HRS) were interviewed every two years. Participants were asked if they had undergone 'surgery on [their] heart' or 'cardiac catheterization, coronary angiogram or angioplasty' in the preceding two years. Group membership was determined by the first self-report of a cardiac catheterization procedure or heart surgery at any HRS interview between 2000 and 2012. If both procedures were reported at a single HRS interview, the participant was assigned to the surgery group. The primary outcome was change in composite memory score from the pre-procedure HRS interview to the post-procedure interview, derived from objective memory testing scored according to published methodology[1] and evaluated with multivariable linear regression. Secondary outcomes were self-reported memory decline at the interview following the cardiac procedure and decline in 5-item Likert scale rating of post-procedure memory compared with the pre-procedure interview wave, evaluated with multivariable logistic regression. Adjustment factors included demographics, economic indicators, and medical comorbidities reported at the 2000 wave.

Figure 1. Pre-procedure and post-procedure objective memory score, for each participant, by procedure group. Identity line is included to assist with interpretation. Higher memory scores indicate better summary memory performance.



Results: Of the 2,363 participants who underwent a cardiac procedure during the study period, 1,457 (61.7%) underwent cardiac catheterization and 906 (38.3%) had heart surgery. Participants in the surgery group were more likely male, Caucasian, married/partnered, and had lower levels of depressive symptoms and functional limitations than participants in the catheterization group (Table 1). There was no association between type of procedure and rate of decline in objective memory score in bivariate or multivariable adjusted models (Figure 1; Table 2). Surgery was also not associated with lower Likert scale memory rating following the procedure (adjusted OR 1.13 [0.93-1.38], p=0.23) or self-reported worsening of memory in the interview following surgery (adjusted OR 1.13 [0.93-1.38], p=0.21).

Conclusion: There were no statistically significant associations with subjective or objective memory decline following patient-reported heart surgery, compared with cardiac catheterization, in this large population-based study. While the point estimate for objective memory score suggests no clinically-relevant procedural impact on memory, trends in measures of subjective memory invite the intriguing interpretation that patients perceive but do not objectively demonstrate a decrement in memory following cardiac surgery.

References:

1. Alzheimer Disease and Associated Disorders 2013, 27(3):207-212

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PED 31 (2107)
Quantitative MRI Study Evaluating Prolonged Sedation on the Brain Growth in Infants Younger than 6 Months

David M. Gilman, MD Candidate[1]; Hannah W. Kilcoyne, BS Candidate[1]; Sophie L. Wilcox, PhD[1]; Russell W. Jennings, MD[1]; Patricia E. Grant, MD[1]; **Dusica M. Bajic, MD, PhD**[1]

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Introduction: Neonates and infants are routinely treated with prolonged administration of opioids and benzodiazepines for pain and sedation management [1,2]. This prolonged sedation treatment is associated with a high incidence of tolerance and dependence to drugs. There is a lack of knowledge regarding the impact of such treatment on the developing brain. We hypothesized that prolonged sedation associated with opioid and benzodiazepine dependence in premature and full-term infants younger than 6 months of age is associated with significant decrease in (1) total brain volumes, and (2) volumes of subcortical structures, when compared to controls.

Methods: Both full-term (N=4) and pre-term patients (N=5-7), and otherwise healthy controls (N=3) were scanned non-sedated at Boston Children's Hospital using a 3T magnetic resonance imaging (MRI) scanner as per IRB approval. 3D T1 anatomical images were acquired using a 32-channel head coil (TR 2520ms; TE 1.75ms; FOV 180x180; slice thickness 1mm; voxel size 1.0x1.0x0.99 mm). Total brain volumes and volumes of subcortical structures were estimated using FSL's Integrated Registration and Segmentation Tool (FIRST; Fig. 1A-C), and subsequently manually edited for accuracy. End-point analyses included: (1) neuroradiology reports, (2) individual and averaged total brain volumes (mm3), and (3) averaged estimated (mm3) and normalized volumes (% total brain volume) of forebrain subcortical structures (caudate, putamen, globus pallidus, n. accumbens, hippocampus, thalamus, and amygdala) and that of the brainstem.

Results: The majority of both full-term and premature infants showed several abnormalities on neuroradiology reports (e.g. abnormalities in extra-axial space volume, parenchymal changes, and/or immaturity of myelinated tracts) that were not found in controls. Structural analysis by FIRST underestimated total brain volumes by 34.91% ± 0.06 in comparison to manual segmentation and as a result required subsequent manual editing of segmented volumes. We found no differences in average volumes of either total brain or any subcortical structures analyzed between the 3 groups using FIRST (Fig.1 D-F).

Conclusion: Considering the discrepancy between neuroradiology reports and volumetric analysis of our data, future studies should further investigate the effects of prolonged sedation with opioids and benzodiazepines in the developing brain of the youngest of patients. Techniques to improve automated segmentation of infant brains that would elucidate subtle drug effects should be developed. Supported by NIH K08DA035972 (DB).
Figure 1 Legend. Brain segmentation: Panel A shows representative brain MRI of an infant < 6 months in sagittal, coronal, and transverse planes. Panel B shows total brain segmentation (illustrated in red) that was manually edited. Panel C shows subcortical structures segmentation as obtained by FIRST. Average total brain volume (mm3)/ group was shown in Panel D. Although the average total brain volume for premature infants was smaller, there were no statistical differences between groups analyzed. Panel E illustrates the total brain volumes for individual infants/ group, while Panel C shows the same with age (corrected age for premature infants) at the time of MRI scan (months). The latter graph also implicates no difference in total brain volume in patients (full-term or premature) versus controls.

References:

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2. Attarian S, et al. (2014). The Neurodevelopmental impact of neonatal morphine administration. Brain Sci 4(2):321-334.

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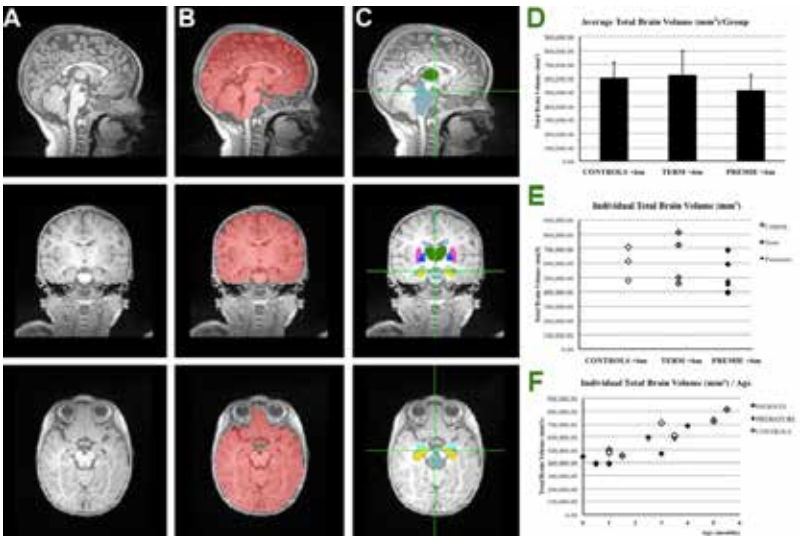
Poster Presentations, *continued from page 157*

Postoperative Opioid Consumption											
Fixed Effects	Estimate	SE	p	Fixed effects	Estimate	SE	p	Fixed effects	Estimate	SE	p
Intercept	99.8	50.3	0.05	Intercept	111.5	48.4	0.02	Intercept	97.1	49.6	0.05
PCS	0.4	0.3	0.11	Depression	1.1	0.7	0.14	Anxiety	1.2	0.7	0.07
Preoperative Morphine	0.9	0.2	< 0.001	Preoperative Morphine	0.9	0.2	< 0.001	Preoperative Morphine	0.9	0.2	< 0.001
Procedure (Redo)	14.0	5.5	0.01	Procedure (Redo)	12.2	5.4	0.02	Procedure (Redo)	13.1	5.4	0.02
Osteotomies	3.3	1.7	0.05	Osteotomies	3.6	1.7	0.03	Osteotomies	3.4	1.6	0.04
Intraop opioids	0.1	0.10	0.10	Intraop opioids	0.2	0.10	0.09	Intraop opioids	0.1	0.1	0.14
Random effects (σ^2)											
Intercept	1165				1103				3.47		



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PED 32 (2212)
Long-Term, Persistent Deficits in Neurotransmission Following Multiple Exposures to Anesthesia in Infant Non-Human Primates

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Introduction: The US Food and Drug Administration warns that long or repeated administration of anesthetics in fetuses to young toddlers can lead to deleterious effects on brain development. We previously published data that a single exposure to anesthetics causes cell death to the developing brain in a region specific manner with higher injury to cortical regions and less to subcortical regions such as the striatum(1). In the current study, a detailed analysis of the long-lasting neurocircuitry effects observed two years after a one-time exposure (1X) versus multiple exposures (3X) to the inhaled anesthetic isoflurane (ISO) in infant non-human primates (NHPs) was performed. At two years of age, we examined membrane properties, action potential firing, GABAergic and glutamatergic neurotransmission in cortical regions displaying the highest neuroapoptosis (visual and somatosensory cortex) and a subcortical region (putamen) that was less-sensitive to 1X ISO. Specifically, the hypothesis tested was that ISO exposure of infant NHPs will cause long-lasting impairments in neurotransmission observed at 2 years of age that is most severe in cortical regions and that these impairments are exacerbated in individuals exposed to 3X ISO.

Methods: With IACUC approval, 6 day-old rhesus macaques (n=8 per group, 4 male and 4 female) were divided into control, 1X ISO and 3X ISO. ISO was administered via face-mask and spontaneous ventilation for 5 hours. The 1X ISO were exposed at P6, while 3X ISO were exposed at P6, P9, and P12. The control group underwent similar procedures on the same postnatal days (P6, P9, P12) including IV cannula, physiological measurements and handling without ISO administered. 1X ISO underwent this control protocol on days P9 and P12. At 2 years of age, monkeys were sent to necropsy and their brains were harvested for ex vivo whole cell patch clamp electrophysiology targeting projection neurons of the putamen (a striatal structure), visual cortex (V1) and somatosensory cortex (S1/2). We also examined resting membrane properties and action potential characteristics in projection neurons from these brain regions.

Results: Developmental ISO exposure did not alter resting membrane properties, but led to a dose-dependent increase in action potential frequency and decreased rheobase, the minimum current needed to reach action potential threshold. Excitatory postsynaptic current frequency was increased 2 years after a single ISO exposure (1X ISO) in all brain regions examined and even more pronounced after multiple exposures (3X ISO) in the somatosensory cortex, suggesting a dose dependent persistent functional injury in that brain region. 3X ISO also resulted in increased GABAergic transmission in all three brain regions but not in individuals exposed to 1X ISO. These changes in GABAergic and glutamatergic transmission suggests impairments in excitatory to inhibitory balance.

Conclusion: A dose-dependent alteration in excitation/inhibition balance was observed 2 years after ISO exposure during infant brain development in rhesus macaques. This effect was seen in areas with high cell death (cortex) and regions with less cell death (putamen) observed hours after ISO exposure. Therefore, the degree of cell death may not be a measure that precisely predicts impaired neural circuitry later in life. Translationally, our results are concerning as they suggest that similar anesthetic exposure during brain development may lead to long-lasting changes in neurotransmission in children.

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Poster Presentations, *continued from page 159*

PED 33 (1756)
An Objective Measure of Neuraxial Block Onset and Offset

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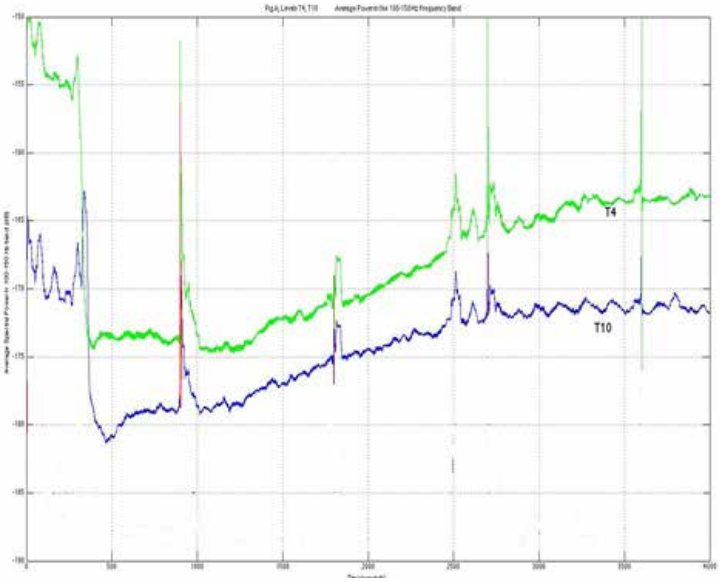
Introduction: Introduction: Caudal anesthesia is commonly performed using local anesthetics to afford intra- and post-operative pain relief. However, no objective monitor exists to gauge the onset and offset of the medication administered epidurally. A novel monitor objectively measures and reports the effect of local anesthetics by detecting changes in the underlying (non-stimulated) electromyogram (EMG) during administration of local anesthetic.



Methods: We performed a pilot study to evaluate the monitor's performance. 10 piglets were anesthetized, intubated, and mechanically ventilated. ECG, rectal temperature, pulse oximetry, end-tidal CO2, end-tidal isoflurane, and arterial pressure were continuously monitored. The blockade monitoring system (Biopac MP150) was applied to each piglet using percutaneous needles at the T4 and T10 dermatomal and monitored using EMG and EKG amplifiers. Continuous measurements were taken and reported at baseline, dose (chloroprocaine 3% caudal vs extra-caudal ('failed'), (1ml/kg bolus injection at 300sec). After 60 minutes of monitoring, the piglets were euthanized and a laminectomy (T4-S1) was performed to confirm and document the placement and distribution of the injectate.

Results: After randomization and confirmed correct placement of the block, 4 piglets received caudal injection of local anesthetic.Graph analysis was used to plot data in time vs EMG power response (100-150Hz). Timing to peak effect and timing to 50% recession of peak effect were measured. Average time to peak effect in T4 and T10 was 5.63 ±3.35 and 8.33 ±2.17 seconds, respectively (T-test p=NS). Average time to 50% recession of peak effect was 27.9 ±4.53 and 21.9 ±1.38 seconds, respectively (T-test p=NS). Data was not significant between levels (T4 vs T10).

Conclusion: Objective measurement of real time changes associated with acute injection of local anesthetic in the caudal space were performed at T4 and T10 levels. Time from dose to peak effect and time from peak effect to 50% return to baseline were easily measured. These preliminary measurements are consistent with clinical reports using local anesthetics and suggest that it is possible to objectively measure real-time changes from epidural blockade. This preliminary data justifies further investigation regarding the feasibility of real-time objective measurement of local anesthetic effect in neural blockade. Larger groups to confirm preliminary data are warranted. Further study would include modifications of injection characteristics (drug, dose, volume, rate, adjuncts temperature, etc.) and elaboration of previously performed clinical studies.

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Poster Presentations, *continued from page 160*

PED 34 (2174)
Hemostasis Management in a Pediatric Patient with Hermansky-Pudlak Syndrome

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Introduction: Hermansky-Pudlak Syndrome (HPS) is a rare, autosomal recessive disorder with genetic heterogeneity that impairs protein trafficking to lysosomal organelles. To date, ten genetically distinct subtypes have been described. Diagnosis requires tyrosinase-positive oculocutaneous albinism and a platelet storage pool deficiency. Other associated manifestations include interstitial lung disease and granulomatous colitis[1,2,3]. While the worldwide frequency is unknown, since 1992, only 1,200 patients have registered with the Hermansky-Pudlak Syndrome Network, an organization that provides support and resources for affected individuals [2]. Given the rarity of the disease, little is known about HSP patients undergoing surgery and how to address their associated bleeding diathesis. The only known test to quantify the extent of platelet dysfunction is by establishing the presence or absence of dense bodies (delta granules) in platelets by electron microscopy [1,2,4]. Thus, the use of platelet transfusions or desmopressin is often suggested empirically in the event of hemorrhage during surgery [1,2,5]. We report the management of a pediatric patient with HPS who presented for a video-assisted thoracic surgery.

Methods: A thirteen y.o. boy with history of HPS type 9 and episodes of significant epistaxis and bruising presented for a thoracoscopic right apical blebectomy and mechanical pleurodesis after sustaining a spontaneous pneumothorax secondary to bleb rupture. The patient was intubated with a 32 French left-sided double-lumen endotracheal tube after uneventful intravenous induction with propofol, fentanyl and rocuronium. Anesthesia was maintained with isoflurane. The patient tolerated one-lung ventilation well. Hematology was consulted preoperatively regarding management of the bleeding diathesis and recommended platelet transfusion prior to incision and after closure. A total of 399 mL of apheresis-platelets was given. Intraoperative blood loss was minimal (10 mL) and the patient remained hemodynamically stable. After the surgical procedure, a right paravertebral catheter was placed under ultrasound guidance prior to emergence. The paravertebral catheter was removed on the second postoperative day, and absence of bleeding and neurological complications was confirmed by observation for several hours prior to discharge.

Results: Case report.

Conclusion: We report the successful anesthetic management of a patient with HPS undergoing thoracoscopic surgery. In this patient, hemostasis was maintained both intraoperatively and postoperatively during placement of a regional block by empiric transfusion of platelets for the assumed bleeding diathesis. Because of his platelet dense body deficiency and a history of prolonged, spontaneous episodes of epistaxis, the hematology team recommended transfusing platelets perioperatively despite his normal platelet count. Indeed, there was no viable method to quantify the extent of his coagulopathy. Given the apparent effectiveness of this platelet transfusion therapy and associated minimal intraoperative bleeding, we felt comfortable placing a right paravertebral catheter. The patient remained stable in the immediate postoperative period and two days later upon removal of the paravertebral catheter. While our anesthetic management may not be applicable to every HPS patient during surgery, we recommend perioperative platelet transfusions as a viable option to augment hemostasis in the setting of a platelet storage pool disorder.

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PED 35 (2081)
Anesthetic Management of Combined Renal-Liver Transplant in a Pediatric Patient with Primary Hyperoxaluria

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Introduction: Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disorder caused by mutations in the AGXT gene which encodes the vitamin B6-dependent liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase. This deficiency leads to elevated levels of oxalate and glycolate. Oxalate is excreted in the urine, where it forms crystals with calcium, leading to oxalate stones, nephrocalcinosis, tubular epithelial damage, and renal failure. Systemic crystal deposits may lead to bone fractures, decreased vision, arthritis, neuropathy and cardiac failure.[1] For over two decades the predominant strategy for management of PH1 has been to directly pursue combined renal-liver transplant (CRLT) for patients with kidney failure.[2] The anesthetic management of pediatric patients undergoing CRLT can be challenging: intraoperative blood loss and coagulopathy are common and fluid management goals differ significantly between the two parts of the procedure with limited literature available to guide practice.

Methods: Case Report.

Results: A 13-year old male with end-stage renal disease secondary to PH1 on intermittent hemodialysis (IHD) six days a week, presented for CRLT using a deceased-donor whole liver and kidney graft. Preoperative laboratory evaluation showed: hemoglobin 11.6 g/dL, platelet count 137,000/mm^3, INR 1.06, fibrinogen 291 mg/dL and PTT 26s. The liver transplant was performed first. Hemodynamics were supported with an epinephrine infusion around the time of reperfusion. Central venous pressure (CVP) was maintained between 6-8 mmHg. For the subsequent renal transplant, the vasoactive agent was switched to dopamine for hemodynamic support and the CVP was raised to 10-14 mmHg. Estimated blood loss was 700mL. The patient received 270mL packed red blood cells, 116mL cryoprecipitate, 125mL cellsaver, and 2500mL 5% albumin. After completion of the surgery, the patient remained intubated and was transferred to the surgical intensive care unit in stable condition. IHD was continued postoperatively to avoid kidney graft damage from oxalate released from tissue stores.

Conclusion: Management of volume status, coagulopathy and hemodynamics are crucial aspects of anesthetic care for CRLT. We aimed to maintain a lower CVP during the liver transplantation part to facilitate dissection and decrease bleeding,[4,5] thereby reducing the need for blood product transfusion and its associated negative impact on postoperative patient outcomes.[6] The CVP was raised with colloid infusion for the renal transplantation part to facilitate graft perfusion, earlier diuresis and to decrease the incidence of postoperative acute tubular necrosis.[7] Our patient had stable liver function without signs of coagulopathy at time of transplant which simplified management. There are no published studies to guide the choice of vasopressors/inotropic agents for CRLT. Epinephrine was chosen for reperfusion due to its strong inotropic and vasoconstrictive properties; the agent was switched to low-dose dopamine for the renal transplant part to avoid constriction of renal allograft vasculature. In conclusion, we present the successful anesthetic management of a patient with PH1 undergoing CRLT. The patient had an uncomplicated postoperative course with good liver and kidney graft function. He was continued on IHD to address oxalate tissue stores that may remain elevated for up to 3 years.[8]

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Poster Presentations, *continued from page 162*

L 36 (1524)
IL-33 Critically Modulates Foxp3+Treg Responses in a Mouse Model of Drug-Induced Hepatitis

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Introduction: Liver disease is the sixth most common cause of death in adults between the ages of 25 and 64. Liver disease can be triggered by many agents and occurs through common mechanisms. Drug-induced hepatitis is a rare complication of halogenated volatile anesthetic administration, antibiotics, NSAIDS and other drugs[(1)]. Studies suggest that IL-4-mediated, Th2-polarized, immune reactions initiate drug-induced hepatitis[(3,4)] while mechanisms that modulate the severity of hepatitis remain elusive. We modeled hepatitis in BALB/c mice by immunizing them with liver proteins covalently modified by trifluoroacetyl chloride anesthetic metabolites (TFA-JHDN5)[(4)]. We previously found that IL-33-/- mice developed drug-induced hepatitis by histology, but had higher rates of death as well as diminished hepatic IL-10, Foxp3+ regulatory T cell (Treg) RNA, and fewer splenic Foxp3+ Tregs when compared to BALB/c, wild-type mice. Foxp3+ Tregs regulate the response of effector T cells by down-regulating pro-inflammatory genes such as IL-2, and activating CTLA-4 (5). IL-33 is a Th2 cytokine that mediates inflammation through IL-4 and is associated with severe allergic and autoimmune inflammation[(2,3)]. We hypothesized that in drug-induced hepatitis, IL-33 modulates severity by promoting Foxp3+ Treg maturation and function.

Methods: Treg numbers and CD4+ T cell proliferation were assessed in BALB/c and IL-33-/- mice ± TFA-JHDN5 subcutaneous immunization on days 0 and 7. CD45+(PerCP)CD4+(FITC) CD25+(PE)Foxp3+(APC) Tregs and proliferation were measured by flow cytometry. Proliferation (CD4+(APC) in BALB/c and IL-33-/- splenocytes was measured following CFSE labeling, stimulation with anti-CD3e/anti-CD28 and co-culture ± Tregs (1:100) isolated using magnetic beads, with and without IL-10 supplementation in vitro.

Results: IL-33-/- mice produced fewer Tregs in the liver and spleen following immunizations. CD4+ T cell proliferation between IL-33-/- and BALB/c mice were similar, with or without immunizations. Tregs from BALB/c mice suppressed proliferation of CD4+ T cells in both strains while Tregs from IL-33-/- mice did not. IL-10 supplementation (0-10ng) of IL-33-/- splenocyte cultures surprisingly increased CD4+ T cell proliferation; however, Treg numbers were essentially unchanged.

Conclusion: We demonstrated that IL-33 may not regulate CD4+T cell proliferation, which is known to initiate drug-induced hepatitis but is necessary for Treg maturation and function. We also demonstrated that IL-10 could not up-regulate IL-33-/- Tregs. Instead, we discovered that IL-10 induced CD4+ T cell proliferation in splenocytes from IL-33-/- mice. We conclude that IL-33 deficiency may disable regulation of inflammation once it is initiated. This immune dysregulation could result in destructive effects similar to those seen in patients with autoimmune disorders. Our findings may have implications in morbidity and mortality in drug-induced hepatitis and other liver diseases.

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GH 37 (2014)
Monitoring Pediatric Perioperative Anesthesia Care and Mortality Rates in a Sample of Kenyan Hospitals: Initial Results from over 5,000 Cases

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Introduction: Perioperative mortality rate (POMR) serves as an important indicator for the quantification of the safety of anesthesia and surgical care[(1)]. However, pediatric POMR data is particularly lacking in low and middle-income countries (LMIC). We report preliminary results in a sample of various types of hospitals in Kenya.

Methods: After IRB approval, anesthesia care providers were educated on data collection logistics and pediatric case-specific data collection was started in January 2014 using a novel electronic collection tool. Data fields included hospital setting (pediatric referral, private, government), provider training level, patient demographics, surgery and anesthetic details, and POMR. Pediatric case was defined as any patient under the age of 18 undergoing any surgical procedure except cesarean section. A logistic regression model was created for the cases performed at the pediatric referral hospital, including gender, age, weight, ASA c8 relassification, emergent status, and time of surgery.

Results: Data was collected on 5,053 surgical cases from 22 hospitals in the last 36 months. Most cases (3,783; 74.9%) were collected at a major pediatric referral and teaching hospital, whereas 580 (11.5%) cases were from 14 government hospitals and 690 (13.6%) were from 7 private hospitals. Case characteristics revealed the following: ASA 1/2 (4,786; 95%), age less than 3 years (1,480; 29.3%) and between 3 and 18 years (3,105; 61.4%), general anesthesia (4,523; 89.5%). Two thousand one hundred four cases (41.6%) were done in patients who weighed less than 10kg, of which 1,806 (85%) were performed at the pediatric referral hospital. While neurosurgical (635; 16.8%) and plastics and burn surgery (943; 24.9%) were a higher percentage of the case mix in the referral hospital, orthopedic cases (299; 43%) were the highest in the private setting and general surgery cases (215; 37%) were highest in government hospitals. Performance of Safe Surgery Checklist was recorded for 99.5% and 97% of cases at the referral and private hospitals respectively, while it was only recorded for 72% of cases in government hospitals. Cumulative perioperative mortality for all hospital types at 24hrs, 48hrs, and 7day was 67 (1.32%), 77(1.52%), and 88 (1.74%) patients, respectively. Seven-day mortality data was available for 3,582 (70.9%) patients. Logistic regression analysis for cases performed at the referral hospital revealed that patient weight less than 2kg was a significant predictor of mortality at 48hr (OR=9.28, 95%CI: 1.92-44.93, p<0.01) and 7day (OR=12.24, 95%CI: 2.31-64.71, p<0.01), while emergency case status was a significant predictor of mortality at 24hr (OR=3.13, 95%CI: 1.22-8.01, p<0.01), at 48h (OR=2.81, 95%CI: 1.10-7.16, p<0.01) and 7day (OR=3.00, 95%CI: 1.27-7.12, p<0.01).

Conclusion: Prospective pediatric POMR data collection by anesthesia care providers, using electronic point of care devices is possible in a LMIC country. Patient weight and emergency status appear to be associated with increased pediatric POMR, although this model needs to be tested in future patient cohorts from various hospital settings. These findings provide vital information regarding the feasibility of case-specific data collection and overall POMR in Kenya to further inform quality improvement measures. (Funding: GE Foundation)

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RES 38 (1459)
Incidence of Respiratory Depression Following Inpatient Surgery

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Introduction: Respiratory depression is a potential adverse event in the perioperative setting. It is attributed to drugs used to anesthetize, sedate, paralyze and control pain as well as comorbid medical conditions.[1,2] As respiratory depression may negatively affect patient outcomes, much effort is made to effectively monitor and manage respiratory depression post-operatively. In this study, the incidence of respiratory depression was assessed for inpatient surgeries.

Methods: A retrospective cohort study using QuintilesIMS Charge Data Master (CDM) database covering over 450 hospitals across the United States was performed. All charge claims of inpatient surgeries from participating hospitals were collected if a patient underwent a planned surgery with an inhaled anesthetic during July 1, 2014 – June 30, 2015. To avoid other clinical conditions that potentially affect the occurrence of respiratory depression, any surgeries of the nervous, respiratory, or cardiovascular systems as well as obstetrical surgeries were excluded. After exclusions, the 10 most frequent surgeries were identified by their ICD-9 or CPT procedure code. Based on procedures and medications prescribed during hospitalization, seven post-surgical conditions were specified as indicators of respiratory depression. The incidence of respiratory depression was recorded and further described by surgery type.

Results: A total of 17,727 patients with inpatient surgeries were included according to the selection criteria and 715 (4.03%) events of respiratory depression were observed (Table 1). Among the top 10 most frequent surgeries, the incidence rate of respiratory depression ranged from 1.08% to 7.80%. Patients with laparoscopic vertical sleeve gastrectomy (ICD-9 code 43.82) had the highest likelihood of experiencing respiratory depression while patients undergoing an excision of intervertebral disc (ICD-9 code 80.51) were least likely to be associated with respiratory depression.

Table 1. Incident rate of respiratory depression after planned inpatient surgery

Procedures	ICD-9 Procedure Code	Total N	Incidence Rate (%)
All surgeries	-	17,727	4.03
Other cervical fusion anterior column anterior technique	81.02	1,871	3.21
Total knee replacement	81.54	1,867	4.66
Total hip replacement	81.51	1,153	4.25
Lumbar lumbosacral fusion post column post technique	81.07	760	3.82
Laparoscopic vertical sleeve gastrectomy	43.82	667	7.80
Other & unspecified total abdominal hysterectomy	68.49	554	1.99
Excision of intervertebral disc	80.51	553	1.08
Laparoscopic cholecystectomy	51.23	518	5.79
Lumbar lumbosacral fusion ant column anterior technique	81.06	479	5.43
Lumbar lumbosacral fusion ant column post technique	81.08	387	4.13

Conclusion: This nationwide study illustrated that a portion of patients experienced respiratory depression after a planned surgery and demonstrated that the incidence of respiratory depression varied up to 7.2 fold across different surgical procedures. In addition to considering patients' clinical presentation and existing risk factors for respiratory depression, it is important for clinicians to understand which procedures are associated with higher rates of respiratory depression in order to anticipate and minimize the likelihood of respiratory depression. Furthermore, this study may point to the need for improving the management of patients at high risk of respiratory depression in the perioperative setting. Applying a personalized medicine approach utilizing pharmacogenomics may help reduce the occurrence of respiratory depression.

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Poster Presentations, *continued from page 165*

RES 39 (2063)
Minimizing Parenchymal Strain Heterogeneity During Oscillatory Ventilation

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Introduction: Gas flow in the lung during oscillatory ventilation is distributed in a heterogeneous and frequency-dependent manner [1]. However severe ventilation heterogeneity may contribute to impairments in gas exchange, ventilation-to-perfusion mismatch, and ventilator-induced lung injury (VILI). Minimizing acinar strain heterogeneity may reduce the risk of VILI while producing efficient carbon dioxide elimination. In this study we used a gas transport model to optimize oscillatory ventilator waveforms, in which the spectral content of each flow waveform was adjusted to minimize parenchymal strain heterogeneity during eucapnic ventilation [2,3].

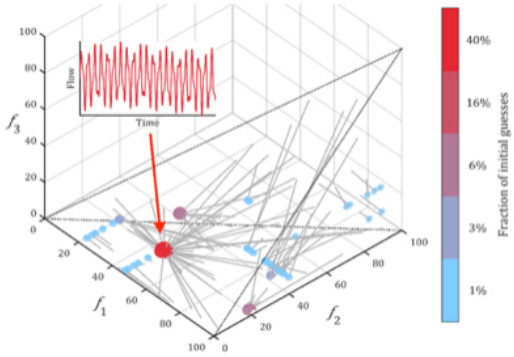

Figure 1. Convergence of the minimization algorithm from randomized initial guesses (indicated by grey lines) to local minima (colored spheres). In this case, the optimal solution (red sphere) for frequencies (, , shown in Hz) yielded 27% reduction in compared to the optimal solution for frequency. The resulting optimized flow waveform over one second is shown.

Methods: A heterogeneous canine lung model consisting of N terminal viscoelastic acini was ventilated with a simulated oscillatory flow waveform composed of M simultaneous frequencies. The relative magnitudes of flow at each frequency was numerically optimized according to a cost function $\hat{I}_i^1$, defined as the coefficient of variation of acinar volumetric distension. Using a Monte Carlo technique, we estimated the optimal oscillatory waveform that produced the lowest $\hat{I}_i^1$, and thus the lowest degree of parenchymal strain heterogeneity. The relative magnitudes of each oscillatory component was adjusted to achieve eucapnia.

Results: Optimal oscillatory waveforms were characterized by flows with large amplitudes at low frequencies, combined with small amplitude flows at high frequencies. Average acinar strain during eucapnic ventilation was reduced when additional higher frequency components were included in the waveform.

Conclusion: Superposition of multiple simultaneous oscillatory frequencies provides more uniform ventilation distribution compared to single frequency oscillatory ventilation, as well as more mechanically efficient gas exchange to achieve eucapnia. An optimal combination of frequencies, amplitudes, and phases in an oscillatory ventilator waveform may be determined according to the distribution of flows throughout the heterogeneous lung periphery. Work supported by DOD grant PR151761.

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Poster Presentations, *continued from page 166*

RES 41 (1503)
AMPK Activators Increase Survival after Bromine Inhalation

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Introduction: Exposure to irritant gases such as smoke, ozone, chlorine and bromine (Br2) constitute environmental and occupational hazards that induce multi-organ injury which can lead to death. Our focus is to develop therapeutic agents which when given post exposure decrease mortality in animal models of acute lung injury (ALI) or its more severe form acute respiratory distress syndrome (ARDS). AMP-activated kinase (AMPK) is known to be a metabolic sensor that maintains ATP levels during periods of metabolic stress. However, AMPK also acts independently of AMP and enhances vascular integrity by impairing actin stress fiber formation and limiting changes in cell morphology necessary for increased endothelial permeability. Herein we tested the hypothesis that a single injection of an AMPK activator, such as AICAR or metformin, administered intraperitoneally post exposure of mice to a lethal dose of inhaled Br2 decreased lung injury and increased survival.

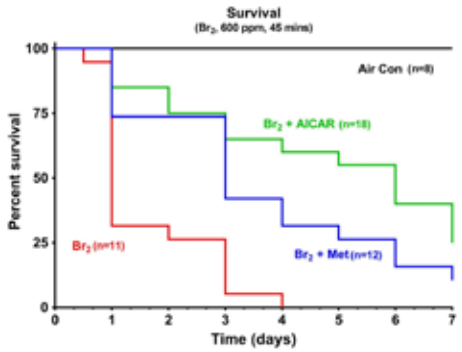

Figure 1. AMPK stimulation increases survival in a mouse model of severe Br_2-induced lung injury. C57BL/6 mice were exposed to Br2 (600ppm, 45min) in environmental chambers then returned to room air. Control mice breathed ambient air. Six hours after exposure, mice were injected intraperitoneally with 100 ul of (i) Earle's balanced salt solution, (ii) AICAR (10mg/kg, BW), or (iii) metformin (Met) (30mg/kg, BW). The mice were monitored every 6hr for 7 days. AICAR and metformin given 6hr post exposure. n=number animals/group. Kaplan-Meier, significance among all groups p<0.0001. Mantel-Cox log rank test, significance = p<0.0001 for Br_2 vs Br_2+ AICAR, and p<0.0005 for Br_2 vs Br_2+ metformin.

Methods: C57BL/6 mice were exposed to Br2 (600ppm, 45min) in environmental chambers as previously described [(1)] and then returned to room air. Control mice breathed ambient air throughout this protocol. Six hours after exposure to Br2, mice were injected intraperitoneally with 100 ul of (i) Earle's balanced salt solution, (ii) AICAR (10mg/kg, BW), or (iii) metformin (30mg/kg, BW). The mice were monitored every six hours for seven days. In a second set of experiments, mice were sacrificed 24 hours post Br2 inhalation and were either lavaged with one ml of normal saline for protein and inflammatory cell counts or their lungs were fixed by instillation of formalin at 25 cm H20; and processed for histology.

Results: Kaplan Meier curves were generated for the different groups. Sham controls developed progressive respiratory distress. Median survival of the sham control group was one day, Br2+metformin was three days and Br2+AICAR was six days (Figure 1). Exposure to Br2 caused significant increase in total protein and number of inflammatory cells in BALF at 24 hours post exposure, consistent with severe injury to the blood gas barrier. AICAR and metformin returned these values to their corresponding air controls (Figure 2). Histology showed that Br2-exposured mice receiving AICAR had reduced lung edema, alveolar congestion, septal thickening, neutrophil infiltration, hyaline membrane and perivascular cuffing.

Conclusion: Two structurally and mechanistically unrelated activators of AMPK significantly increased animal survival following a lethal dose of Br2 and reversed many histological markers of acute lung injury. Thus activation of lung AMPK might be a useful target for a therapeutic intervention to reverse Br2-induced acute lung injury. (This study was supported by 1U01ES027697-01 and 5U01ES026458-02 to S. Matalon.)

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Poster Presentations, *continued from page 167*

NR 42 (1408)
Isoflurane Exposure During Brain Development Activates the mTOR Pathway

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Introduction: Epidemiologic and laboratory studies suggesting that exposure to general anesthetic agents (GAs) could have harmful effects on brain development has led the FDA to issue a safety announcement and a call for further research [(1)]. Animal models show that GA exposure during early postnatal life can cause subsequent deficits in learning, but there is no consensus as to the mechanism of injury [(2)]. We hypothesize that anesthetics act on the mechanistic target of rapamycin (mTOR) pathway, a signaling system that is perturbed in several well-studied neurodevelopmental disorders [(3)].

Methods: For in vivo experiments C57BL/6 mice at P18 were exposed to 1.5% isoflurane for 4 hours and the control groups consisted of naÃ¨ve littermates. Rapamycin groups received IP injections of 20 mg/kg from P21 to P29 at 48 hour intervals. Behavioral testing was conducted at P60 using an object-place recognition paradigm assessed by an observer blind to condition. Immunohistochemistry (IHC) was conducted using an antibody against phosphorylated S6 (pS6) to assess mTOR activation and an antibody against parvalbumin (PV) to identify interneurons. Confocal microscopy was performed and analysis was conducted by an investigator blind to condition. Dissociated primary neuronal cultures obtained from E18 rat neocortex plated on glass coverslips were used for in vitro experiments. Exposure to isoflurane in 5% CO2 and 95% O2 carrier gas was conducted for 6 hours. For rapamycin treatment a concentration of 100 nM was used. Neurons were exposed at 7 DIV, and harvested at 10 DIV. IHC using anti-pS6 antibodies along with counterstaining using fluorescently labeled phalloidin was performed and analysis via fluorescence microscopy was conducted by an investigator blind to condition.

Results: The isoflurane-treated groups showed substantial deficits in recognition of novel object positioning that was reversed with rapamycin treatment (Fig 1). Using IHC in vivo, we found a significant increase in pS6 immunoreactivity in neurons of the dentate gyrus at P30 and P40 (Fig 2), demonstrating a substantial upregulation of activity in the mTOR pathway. Interestingly, we noted a large number of interneurons exhibited enhanced pS6 labeling (Fig 2). Next, we used a dissociated cortical culture model to determine whether the effects of isoflurane on mTOR activation are specific to the neurons of the dentate gyrus or might be broadly applicable to a wider range of neurons regardless of environment. We found isoflurane caused a concentration-dependent increase in pS6 immunoreactivity that was reversible with rapamycin (Fig 3).

Conclusion: Rapamycin, an inhibitor of the mTOR pathway, reverses learning deficits caused by developmental isoflurane exposure. Isoflurane causes an upregulation of pS6 immunoreactivity both in vivo and in vitro, suggesting a broadly generalizable mechanism of potential isoflurane toxicity.

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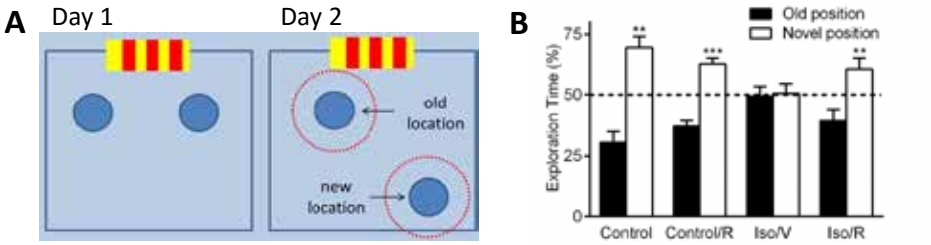

Figure 1: Isoflurane exposure impairs spatial learning. (**A**) A schematic diagram of the object-place recognition test. (**B**) Control animals spend significantly more time exploring objects in novel positions, but isoflurane-exposed animals exhibit no exploration preference. Rapamycin treatment restores performance in isoflurane treated animals to near control levels.

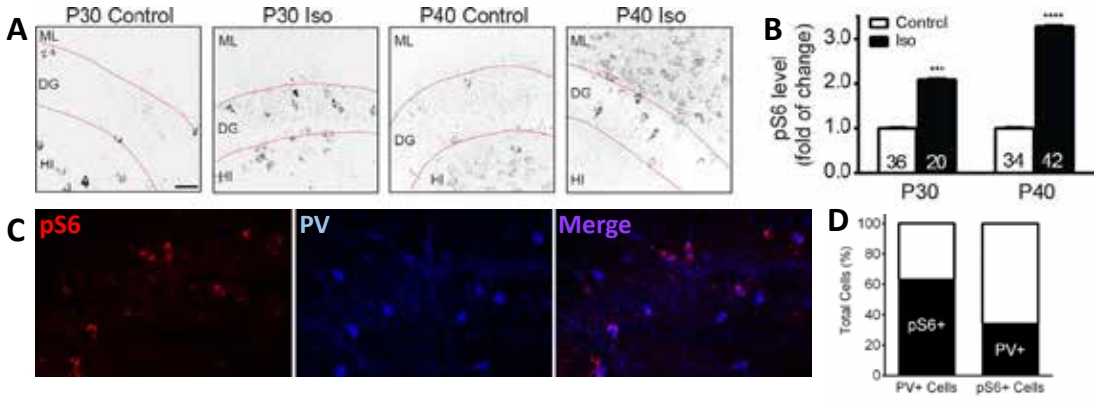

Figure 2: Isoflurane activates the mTOR pathway in the mouse model. Representative images (**A**) and quantification (**B**) showing immunoreactivity for pS6 obtained at P30 and P40 is increased in the hippocampus of mice exposed to isoflurane at P18. Representative images (**C**) and quantification (**D**) showing a majority of interneurons, stained by PV, exhibited enhanced pS6 labeling.

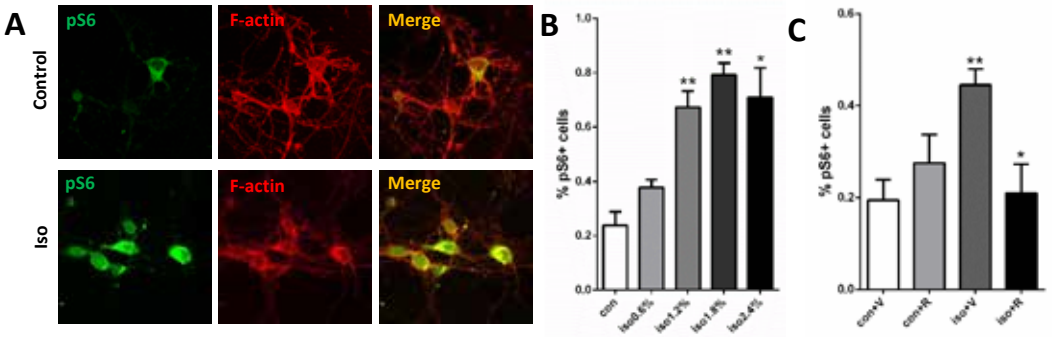

Figure 3: Isoflurane activates the mTOR pathway in the cortical culture model. Representative images (**A**) and quantification (**B**) showing immunoreactivity for pS6 is significantly increased between isoflurane concentrations above 1.2% and the control group (**p*<0.05, ***p*<0.01). Adding rapamycin 1h before 1.8% isoflurane exposure (**C**) reverses the activation of phosphorylated S6-kinase (**p*<0.05, ***p*<0.01).

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NR 43 (1033)
Awake Craniotomy: Comparison of Monitored Anesthesia Care versus Asleep Awake Asleep

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Introduction: An awake craniotomy (AC) with intraoperative brain mapping, allows for maximum tumor resection while monitoring neurological function. It is often used for lesions that involve eloquent areas of the brain, such as Broca's, Wernickes, or the primary motor area. The commonly used techniques for an awake craniotomy includes monitored anesthesia care(MAC), using an unprotected airway, or the asleep-awake-asleep(AAA) technique, using a partially or totally protected airway. We present a comparative analysis between the MAC and AAA technique evaluating anesthetic management, perioperative outcomes, and complications in a consecutive series of patients undergoing the removal of an eloquent brain lesion.

Methods: A prospective data collection and subsequent retrospective data analysis was conducted on eighty one patients who underwent an awake craniotomy for an eloquent brain lesion through a nine year period. Surgery was performed by a single surgeon and anesthesia was given by a team of anesthesiologists. Fifty patients underwent the MAC technique and thirty-one patients underwent the AAA technique. We did not have a set protocol for sedation and different anesthesiologists use different medications for MAC based on their comfort level. Infusions were titrated to effect. The nose was sprayed with phenylephrine and the posterior pharynx was sprayed with lidocaine. A nasal trumpet coated with 5% lidocaine ointment was inserted into the more patent nostril. The anesthesia circuit was then attached to the nasal trumpet and oxygen was given. For the AAA technique GA with LMA was used. Scalp block was performed in all patients. Prior to duramater incision local anesthesia is used to block the nerves suppling the dura. Retrospective analysis regarding anesthetic management, intraoperative complications, postoperative outcomes, pain management, and complications were presented.

Results: Preoperative patient and tumor characteristics was similar in two groups (Table 1). Operative time was found to be shorter in the MAC group(283.5 mins) versus the AAA(313.3 mins, p=0.038). Hypertension was commonest intraoperative complication encountered (MAC: 8% vs AAA: 9.7%, p=0.794) (table2). Conversion to general anesthesia with endotracheal intubation 3.2% of the AAA cohort (p=0.201). No cases were aborted in either cohort. The mean hospital stay was 3.98 and 3.84 days in the MAC and AAA group, respectively (p=0.833). Postoperative pain medications used were similar for the two cohorts (Table 3). Postoperative Karnofsky performance status (KPS) score was 91.4 in the MAC group and 88.7 in the AAA group (p=0.957). The length of hospitalization was similar in both groups (MAC 3.98 days versus AAA 3.84 days, p=0.833). New neurological deficits and discharge status were seen in similar frequencies between the two groups (Table 4).

Conclusion: Both MAC and AAA techniques provide efficacious and safe methods for managing awake craniotomy. Important issues to consider: ensuring analgesia during pain inducing parts (clamp placement, surgical incision, opening of the dura) by local anesthetic agents.

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Table 1: Preoperative characteristics of 81 patients undergoing an awake craniotomy

	Group		
	MAC	AAA	
Characteristic	(n=50)	(n=31)	p
Age, mean (SD)	44.6 (15.8)	50.9 (13.4)	0.068
Male Gender, n (%)	35 (70.0%)	17 (54.8%)	0.167
ASA Score, n (%)			0.883
1	2 (4.0%)	1 (3.2%)	
2	25 (50.0%)	14 (45.2%)	
3	23 (46.0%)	16 (51.6%)	
Mallampati Score, n (%)			0.776
1	25 (50.0%)	15 (48.4%)	
2	13 (26.0%)	7 (22.6%)	
3	10 (20.0%)	6 (19.4%)	
4	2 (4.0%)	3 (9.6%)	
Body Mass Index (BMI), mean (SD)	28.0 (2.8)	24.3 (5.2)	0.122
Preoperative KPS, mean (SD)	95.8 (7.6)	94.8 (8.9)	0.619
Headaches, n (%)	11 (22.0%)	6 (19.4%)	0.776
Seizure, n (%)	32 (64.0%)	17 (54.8%)	0.412
Motor Def, n (%)	10 (20.0%)	5 (16.1%)	0.663
Sensory Def, n (%)	4 (8.00%)	1 (3.23%)	0.644
Dysarthria, n (%)	3 (6.0%)	1 (3.23%)	0.575
Cognitive Def, n (%)	6 (12.0%)	3 (9.68%)	0.746
Visual Def, n (%)	2 (4.00%)	4 (12.9%)	0.196

Table 2: Intraoperative characteristics of the 81 patients during the awake period

	Group		
	MAC	AAA	
Characteristic	(n=50)	(n=31)	P
Duration of Surgery, mean minutes (range)	283.5 (148-445)	313.3 (179-454)	0.038
Sedative			0.607
Propofol, n (%)	35 (70.0%)	20 (64.5%)	
Dexmedetomidine, n (%)	15 (30.0%)	11 (35.5%)	
Intraoperative Seizure, n (%)	2 (4.00%)	1 (3.2%)	0.858
Aborted Case/Converted to Sleep, n (%)	0 (0.00%)	1 (3.2%)	0.201
Hypertension, n (%)	4 (8.00%)	3 (9.7%)	0.794
Hypotension, n (%)	0 (0.00%)	0 (0.0%)	-----
Tachycardia, n (%)	1 (2.00%)	2 (6.5%)	0.304
Bradycardia, n (%)	0 (0.00%)	1 (3.2%)	0.201
Desaturation, n (%)	0 (0.00%)	0 (0.0%)	-----
Brain swelling, n (%)	0 (0.00%)	0 (0.0%)	-----
Nausea/Vomiting, n (%)	1 (2.00%)	0 (0.0%)	0.428

Table 3: Postoperative pain medications of 81 patients

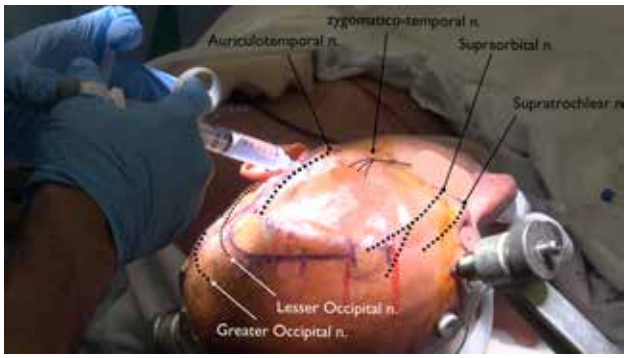
	Group		
	MAC	AAA	
Characteristic	(n=50)	(n=31)	p
Oxycodone, n (%)	34 (68.0%)	23 (74.2%)	0.553
Hydromorphone, n (%)	1 (2.00%)	1 (3.23%)	0.730
Fentanyl, n (%)	42 (84.0%)	26 (83.9%)	0.988
Tramadol, n (%)	1 (2.00%)	0 (0.00%)	0.428
NSAID, n (%)	0 (0.00%)	1 (3.23%)	0.383
Acetaminophen, n (%)	19 (38.0%)	9 (29.0%)	0.409

Table 4: Postoperative Conditions of 81 patients

	Group		
	MAC	AAA	
Characteristic	(n=50)	(n=31)	p
Postoperative KPS, mean (SD)	91.4 (10.4)	88.7 (18.8)	0.957
Length of Stay, mean (range)	3.98 (2-25)	3.84 (2-26)	0.833
New motor deficit, n (%)	19 (38.0%)	12 (38.7%)	0.949
Transient deficit	16 (32.0%)	9 (29.0%)	0.779
Permanent deficit	3 (6.0%)	3 (9.68%)	0.539
New language deficit, n (%)	5 (10.0%)	4 (12.9%)	0.686
Transient deficit	5 (10.0%)	4 (12.9%)	0.686
Permanent deficit	0 (0.0%)	0 (0.0%)	---
Nausea/vomiting, n (%)	3 (6.0%)	2 (6.5%)	0.935
Discharge status			0.943
Home, n (%)	40 (80.0%)	25 (80.7%)	
Rehab, n (%)	10 (20.0%)	6 (19.3%)	

KPS, Karnofsky Performance Status

Figure 1: Complete scalp block of the supraorbital, supratrochlear, auriculo-temporal, zygomatico-temporal, greater occipital, and lesser occipital nerves



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Poster Presentations, *continued from page 171*

NR 45 (1339)
Propofol-Induced Decrease in Spectral Complexity

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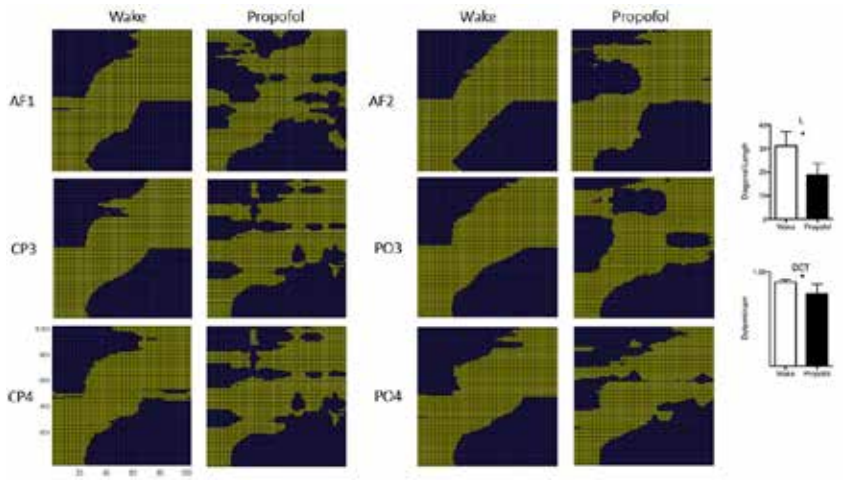
Introduction: Propofol-induced loss of consciousness has been associated with reduced global complexity of cortical responses to transcranial magnetic stimulation (TMS; [1,2]). Here we hypothesized that these decreases in the complexity would be observed locally in the form of increased recurrence of the same time-frequency response patterns and that decreases in both local and global complexity could be related to decreased non-linear (cross-frequency) coupling across hierarchical levels of cortex.



Methods: Eight human subjects underwent occipital TMS coupled with high-density electroencephalograph (EEG) recordings during wakefulness and propofol-induced unconsciousness. Sensor-space and source space time-frequency were conducted in SPM12 or through custom written matlab scripts. All analyses were adjusted for multiple comparisons using family wise error correction.

Results: Sensor-space time-frequency analyses demonstrated that propofol-induced unconsciousness was associated with local decreases in Lempel-Ziv complexity of TMS-evoked responses, at 5 out of 6 single electrodes overlying frontal, parietal and occipital cortex ($p<0.05$ for 5/6; $p=0.07$ for PO4). Recurrence quantification analysis [(3)] of these sensor space data revealed that propofol reduced determinism and increased spectral recurrence of local responses ($p<0.05$). The recurrence plots are shown in Figure 1. The yellow dots show the 50 nearest neighbours in Euclidean space, 'L' refers to the average length of diagonal lines, determinism or 'DET' refers to the percentage of points that form diagonal lines. Puddles of spectral recurrence (off the diagonal) are evident under propofol sedation in the figure. This analysis implies a reduced repertoire of available cortical states. Additionally, changes in spectral recurrence over time were less correlated between frontoparietal ($p<0.05$) and occipitoparietal ($p<0.05$) electrodes implying changes in connectivity of the deterministic response. Source space dynamic causal modelling analysis [(4)] of frontal, parietal and occipital regions revealed that the loss of local and global complexity observed during propofol-induced unconsciousness was related to decreased cross-frequency coupling throughout the cortical hierarchy. This involved ascending connectivity in the alpha and gamma frequency ranges and descending connectivity in the gamma frequency range (family wise error corrected $p<0.05$).

Conclusion: Our data suggest that propofol-induced loss of consciousness may reduce complexity, and increase recurrence, of cortical activity through impairment of non-linear and linear cortico-cortical connectivity.

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NR 47 (1758)
Ketamine Reduces Post-Traumatic Brain Injury Neurogenesis and Improves Outcomes in Mice

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Introduction: Traumatic brain injury (TBI) is a potentially devastating condition affecting millions of people each year[1], which can burden survivors with memory deficits, depression, emotional lability and loss of independence[2]. TBI induces a dramatic neurogenic response in the hippocampus with unknown longer-term consequences[3]: new neurons may compensate by assuming the functions of disrupted circuits, or interfere with hippocampal function, as injury-generated neurons have aberrant positioning and branching phenotypes. As anesthetic and sedative drugs are known to modulate neurogenesis, here we evaluate how ketamine-induced modulation of NMDA receptors, which are known to affect neurogenesis, impact the production of adult-born neurons and behavioral outcomes after TBI in mice.

Methods: In accordance with IACUC-approved protocols, wild-type mice underwent controlled cortical impact (CCI) model of TBI vs. sham (non-injury), followed by immediate initiation of ketamine or vehicle infusion via osmotic drug pump. Pumps were removed after 1 week. Neurogenesis and other cellular responses were assessed using immunohistochemistry at 2 and 6 weeks post-injury, to evaluate mitotic activity (BrdU) and the production of new neurons (doublecortin & NeuN), astrocytes (GFAP) and microglia (Iba1) in the granule cell layer of the hippocampal dentate gyrus. Behavioral testing of hippocampal dependent tasks was accomplished via Morris Water Maze (MWM) Reversal test at 4 weeks after injury.

Results: CCI induced dramatic cellular proliferation in vehicle-treated animals. Injury-induced neurogenesis was not apparent at the 2-week time point but was significantly increased by 6 weeks, suggesting increased survival of injury-born neurons; ketamine exposure abolished this effect on neurogenesis but not the effect on overall cell proliferation. CCI increased the production of new astrocytes in vehicle-exposed mice and increased new microglia in the ketamine exposed group. Behavioral testing revealed impaired spatial learning and memory after CCI; ketamine exposure prevented this deficit.

Conclusion: CCI triggers a robust proliferative response in the dentate of the hippocampus characterized by increased neuron and astrocyte creation. However, behavioral testing revealed impaired hippocampal learning and memory in these mice. Ketamine administered in the immediate post-injury period reduced this neurogenic and astrogenic response; but surprisingly, these mice performed equivalently to non-injured mice in MWM Reversal. These results suggest that, rather than improving function, injury induced neurogenesis could impair performance in certain hippocampus-dependent tasks, possibly by preventing the generation of aberrantly projected new granule cells.

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Poster Presentations, *continued from page 173*

NR 49 (1795)
Innate Immunity Is Required for Neuronal Regeneration After Cerebral Ischemia

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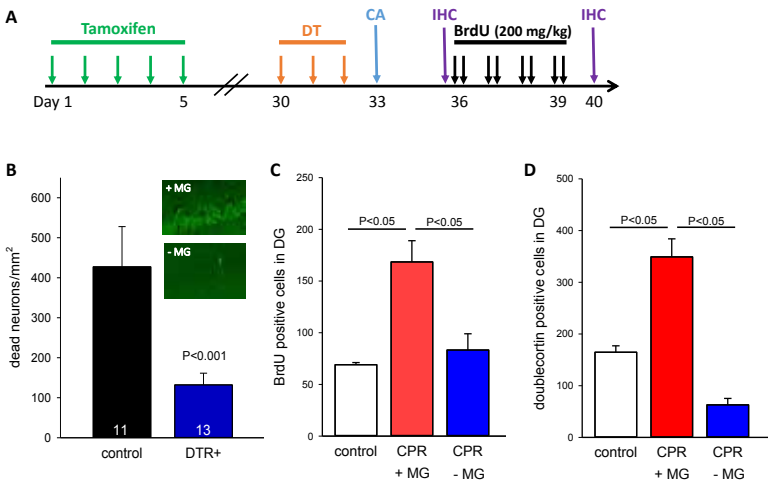
Introduction: Various types of brain injury induce neurogenesis in the adult brain, including stroke, traumatic brain injury, and cardiac arrest (CA) and resuscitation. Increased neurogenesis offers the potential for regeneration of lost neurons and is a promising target to improve recovery from brain injury. Unfortunately, few of the newborn cells survive long-term, limiting translational potential. The cellular mechanisms behind this failure of regeneration remain unclear, but increased inflammation after brain injury has been implicated in limiting survival of adult-born neurons. We investigated the role of microglia, the brain's resident immune cells, for hippocampal neurogenesis after CA, using a novel mouse model that allows targeted ablation of microglia.



Methods: We used the CX3CR1Cre-ER/DTR mouse first described by Parkhurst et al.[1] Tamoxifen injection induced diphtheria toxin receptor (DTR) expression in CX3CR1-positive microglia and macrophages. A 30 days waiting period allowed bone-marrow derived, DTR-negative cells to replace the short-lived peripheral macrophages, while long-lived brain resident microglia maintained DTR expression and were readily ablated by diphtheria toxin (DT) injection. We ablated microglia with three days of DT injection before CA and used FluoroJadeB staining to determine neuronal death in the hippocampal CA1 region 3 days after CA. We injected mice with BrdU to label newborn cells on days 3-6 after CA (Figure 1A). We quantified newborn neurons in the dentate gyrus after double-labeling for doublecortin (DCX) and BrdU.

Results: Ablation of microglia before CA dramatically reduced death of CA1 3 days after CA (427 ±333 dead cells/mm2 (control) vs 132 ±105 (MG ablation), P<0.01, Figure 1B). Proliferation of new cells, measured by BrdU incorporation, increased in the first week after CA (168 ±61 cells (CA) vs 69 ±4 (control), P<0.05). To our surprise, this increase was fully blocked when microglia were absent (83 ±32, Figure 1C). Similarly, the increase of DCX-positive young neurons after CA also required the presence of microglia (164 ±21 (control), 349 ±104 (CA), 63 ±25 (CA after MG ablation), P<0.05, Figure 1D).

Conclusion: Our findings suggest that microglia drive neuronal death after CA, as more neurons survive when microglia are absent during CA. On the other hand, microglia are required for restorative neurogenesis after CA. This adds a new facet to the already diverse microglial response to ischemic brain injury. This Janus-faced microglial response of supporting regeneration while exacerbating injury after CA creates a paradigm shift for neuroprotective interventions. Future therapeutic interventions will need to carefully consider the two opposing capacities, and aim to suppress one without interfering with the other.

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Poster Presentations, *continued from page 174*

NR 51 (1640)
Ubiquitin-Proteasome Associated Mechanisms of Sevoflurane-Induced Cognitive Impairment in Young Mice

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Introduction: Children with multiple, but not single, exposures to anesthesia and surgery may have an increased risk of developing cognitive impairment ([1-5], reviewed in [6]), which was also described in recent Drug Safety Communication Warning by the United States Food and Drug Administration. Multiple exposures of sevoflurane in young mice induce cognitive impairment [7,8] and decrease hippocampus levels of postsynaptic density protein 95 (PSD-95) in the mice 7,9. However, the underlying mechanisms remain largely unknown. Ubiquitin-proteasome pathway of protein degradation is critical for synaptic plasticity and regulates metabolism of PSD-95 10,11. We therefore assessed the effects of sevoflurane on PSD-95 degradation and the interaction with ubiquitin-proteasome pathway in mouse neuron, synaptosome and hippocampus and in young mice.

Methods: Hippocampus synaptosomes of postnatal day 6 (P6) wild-type mice and mouse primary neurons were harvested. The synaptosomes and neurons were then treated with 21% O2, 5% CO2, and 4.1% sevoflurane for four hours. Proteasome inhibitor of the ubiquitin-proteasome pathway MG132 (50 Î¼M) and MDM2 inhibitor Nutlin-3 (10 Î¼M) were administrated to the neurons or synaptosomes one hour before the sevoflurane treatment. The P6 mice were anesthetized with 3% sevoflurane for two hours daily for three days. MG132 (0.5 mg/kg/day) or Nutlin-3 (10 mg/kg/day) was administered to the mice via intraperitoneal injection one hour before the sevoflurane anesthesia. The cognitive function was assessed in Morris Water Maze at P31 to P37. PSD-95 levels were determined using RT-PCR and Western blot. Co-immunoprecipitation (Co-IP) was employed to determine the interaction between PSD-95, ubiquitin and its E3 ubiquitin ligase MDM2.

Results: The sevoflurane anesthesia decreased protein, but not mRNA, levels of PSD-95 (100% versus 48%, P=0.0017, N=6). Proteasome inhibitor MG132 and MDM2 inhibitor Nutlin-3 attenuated the sevoflurane-induced PSD-95 degradation. Sevoflurane facilitated the interaction of MDM2 with PSD-95. Finally, both MG132 and nutlin-3 mitigated the sevoflurane anesthesia-induced cognitive impairment in the young mice.

Conclusion: These data showed that sevoflurane would reduce PSD-95 levels and induce cognitive impairment via ubiquitin-proteasome pathway. Pending further investigation, sevoflurane may facilitate the interaction of MDM2 and PSD-95, leading to the degradation of PSD-95 and consequently cognitive impairment as demonstrated in the diagram. These results suggest that ubiquitin-proteasome could be one of the underlying mechanisms by which sevoflurane reduces levels of synaptic marker in hippocampus and induces cognitive impairment in young mice. These findings would promote further investigation of cognitive impairment induced by anesthesia or other environmental factors in young mice.

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Poster Presentations, *continued from page 175*

NR 52 (1632)
The Influence of Catastrophizing, Anxiety and Depression On Opioid Consumption, Postoperative Pain and Quality of Recovery After Adult Spine Surgery

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Introduction: Perception of perioperative pain is influenced by various psychological factors. The aim of this study was to determine the impact of catastrophizing, anxiety and depression on postoperative opioid consumption and pain scores in patients presenting for adult spine surgery.

Methods: This was a prospective single-center observational study involving adult patients undergoing spine surgery. The University of Virginia Institutional Review Board for Health Science Research approved the study (HSR-17994) and the need for written consent was waived. Patients undergoing spine surgery were enrolled in this study and questionnaires completed preoperatively included the Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale (HADS) and the Oswestry Disability Index (ODI). Quality of recovery was assessed using the Quality of Recovery Score-QoR40. Opioid consumption and pain scores using a Verbal Rating Scale (VRS) were recorded daily until discharge.

Results: One hundred and thirty nine patients were recruited and 103 completed the QoR40 assessment postoperatively. Patients with higher catastrophizing scores were more likely to have higher maximum pain scores postoperatively [Estimate: 0.03, SE: 0.01, p= 0.02), without increased opioid use [Estimate: 0.44, SE: 0.27, p=0.11). Preoperative anxiety [Estimate: 1.18, SE: 0.65, p= 0.07) and depression scores [Estimate: 1.06, SE: 0.71, p= 0.14) did not correlate with increased postoperative opioid use; however, patients with higher preoperative depression scores have lower quality of recovery after surgery [Estimate: -1.9, SE: 0.56, p < 0.001). [Table 1 and 2]

Postoperative Opioid Consumption

Fixed Effects	Estimate	SE	p	Fixed effects	Estimate	SE	p	Fixed effects	Estimate	SE	p
Intercept	99.8	50.3	0.05	Intercept	111.5	48.4	0.02	Intercept	97.1	49.6	0.05
PCS	0.4	0.3	0.11	Depression	1.1	0.7	0.14	Anxiety	1.2	0.7	0.07
Preoperative Morphine	0.9	0.2	< 0.001	Preoperative Morphine	0.9	0.2	< 0.001	Preoperative Morphine	0.9	0.2	< 0.001
Procedure (Redo)	14.0	5.5	0.01	Procedure (Redo)	12.2	5.4	0.02	Procedure (Redo)	13.1	5.4	0.02
Osteotomies	3.3	1.7	0.05	Osteotomies	3.6	1.7	0.03	Osteotomies	3.4	1.6	0.04
Intraop opioids	0.1	0.10	0.10	Intraop opioids	0.2	0.10	0.09	Intraop opioids	0.1	0.1	0.14
Random effects (σ^2)											
Intercept	1165				1103				3.47		

Conclusion: Catastrophizing, anxiety and depression play an important role in modulating postoperative pain. Preoperative evaluation of these factors, utilizing a validated tool, helps to identify patients at risk. This might allow for earlier psychological intervention that potentially can reduce pain severity and improve the quality of recovery.

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PM 53 (1439)
AMPAkines As Novel Analgesics in Rat Pain Models

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Introduction: AMPAkines are synthetic agents that have been developed in the last twenty years. These drugs can bind to Î±-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to slow the kinetics of channel deactivation[1-2]. Thus, AMPAkines can increase excitatory outputs in the brain. Interestingly, recent studies have shown that AMPAkines can stimulate the respiratory drive in the context of hypoventilation caused by opioids or other sedatives[3-5]. AMPAkines are known to have an affinity to the nucleus accumbens (NAc), the reward center that has been implicated in pain regulation[5-9]. However, it is not clear whether these drugs have analgesic properties. If so, AMPAkines can potentially improve pain control and at the same time limit the side effects of sedatives, making them ideal options for the treatment of postoperative and chronic pain.

Methods: We investigated the analgesic role of an AMPAkine, CX546, in a rat paw incision (PI) model of acute postoperative pain and a spared nerve injury (SNI) model of persistent postoperative neuropathic pain. We measured the effect of AMPAkines on sensory as well as depressive symptoms of pain using mechanical hypersensitivity and forced swim tests. Finally, we asked whether AMPA receptors in the NAc can be a target for AMPAkine analgesia.

Results: We found that systemic administration of CX546 (n=13), compared with control (n=13), reduced mechanical hypersensitivity (50% withdrawal threshold of 6.05+1.30g (mean+SEM) vs. 0.62+0.13g). It also reduced depressive symptoms of pain by decreasing immobility on the forced swim test in PI-treated rats (89.0+15.5s vs. 156.7+18.5s). In addition, CX546, compared with control, reduced sensory (control group, n = 9. CX546 group, n = 11) and depressive symptoms of pain (n = 8) in the SNI model of persistent postoperative neuropathic pain. Meanwhile, CX546 delivered locally into the NAc provided pain-relieving effects in both PI (50% withdrawal threshold of 6.81+1.91g vs. 0.50+0.03g; control n=6, CX546 n=8) and SNI models (50% withdrawal threshold of 3.85+1.23g vs. 0.45+0.00g; control n=7, CX546 n=11). Furthermore, blocking AMPA receptors in the NAc with 3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2, 3-dione (NBQX) inhibited these pain-relieving effects (50% withdrawal threshold of 7.18+1.52g vs. 1.59+0.66g; n=8 for PI groups; 10.70+3.45g vs. 1.39+0.88g; n=4 for SNI groups).

Conclusion: These results indicate that AMPAkines have novel analgesic properties in both acute postoperative pain and chronic pain states. Furthermore, AMPA receptors in the NAc are likely a potential molecular target for these analgesics.

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PM 54 (1664)
Widespread Pain Three Months after Traumatic Injury: Preliminary Results

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Introduction: There are no prospective studies on persistent pain after trauma. Widespread pain is a clinically relevant manifestation of persisting pain. In this preliminary analysis of an ongoing prospective study on predictors of chronic post-traumatic pain, we examined the changes in widespread pain index three months after traumatic injury.

Methods: At hospitalization, we assessed the pre-trauma widespread pain index (WPI) by recalling [1]. Three months after hospital discharge, patients were interviewed via phone or internet-based survey to assess WPI. Data are presented as mean SD.

Results: One hundred and seventy-six patients, age 47.5 X years were enrolled. 131 (74%) were eligible for 3-month follow-up. Of these, 38% reported pre-existing pain and 75% reported pain at 3 months. Overall (N=128), WPI was higher at three months than at baseline (1.81 1.80 vs. 1.41 2.30, respectively), but statistical significance was not reached (p = 0.12). Within patients with no pre-trauma pain, WPI significantly increased at three months from baseline (N=82; 1.82 2.01 vs. 0.68 1.15; p < 0.001).

Conclusion: These preliminary results suggest that injured patients are at risk of developing persisting pain. The WPI scores were low after 3 months, suggesting that most patients develop localized, rather than widespread, pain.

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Poster Presentations, *continued from page 178*

PM 55 (1563)

Intraoperative Esmolol Decreases Intraoperative Opioid Use, PACU Opioid Use, and PACU Pain Scores: A Systematic Review, Meta-Analysis, and Meta-Regression

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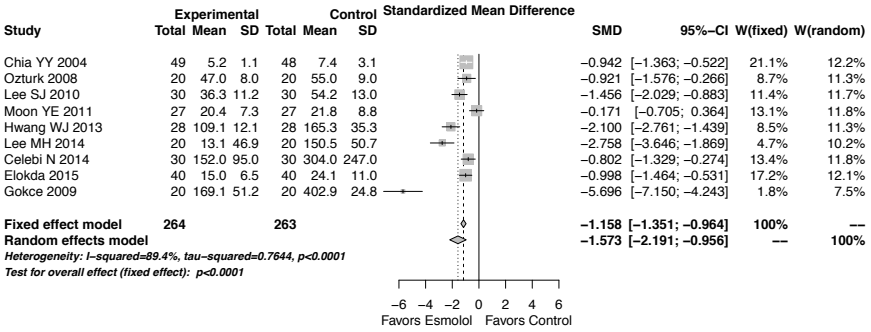
Introduction: Esmolol is an ultrashort beta-1 receptor antagonist. Recent studies suggest a role for esmolol in pain response modulation. Perioperative analgesia typically includes a combination of opioid and non-opioid pharmacologic agents. However, opioids have a large number of concerning side effects [1-3] and the reduction of their use perioperatively enhances recovery and decreases morbidity in adult [4-6]. The authors performed a meta-analysis to determine if the intraoperative use of esmolol reduces opioid consumption or pain scores.



Methods: PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Pubget, and Google Scholar were searched. Studies were included if they were randomized, placebo- or opioid-controlled trials written in English, and performed on patients 18 years of age or older. For comparison of opioid use, included studies tracked opioid consumption intraoperatively and/or in the post-anesthesia care unit. Pain score comparisons were performed during the first hour after surgery.

Results: Seventy-three studies were identified and 21 were eligible for one or more comparisons. In 527 patients from 9 trials, intraoperative opioid consumption favored esmolol, Figure 1 (MD, -1.57 mg IV morphine equivalents; 95% CI: 0.96, 2.19, p = <0.001). In 609 patients from 11 trials, PACU opioid consumption favored esmolol, Figure 2 (MD, -1.31 mg morphine equivalents; 95% CI: 0.86, 1.76, p = <0.001). In 638 patients from 10 trials, pain at 1 h favored esmolol, Figure 3 (MD, -0.68, 95% CI: 0.55, 1.96, p = <0.001).

Conclusion: This meta-analysis suggests that intraoperative esmolol use reduces intraoperative opioid consumption, postoperative opioid consumption in the PACU, and postoperative pain scores at 1 h. Significant data heterogeneity was encountered that was unable to be accounted for by meta-regressions. Medical comorbidities, pain, and nausea and vomiting are the most common causes of prolonged hospital stay or unanticipated hospital admission in patients scheduled for ambulatory surgical procedures [7-10]. Despite the beneficial effects of opioids in the management of perioperative pain, the negative effects including respiratory depression, increased nausea and vomiting, ileus, and opioid induced hyperalgesia often contribute to a prolonged PACU or hospital stay [11-14]. The intraoperative use of esmolol may be prove beneficial, especially for patients undergoing ambulatory surgery, patients at risk of postoperative respiratory compromise due to comorbidities in whom opioid sparing techniques are desirable, and patients with an existing chronic pain diagnosis or at risk of developing chronic pain.

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RA 56 (1126)
Comparison of Ultrasound Guided Paravertebral Block with Serratus Plane Block for MRM

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Introduction: Modified Radical Mastectomy (MRM) may be associated with severe post-operative pain, leading to chronic pain syndrome in 25-40% of patients [1]. Hence, regional analgesic techniques have been advocated for effective pain management. We compared the analgesic profile of two ultrasound guided nerve blocks: paravertebral block (PVB) and serratus anterior plane block (SPB) post-MRM.

Methods: This double blind, randomized, study was conducted on 50 adult females, scheduled for MRM with axillary dissection, after obtaining approval from Hospital Ethics Committee and written informed consent from the subjects. Inclusion criteria were age 18-65 years and ASA physical status I and II. Exclusion criteria were coagulopathy, infection at site of block and local anesthetic allergy. In the operation room, after inducing general anesthesia with I.V. midazolam 1mg, fentanyl 1.5 mcg/kg, propofol 1- 2 mg/kg and vecuronium bromide 0.1 mg/kg, subjects were administered either ultrasound guided PVB (n=25) or SPB (n=25) with 20 ml of 0.5% bupivacaine. Anesthesia was maintained with O2/ N2O/ 0.8-1% isoflurane to maintain MAC of 1.0. At the end of surgery, neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/ kg were administered I.V and trachea was extubated. In PACU, PCA pump (morphine-1 mg/ml; bolus dose - 1 mg, lock out interval 10 min and maximum dose 4 mg/h) was attached I.V. The primary outcome was duration of analgesia i.e. time to first rescue analgesia. The secondary outcomes were post-surgery morphine consumption in 24 h, 48 h and 72 h; VAS pain score and block related side effects. The recordings were done by an investigator, who was blinded to type of block administered to subject. Statistical analyses: The data was entered in MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. The categorical variables were presented in numbers and percentage (%); and continuous variables were presented as mean ± SD. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then non-parametric test was used. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-Square test /Fisher's exact test. A p value of <0.05 was considered statistically significant.

Table 1: Duration of block

Duration of block (min)	Group PVB	Group SPB	
Mean ± Standard deviation	346 ± 57.9	245.6 ± 57.5	<.001
Median	320	220	
Minimum-Maximum	240-480	180-360	
Inter quartile Range	307 - 380	200 – 285	

Results: The duration of analgesia was significantly longer in PVB group [346 ± 57 min, mean ± SD], compared to SPB group [245.6 ± 58 min, mean ± SD) (p <0.001) (Table 1)]. Post-operative VAS scores in the two groups were similar (p>0.05, Figure 1); while 24 h morphine consumption was significantly higher in SPB group (9.7 ± 2.1 mg, mean ± SD), compared to PVB group [(6.5 ± 1.5 mg, mean ± SD) (p <0.001, Table 2)]. Two patients in each group had nausea and vomiting.

Conclusion: SPB is an easy to administer analgesic technique, as an alternative to PVB for MRM with axillary dissection, although, PVB provides a longer duration of analgesia.

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RA 57 (1714)
RCT of US-paravertebral vs US-Proximal Intercostal Block in Mastectomy Patients

Kristin Schreiber, MD, PhD[1], Avery Williams-Vafai, MD[1]; Atif Chowdhury, MD[1]; David Ende, MD[1]; Jose Zeballos, MD[1]; David Janfaza, MD[1]; Kamen Vlassakov, MD[1]

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Introduction: Thoracic paravertebral blockade (PVB) is an accepted technique to provide analgesia both during and after breast surgery. The simple addition of ultrasound (US)-guidance to traditional PVB does not automatically bring BOTH safety and technical ease. An ideal ultrasound technique would be easy to perform, avoid neuraxial injection and lung injury, while permitting real-time visualization of needle tip and injectate spread. In this study, we compare ultrasound imaging quality, technical performance times, and clinical outcomes between a modified ultrasound-guided proximal intercostal block (PICB) and a traditional US-guided PVB. We hypothesized that PICB would allow a clearer simultaneous visualization of block needle, parietal pleura, bony landmarks and injectate spread, while achieving comparable analgesia.

Methods: Women undergoing total mastectomy were randomized to receive PVB or PICB at 2-4 block sites with a total of 2.5mg/kg ropivacaine. US images were obtained before and after needle placement, including video recording of local anesthetic injection. Primary outcome was overall US imaging score (0-18), as determined by an independent reviewer for visualization of pleura, bony elements, relevant ligament, needle, and intended local anesthetic spread.Secondary outcomes included block performance times, postoperative pain scores and opioid consumption in the first 24 hours after surgery. T-test or Mann-Whitney-tests were used to compare groups as appropriate.

Results: All patients who were enrolled received the intended randomized block treatment and were followed through 24 hours postoperatively. Overall image rating scores were superior for PICB compared to PVB. However, postoperative pain ratings and opioid consumption were similar between groups.

Conclusion: PICB may offer sonoanatomical and technical advantages over traditional PVB, while providing effective postoperative analgesia for mastectomy patients.

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Poster Presentations, *continued from page 181*

RA 59 (2243)
Ultrasound Guided Single Injection Quadratus Lumborum Block for Postoperative Pain Control in Patients Undergoing Total Hip Arthroplasty

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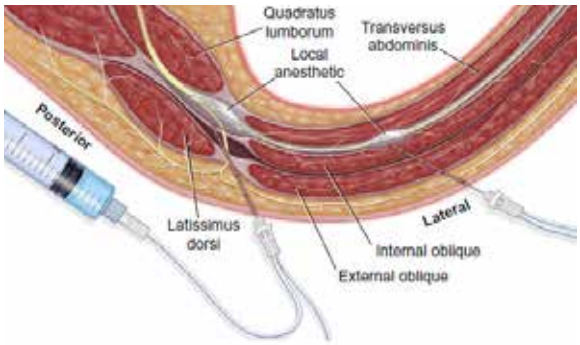
Introduction: Adequate pain control is essential to patient recovery following joint replacement surgery. Pain management following total hip arthroplasty (THA) continues to be a concern despite the growing number of procedures performed. The goal of contemporary analgesic interventions after THA is to minimize pain while promoting early mobilization and reducing opioid use. Postoperative THA pain control modalities include techniques such as non-steroidal anti-inflammatory drugs, local infiltration analgesia, intrathecal opioids and lumbar plexus block. Because of the lack of evidence-based recommendations a gold standard has not been established. This case series describes the effective use of a single shot quadratus lumborum block for postoperative pain control in two patients who presented with challenging aspects to their anesthetic management due to comorbidities such as obesity, coronary artery disease with drug eluting stent placement and poorly controlled hypertension undergoing total hip arthroplasty.



Methods: Our institution was able to utilize a single injection ultrasound guided quadratus lumborum block to manage postoperative hip arthroplasty pain effectively. Firstly, a 79 year old male with history of poorly controlled primary hypertension and hyperlipidemia who underwent a direct anterior approach right hip replacement with 15 mL bupivacaine 0.25% infiltration of the right quadratus lumborum. Second case is a 52 year old female BMI 40 kg/m2 with history of gallstones and menorrhagia who underwent a direct anterior approach right hip replacement with 40 mL bupivacaine 0.125% infiltration of the right quadratus lumborum.

Results: The 79 year old male did not require any intravenous narcotics. He complained minimally of pain during his recovery in the post anesthesia care unit and was able to tolerate physical therapy by ambulation with a walker. Length of stay was a minimal three days. During the operative course the 52 year old female only required ketorolac, as per surgeon's request, however no narcotics were needed. In the post anesthesia care unit, the patient received minimal intravenous narcotic however did not experience any discomfort nor required any narcotic during her subsequent course. Patient was able to tolerate and participate in physical therapy without any complains and achieved milestones at goal.

Conclusion: The ultrasound guided transversus abdominis plane (TAP) block, covering nerve roots T10-T12, has gained popularity for analgesia in abdominal and retroperitoneal procedures. Recently, the quadratus lumborum block has been utilized for similar procedures and found to be further effective given wider blockade comprising T6-L1 is achieved. Given the potential for extensive sensory analgesia, the quadratus lumborum block has been expanded to lower extremity procedures. In particular, a continuous quadratus lumborum catheter was noted to be successful for total hip arthroplasty which was expanded to a single shot injection of quadratus lumborum utilized for minimally invasive hip surgery. Our case series enhances the potential of a single shot injection quadratus lumborum block to be effective pain control for postoperative total hip arthroplasty. This regional method provided an effective method of analgesia for otherwise challenging cases due to patients' complex comorbidities.

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PA 61 (2078)
Enhanced Recovery after Surgery (ERAS) — An Assessment Six Months after Discharge

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Introduction: Enhanced Recovery After Surgery (ERAS) programs have been established as perioperative strategies associated with improved outcomes. Long-term outcomes data for patients undergoing ERAS interventions remains limited. This study collected prospective telephone questionnaire data six months post-colorectal surgery from patients who participated in an ERAS program at University of California, San Francisco (UCSF). Our goal was to detect previously unreported issues and associated predictive factors in patient outcomes.

Methods: We conducted a prospective observational study at UCSF, using an automated telephone survey six months after patients underwent abdominal colorectal surgery. All patients from February 2015 to June 2016 in the ERAS program were included in this post-discharge survey. Prior IRB approval was obtained. Patients who responded to the survey received a follow up call for clarity and accuracy. Six month significant outcomes were defined by persistent pain, hospital readmission, or patient satisfaction. Patients reporting these outcome variables were compared with patients who met none of these criteria. These patients were categorized by age, gender, diagnoses (cancer/non-cancer), ASA rating, use of an epidural, and type of procedure (Open vs Minimally Invasive) to determine what variables correlate with these six month outcomes. Preoperative and postoperative pain scores, length of procedure, and length of hospital stay were also analyzed. A chi-square test was used to determine any relationship for categorical variables, a two independent samples t-test for length of procedure/stay and a Wilcoxon-Mann-Whitney test for pain scores.

Results: 154 of 324 patients contacted six months after surgery completed the telephone survey (47.53%) (Figure 1). There was no statistical difference between patient populations (Figure 2). 30 of 154 (19.48%) reported pain, 31 of 154 (20%) reported hospital readmission, and 21 of 154 (13.6%) reported less than complete satisfaction with their stay. Hospital readmission was associated with patients with a cancer diagnosis (P=.049) and those that had a longer mean length of procedure (282 vs. 206 minutes, P=.006). Median six-month pain scores were significantly higher for patients that underwent an open procedure compared to laparoscopic (Z=-2.06, P=.04). No relationship between pre/postoperative pain and six month outcomes was found. Postoperative pain (9 of 21, 43%) was the most common reason for patient dissatisfaction.

Conclusion: A six-month postoperative telephone survey was an adequate tool to assess outcome measures of interest. Long term benefits of an ERAS program were mostly confirmed. However, longer procedure time and patients with cancer correlated with an increased likelihood of hospital six-month readmission. Type of procedure also had a significant effect on six-month pain score outcomes. Further studies are needed to identify long-term outcomes of ERAS patients.

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Poster Presentations, *continued from page 183*

Questionnaire:

1.) Are you currently having pain related to your colorectal surgery on __/__/__?
YES NO
(If no skip to question 4)
2.) Can you please rate your pain on a scale from 1-9, with 1 being a little and 9 being the worst pain?
1 2 3 4 5 6 7 8 9

3.) Where, specifically, are you experiencing pain?

_____

3.) Are you taking prescription medications to manage your pain?
YES NO
If yes, what medications are you currently taking?

_____

4.) Have you been re-admitted to the hospital since your discharge on __/__/__?
YES NO
If yes,
Why were you admitted to the hospital?_____

_____

When was this hospital admission? _____

How long were you in the hospital?_____

7.) Were you satisfied with your stay at UCSF Medical Center on __/__/__ to __/__/__?

a. COMPLETELY SATISFIED b. SOMEWHAT SATISFIED c. NOT SATISFIED

(If b or c) Can you briefly describe to me what we could have done differently to improve your experience?

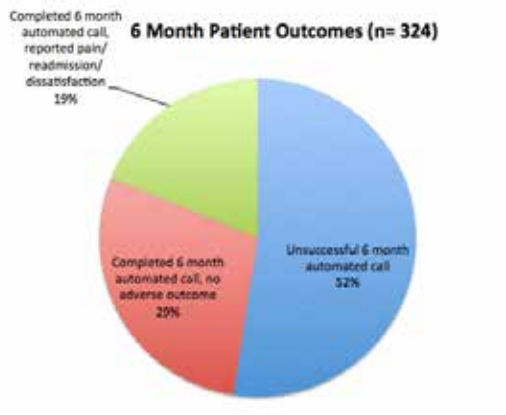
_____

_____

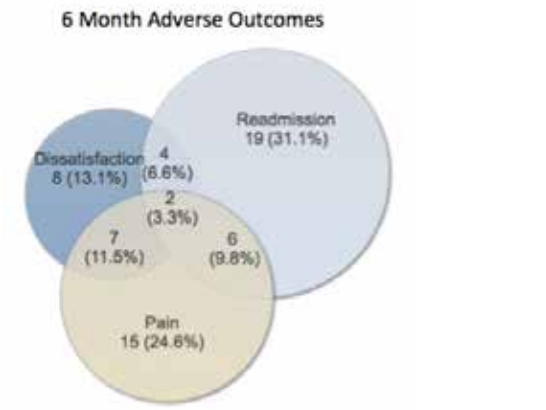
If applicable (reported pain, poor outcome, dissatisfaction):

You reported (stated issue/concerns) during this survey. Have you brought up this issue with your surgical team or primary medical doctor and is it currently being addressed?
YES NO

If no, why not? _____



	Completed 6 month call (N=154)	Unsuccessful 6 month call (N=170)	P-Value
Age	55±14	53±15	0.246
Male Sex	81 (53)	80 (47)	0.319
Dx of Cancer	75 (49)	75 (43)	0.299
Open Procedure	64 (42)	73 (43)	0.801
Length of Stay (hrs)	188±160	184±166	0.839
Length of Procedure (mins)	221±138	230±150	0.572
Median ASA rating	2	2	0.579
Pre-Op Pain	29 (19)	40 (24)	0.302
Post-Op Pain	73 (47)	81 (48)	0.948
Epidural Use	90 (58)	108 (64)	0.348



	Hospital Readmission within 6 Months of Discharge (N=33)	No Hospital Readmission within 6 Months of Discharge (N=123)	P-Value
Age	57±16	54±14	0.290
Male Sex	21 (68)	60 (49)	0.059
Dx of Cancer	**20 (65)**	**55 (45)**	**0.049**
Open Procedure	12 (39)	52 (42)	0.719
Length of Stay (hrs)	202±118	184±170	0.839
Length of Procedure (mins)	**282±167**	**206±126**	**0.006**
Median ASA rating	2	2	0.127
Pre-Op Pain	7 (23)	22 (18)	0.550
Post-Op Pain	14 (48)	61 (50)	0.836
Epidural Use	19 (61)	71 (58)	0.719
Dissatisfaction with Stay	6 (19)	15 (12)	0.299
6 month pain	8 (26)	22 (18)	0.320

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Poster Presentations, *continued from page 184*

PA 62 (2153)
A Comparison of the Responses and Utility of the Capuzzo Likert-Based and Modified Bauer/Brice Perioperative Satisfaction Scales

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[1]Wake Forest University Health Sciences, Winston-Salem, NC

Introduction: Patient satisfaction is assuming more of a role as a measure of the quality of health care. Satisfaction with anesthesia is used as an outcome measure in clinical trials, and patient satisfaction is considered to be an integral part of service quality.(1) Its measurement is also required to fulfill performance improvement and revalidation agendas for healthcare professionals.(2) However, a review of published literature indicates that appropriately developed or validated instruments are not widely used in many settings. Frequently, controlled trials and patient surveys rely on subjective measures of symptoms or quality of satisfaction as primary outcomes. The relative merits of different response options for these measures is an important, but largely unexplored, issue. We set out to compare the responsiveness and utility of 11-point Likert scales used in the preoperative Capuzzo Satisfaction Surveys (3) versus a 3 and 4-point Modified Bauer and Brice Questionnaire (4) used to measure patient perceptions of satisfaction regarding their experience during their perioperative experience.

Methods: During the Capuzzo survey period that we ran during the period from November 1, 2016 through December 20, 2016, we surveyed 225 patients that had either Inpatient or Outpatient Anesthesia, and either with general anesthesia or regional anesthesia with sedation. We excluded cases involving sedation only. We employed the Capuzzo survey as published (see figure). This survey covers the three domains and multiple patient patient experiences. During the Bauer/Brice survey period from January 3, 2017 through January 18, 2017 we surveyed 240 patients undergoing similar procedures. We modified the Questionnaire slightly (see figure) to omit sections that pertained to estimating awareness, as our interests were in common patient experiences (see figure). We also collected data on sampling times and compared time spent for each patient between the two surveys.

Results: Time spent for the Capuzzo was significantly longer than that for the Bauer/Brice (mean +/- SD 15.4 +/- 3.4 vs 10.3 +/- 2.6). The mean and median Capuzzo satisfaction scores (0-10) for most domains and items were above 9.5, with 'Pain' and 'Nausea' resulting in slightly lower values (~9.4). The variances were also quite small (most < 1.0) except slightly higher (1.5) for 'Pain' and 'Nausea.' T-testing indicated no significant differences between items. The mean and median modified Bauer scores were judged by categorical analysis (Chi-Square) and demonstrated signfiicant differences between questions. We compared the Capuzzo and Bauer surveys for skewness and tested this using Pearson's Coefficient of Skewness. The results indicated much lower variation in the Capuzzo scale, with significant differences between the two tests.

Conclusion: 1) Despite a similar number of questions, the Bauer/Brice Survey was quicker to administer than the Capuzzo Survey. 2) Compared to the Bauer/Brice Survey, the Capuzzo demonstrated less variation in answers and a highly negative skew. 3) We suggest using the Bauer/Brice Survey for ease of use and its demonstration of higher variation in responses.

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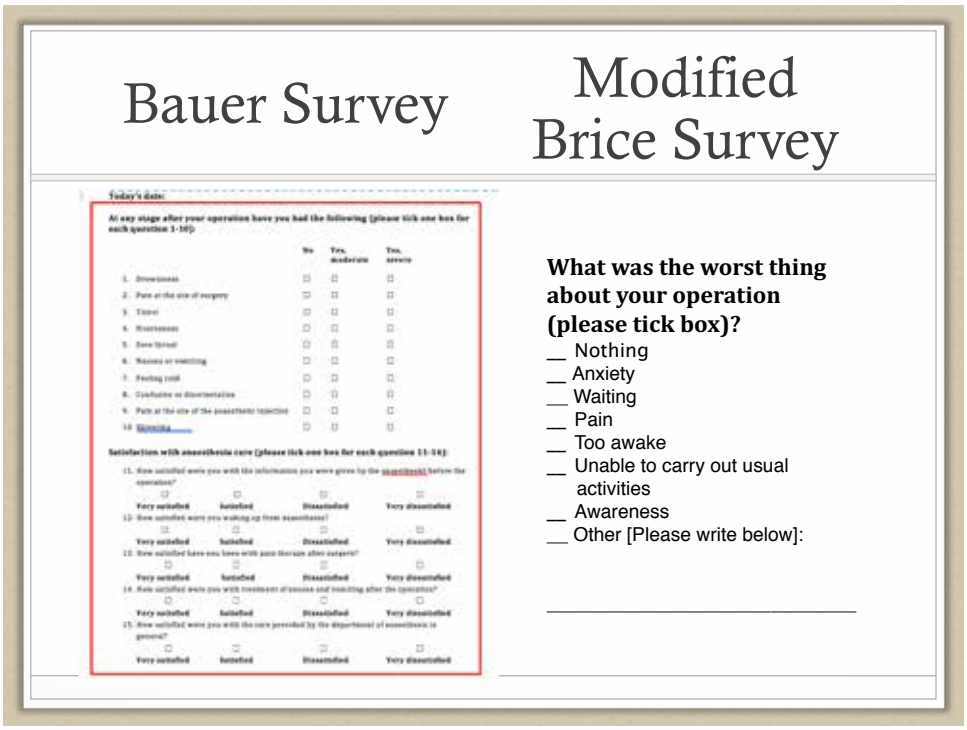

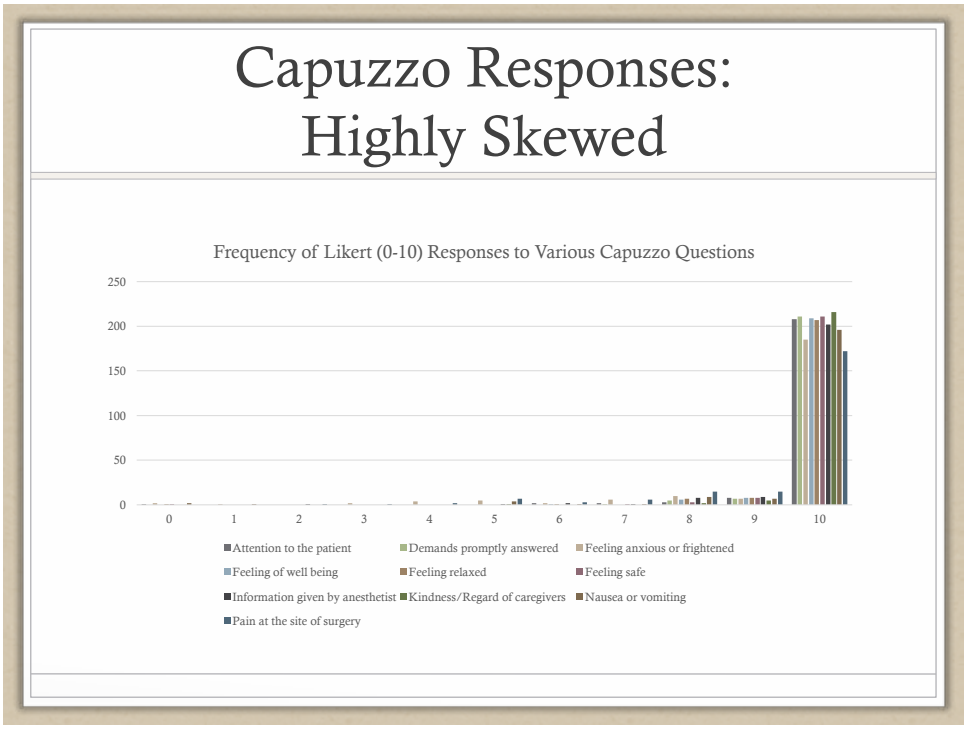

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https://ww4.aievolution.com/ars1701/files/content/abstracts/abs_2153/BauerBricecopy.pdf

Poster Presentations, *continued from page 186*

PA 63 (1977)
Blood Gas Analyzer Glucose Measurement Accuracy

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[1]Vanderbilt University Medical Center, Nashville, TN

Introduction: Intensive blood glucose control, although controversial, has been shown to improve outcomes in several cohorts of hospitalized patients.[1-4] Effective control of blood glucose relies on both accurate and timely glucose measurements. The Centers for Medicare & Medicaid Services (CMS) has proposed restricting the use of blood glucose meters (BGMs) in critically ill patients until their accuracy is demonstrated in this population, and has recently suggested blood gas analyzers (BGAs) as an alternative to BGMs.[5-6] Data regarding the comparability of BGA glucose measurement, however, is limited and controversial.[7-9] The objective of this study is to retrospectively investigate glucose measurement comparability between BGAs and the central lab (CLs).

Methods: Glucose measurements between June 2007 and March 2016 at the Vanderbilt University Medical Center were reviewed. The agreement between CLs (Beckman DxC analyzers and Abbott Architect analyzers) and BGAs (IL-GEM 3000 and 4000 analyzer) were assessed using Bland-Altman (BA), Consensus Error Grid (CEG), and Surveillance Error Grid (SEG) analysis. We further analyzed the BGAs performance against the FDA 2014 draft guidance, FDA 2016 guidance and the ISO 15197-2013 standard.

Results: 2,671 paired glucose measurements, including 50 pairs of hypoglycemic values, were analyzed. Bland-Altman analysis showed a mean bias of -3.1 mg/dL, with 98.1% paired values meeting the 95% limits of agreement (LOA). In the hypoglycemic range, the mean bias was -0.8 mg/dL, with 100% paired values meeting 95% LOA. When using CEG analysis, 99.9% of the paired values fell within the no risk zone. When using SEG analysis, 97.5% BGA values were within the no risk zone, 2.4% were within the slight risk, 0.1% were within the moderate risk zone, and no values were within the great or extreme risk zones. For FDA 2014 draft guidance, 90.5% of data pairs were +/- 10% of the laboratory method when ‰¥ 70 mg/dL and 90.0% of data pairs were within +/- 7 mg/dL when < 70 mg/dL (compared with target compliance rate of 99%). For FDA 2016 guidance, 94.3% of data pairs were +/- 12% of the laboratory method when ‰¥ 75 mg/dL and 96.2% of data pairs were within +/- 12 mg/dL when < 75 mg/dL(compared with target compliance rate of 95%). For ISO standard, 96.2% of the values ‰¥ 100 mg/dL were within the LOA and 97.8% of the values < 100 mg/dL were within the LOA (compared with target compliance rate of 95%).

Conclusion: We demonstrated that the agreement for glucose measurement between common BGAs with CL instruments meets the ISO 2013 standard. However, BGA accuracy did not meet the stricter requirements of FDA 2014 draft guidance or FDA 2016 guidance. Fortunately, plotting these results on either the CEG or the SEG revealed no results in either the great or extreme clinical risk zones.

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PA 64 (2222)
Effect of Using the Taperguard–Endotracheal Tube on the Prevention of Postoperative Ventilator Associated Pneumonia

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[1]Oregon Health and Science University, Portland, OR

Introduction: Ventilator associated pneumonia (VAP) is a serious nosocomial infection associated with tracheal intubation and mechanical ventilation. Various endotracheal tube (ETT) material and cuff shapes may influence the risk of VAP by reducing micro aspiration of subglottic secretions. The Taperguard „¢ ETT (Covidien, Boulder, CO) is designed to prevent micro aspiration around channels that otherwise form with a barrel-shaped cuff. A recent randomized trial of ICU patients requiring >72 hours of mechanical ventilation found a significantly decreased incidence of VAP in patients with a Taperguard ETT that included a subglottic suctioning channel.1 However, the tapered cuff on its own has not been demonstrated to reduce incidence of VAP in small studies,2 even in high risk subpopulations.3 The role of the Taperguard ETT in reducing VAP in an unselected, heterogeneous surgical population is unknown. We investigated the incidence of VAP in an inpatient surgical population after the introduction of the Taperguard ETT, as compared with the standard ETT.

Methods: This was a prospective investigation in the context of a quality improvement measure including all adult surgical inpatients 18 years of age or above who presented at Oregon Health and Science University between June 2011 and February 2014 for elective or emergency surgery. The intervention was deployed on December 1, 2012, when we instituted a practice change to transition from ETTs with barrel shaped cuffs to ETTs with tapered cuff design (Taperguard) for all surgical patients. Subjects were excluded if a specialized ETT including double lumen, reinforced, or laser endotracheal tube or a laryngeal mask airway were used. Data were abstracted from electronic medical records and institutional quality improvement databases. The primary study endpoint was VAP based on ICD-9 codes for bacterial and fungal pneumonia, associated with ventilation. Demographic characteristics were compared between the standard and the Taperguard ETT groups using two-sample Student's t-test or the chi-squared statistic. Logistic regression was used to estimate the odds of VAP in patients with Taperguard ETT relative to the standard ETT.

Results: Over the study period, 17,193 patients were included. There were no clinically important differences in the demographic characteristics between the standard ETT group (n=10,193) and the Taperguard ETT group (n=7,000). There were similar distributions of surgical specialty, procedures duration between the groups. There was no significant difference in the use of nondepolarizing neuromuscular blockade or positive end expiratory pressure. There was no significant difference in the incidence of VAP (standard ETT 1.7% vs Taperguard ETT 1.5%; p=0.38). The odds ratio of VAP comparing Taperguard ETT with the standard ETT was 0.90 (95% CI: 0.70-1.14).

Conclusion: The overall incidence of VAP in this unselected, surgical inpatient population was low. The Taperguard ETT was not associated with a decreased incidence of VAP when broadly implemented in a quaternary care center. Further analyses are necessary to determine potential differential effects in higher risk populations such as emergency surgery, an older population, or patients with other pneumonia risk factors.

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Table 1. Demographic and intraoperative characteristics of patients intubated with standard barrel cuff endotracheal tube compared with the Taperguard tube

Characteristics	Standard (n=10193)	Taperguard (n=7000)	p value
Age, years	54.1 ± 17.8	54.5 ± 18.3	0.23
Male, n (%)	5123 (50.3)	3510 (50.1)	0.88
Caucasian, n (%)	8916 (87.5)	6312 (90.2)	<0.01
Body Mass Index, kg/m^2	29.7 ± 8.0	29.7 ± 8.1	0.61
ASA Class, n (%)			0.05
1	621 (6.2)	428 (5.2)	
2	3907 (39.1)	2649 (38.2)	
3	4463 (44.6)	3052 (44.1)	
4	985 (9.9)	784 (11.3)	
5	22 (0.2)	16 (0.2)	
Procedure Category, n (%)			<0.01
Neurosurgery	899 (8.8)	633 (9.0)	
Otolaryngology	499 (4.9)	339 (4.8)	
Thoracic	221 (2.1)	138 (2.0)	
Cardiac	579 (5.7)	461 (6.6)	
Breast/soft tissue	779 (7.6)	494 (7.1)	
Open abdominal	2011 (19.7)	1399 (20.0)	
Laparoscopic abdominal	1677 (16.5)	1065 (15.2)	
Vascular	402 (3.9)	248 (3.5)	
Orthopedic	1595 (15.6)	997 (14.2)	
Out of OR locations	213 (2.1)	357 (5.1)	
Ophthalmology	44 (.43)	10 (.14)	
Spine	1274 (12.5)	859 (12.3)	
Procedure Duration, min	174.4 ± 118.8	174.8 ± 117.8	0.84
Rapid Sequence Intubation, n (%)	280 (2.8)	187 (2.7))	0.77
Nondepolarizing NMB, n (%)	6188 (60.7)	4451 (63.6)	<0.01
PEEP, n (%)	9626 (94.4)	6770 (96.7)	<0.01
Hospital length of stay, days	6.5 ± 8.1	6.7 ± 9.2	0.01
Ventilator associated pneumonia, n (%)	172 (1.7)	106 (1.5)	0.38

ASA: American Society of Anesthesiologists, NMB: neuromuscular blockade, PEEP: positive end expiratory pressure
*Data are expressed as mean ± standard deviation unless otherwise specified

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Poster Presentations, *continued from page 189*

PA 65 (1953)
Utility of Scoring Tools and Type of Surgery in Predicting Complications and 30-Day Readmission in a Urology Perioperative Surgical Home

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[1]University of Massachusetts Medical School, Worcester, MA, [2]University of Massachsetts Medical School, Worcester, MA, [3]UMass Memorial Medical Center, Worcester, MA

Introduction: We established a urology perioperative surgical home (PSH) pilot at our medical center to improve perioperative care provided to urology patients undergoing cancer surgery [(1)]. As part of this, we sought to identify factors knowable at the time of surgery that could help predict complications and readmission within 30 days.

Methods: We used logistic regression to predict each of hospital complications (e.g. bleeding, septic shock, stroke, renal failure) and readmissions from: the LACE risk score absent the length of stay (LOS) component (ACE), the SF-12 physical component score and surgery type (radical prostatectomy, radical nephrectomy and 'other'), for which prostatectomy was most common and routine, and radical nephrectomy was second most common and more complex. Because LOS is a component of the LACE score and we wanted a method to predict complications and readmissions prior to surgery, the LOS was stripped out. A higher ACE score and a lower SF-12 reflect a worse patient condition.

Results: We analyzed 197 PSH patients, of whom 24 (12.2%) were readmitted and 115 (58.4%) had at least one complication. ACE scores ranged from 0 to 7, SF12 from 20 to 61; 37% had radical prostatectomy and 20%, radical nephrectomy. The distinction between radical nephrectomy and other surgeries was never useful, and none of the potential predictors was individually associated with readmission at usual levels of significance, although fully 6 (27%) of the 22 people with SF12< 30 had complications. The point-estimates for the odds ratio (OR) associated with each 10-point decrease in SF12 was 1.32 (P = 0.16) and for a procedure other than radical prostatectomy was 2.24 (P = 0.15). In contrast, ACE, SF12 and radical prostatectomy (vs. other) were each strongly associated with complications (all P-values <0.002). In multivariable modeling, each unit increase in ACE increased the odds for a complication by about 20%, with OR and [95% Confidence Interval (CI)]: 1.20 [1.01 –1.43], p=0.03, while any surgery other than radical prostatectomy strongly elevated the odds chance of a complication, OR [95% CI]: 5.71 [2.9 – 11.6], p<0.001. Also, quintiles of a model that used ACE and radical prostatectomy to predict complications reveal increasing risk for both outcomes (Table 1.)

Risk Quintiles*	N	% with any complication	% readmitted
Lowest risk	40	25.0	7.5
Low	40	42.5	7.5
Middle	39	61.5	12.8
High	38	78.9	15.8
Highest risk	40	85.0	17.5
*Based on predicting "complication" from radical prostatectomy vs other surgery and ACE score			

Conclusion: With only 24 readmissions, we could not reliably identify predictors for this outcome. However, the ACE score and surgery other than radical prostatectomy together can be used to rank pre-operative patients by increasing risk for postoperative complications, and this ordering also correlates with increasing risk for readmission. Redeployment of resources to high-risk patients in the urology PSH may serve as a potential way to reduce these complications and, perhaps, readmissions as well.

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TRSL/BS 67 (1447)
Post-injury Neurogenesis Drives Aberrant Hippocampal Circuit Function in Mice

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Introduction: The generation of new hippocampal neurons increases after a variety of brain injuries, and these new neurons may contribute to either cognitive recovery or ongoing brain dysfunction. Direct physiologic analysis of neurons born into the post-injury brain has been lacking, however, hampering our understanding of how post-injury neurogenesis affects hippocampal circuit function. In this study, we directly assess the structure and synaptic outputs of neurons born after brain injury, to determine their effects on hippocampal circuits and to assess their possible contribution to hippocampal hyperexcitability in post-injury epilepsy.

Methods: In these studies, we employed two injury models of acquired epilepsy: the pilocarpine model of temporal lobe epilepsy and the controlled cortical impact model of post-traumatic epilepsy, both of which drive significant axonal rewiring in the hippocampus. We used novel combinations of genetically modified mice to pulse label entire cohorts of either neonatally-born or adult-born granule cells in adult mice with either fluorescent or optogenetic markers. Two months after injury, we determined the axonal projection patterns of these cells using confocal microscopy on fixed tissue, and their functional output characteristics using slice electrophysiology in live acutely prepared hippocampal slices.

Results: In both epilepsy models, adult-born hippocampal granule cells contributed significantly to pathologic retrograde mossy fiber axon sprouting. Using optogenetics to specifically activate adult-born neurons, we found that these neurons formed aberrant monosynaptic excitatory connections with other granule cells, establishing a recurrent positive feedback connection that was able to drive burst firing in hippocampal slices. Interestingly, however, the short-term plasticity of these synapses was strikingly altered compared to the synapses typically formed by these cells in healthy brains, revealing an unexpected circuit adaptation of adult-born neurons in epilepsy.

Conclusion: Our data suggest that adult-born neurons may play a functional role in epileptogenesis through their contribution to functional mossy fiber sprouting and the creation of a recurrent positive feedback circuit. Although post-injury neurogenesis is often interpreted as a salutary response contributing to recovery after injury, our work suggests that the miswiring of these neurons could possibly contribute to long-term pathology through the formation of maladaptive circuits. Treatment strategies aimed at modulating or inhibiting pathologic axon growth patterns during the maturation of these neurons might have clinical utility in the prevention of epileptogenesis after brain injury.

References:

n/a

TRSL/BS 69 (1402)
Ketamine Resistance in Mice with Neuronal Type-Specific Knock Out of a Mitochondrial Protein

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[1]University of Washington, Seattle Children's Research Institute, Seattle, WA

Introduction: The mechanisms underlying anesthetic function remain unknown. Knock out (KO) of the mitochondrial electron transport chain complex 1 protein, Ndufs4, has been shown to increase sensitivity to volatile anesthetics while conferring ketamine resistance.(1) Moreover, loss of Ndufs4 in glutamatergic neurons but not cholinergic or GABAergic neurons recapitulates volatile anesthetic hypersensitivity of the global Ndufs4(KO) mouse.(2) Using cell specific Ndufs4(KO) mice, we investigated whether ketamine resistance is dependent on loss in specific neuronal cell types. We also examined the EEG signals of global KO and WT mice anesthetized with ketamine to understand the basic signature of neuronal activity in the two genotypes at their respective ED95s.

Methods: All studies were approved by the SCRI Institutional Animal Care and Use Committee. We compared the ketamine responses of control mice (WT) mice and global Ndufs4(KO) mice to mice with Ndufs4 knocked out selectively in GABAergic, VGLUT2-positive glutamatergic, or cholinergic neurons (Gad2-Cre, VGLUT2-Cre, CHAT-Cre, respectively in floxed Ndufs4 mice). Young mice (P23-P27) (n= 6-15 per group for each dose) were injected with five doses of intraperitoneal ketamine to generate loss of righting reflex data (LORR). Each injection was spaced at least 24 hours apart. The LORR data were fit to a sigmoidal dose-response curve with variable slope with 95% CI for each curve (Figure 1 A-D) with two tailed unpaired T test with Welch's correction. WT (n=5) and global KO (n=4) mice had EEG leads surgically implanted in the left and right cerebral cortices at day P28 and were anesthetized with ketamine at 100mg/kg and 150mg/kg, respectively, on P29. Three minutes of EEG recordings were analyzed in the awake and anesthetized states (Figure 2A) with averaged power spectral density (PSD) analysis (Figure 2B) performed from 1-30 Hz.

Results: The ED50s of global KO mice (100 ± 2 mg/kg) and VGLUT2-[KO] (125 ± 2 mg/kg) were higher ($p<0.01$ in both) than ED50 of control mice (75 ±1.5 mg/kg, Figure 1 A,B) using LORR as an endpoint. In contrast, both CHAT-[KO] (ED50 90 ±4 mg/kg) and GABA-[KO] animals (ED50 ±5 mg/kg) were not ketamine resistant ($p=0.76$, 0.86, respectively, Figure 1 C,D). Representative 20 second tracings of EEGs from global KO and WT mice are shown in Figure 2A. The averaged ratio PSD of EEG tracings of in the global KO were significantly different than WT only in the beta (13-30Hz) frequencies ($p<0.0001$). The anesthetized state of the global KO mouse demonstrates decreases in the beta frequencies from an awake state, whereas WT mice have increases in beta frequency EEG signal from awake state during anesthesia.

Conclusion: Disruption of aerobic metabolism only in glutamatergic cell specific Ndufs4 KO mice confers the same ketamine resistance phenotype as the global Ndufs4 KO. Since ketamine anesthesia requires energy, disruption of glutamatergic metabolism could provide a possible explanation for the resistance phenotype as well as differences in anesthetized EEG states. The broad decrease in EEG power in the beta range for the anesthetized KO at its higher ED50 may reflect an underlying energy deficit unable to respond to ketamine NMDA antagonism. There could also be changes in NMDA receptor trafficking or phosphorylation that could account for these observations. These findings reinforce importance of mitochondrial involvement in understanding the complex neuropharmacology of ketamine anesthesia.

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Figures

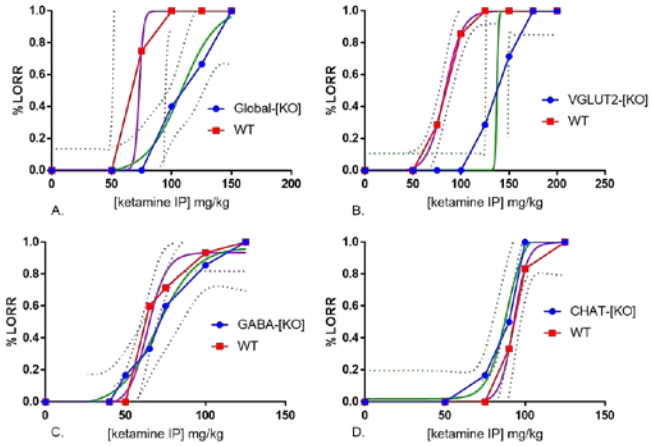
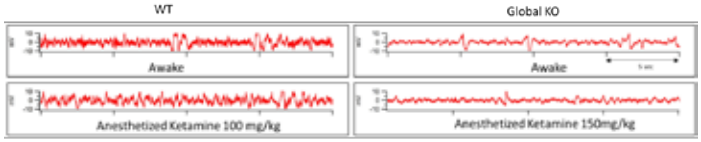
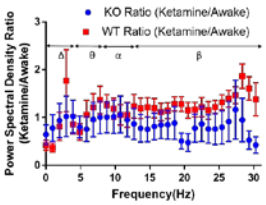


Figure 1 A-D. Loss of Righting Reflex (LORR) Dose Response Curves fitted with Sigmoidal Curve with Variable Slope. Each graph shows the doses of intraperitoneal ketamine tested (red,blue) as well as the interpolated curve fits (magenta, green) with 95% confidence intervals plotted as dotted lines.



A.



B.

Figure 2 A-B. Representative 20 second EEG Tracing and Power Spectral Density Data for Global KO and WT Mice. A. Shows WT and global KO 20 second tracings in the awake and anesthetized states. B. Shows the ratio of power spectra densities for 3 minute anesthetized tracing over awake for each animal averaged with standard mean error bars. Meaningful differences appear in the beta range but not in the delta, theta or alpha spectra.

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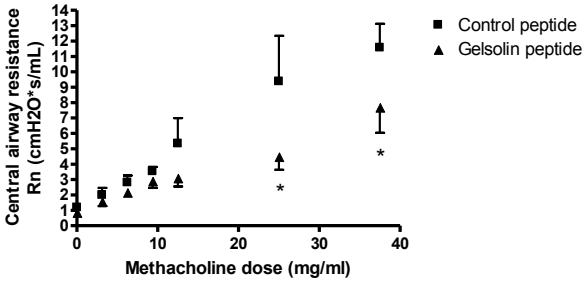
Poster Presentations, *continued from page 193*

TRSL/BS 71 (1255)
Attenuation of Airway Contraction In Vivo in Mice by Inhalation of Gelsolin Peptide

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

[1]*Columbia University, New York, NY*

Introduction: We have previously reported that mice genetically deficient in the actin binding protein gelsolin exhibit impaired airway smooth muscle (ASM) relaxation ex vivo and in vivo. We also reported that primary cultured ASM cells from gelsolin null mice demonstrate enhanced inositol triphosphate (IP3) synthesis and increased intracellular calcium in response to Gq-coupled agonists. We hypothesized that this was due to increased intracellular availability of unbound phosphatidylinositol 4,5-bisphosphate (PIP2), the substrate for Gq-activated phospholipase Cβ (PLCβ) hydrolysis of PIP2 to IP3 and diacylglycerol. This hypothesis was based on the fact that gelsolin includes a region that binds PIP2 [1], presumably making it a less available substrate. We now questioned whether a peptide that corresponds to the PIP2 binding region of gelsolin [2] could modulate airway smooth muscle signaling and contraction.



Fugure: In vivo lung resistance measurements. Following an inhalation of control peptide or gelsolin peptide, A/J mice were exposed to increasing concentrations of methacholine via nebulizer. An increase in central airway resistance (Rn) in response to an escalating dose of methacholine was significantly attenuated in mice treated with gelsolin peptide compared with mice treated with control peptide. n=6-9 (up to 25 mg/ml dose) and n=3-5 (up to 37.5 mg/ml dose), *p<0.05.

Methods: Studies were approved by the Columbia University IACUC. The 10 amino acid sequence of the gelsolin peptide within the PIP2 binding region (QRLFQVKGRR) and a control peptide (QRL) were synthesized and conjugated with rhodamine B by Biomatik (Wilmington, DE). [3H]-IP3 synthesis was measured in response to a Gq-coupled agonist in primary cultures of human ASM cells with and without gelsolin or control peptide pretreatment. Acetylcholine-induced contractile force was measured in isolated tracheal rings from wild type and gelsolin null mice in myograph organ baths in the presence or absence of exogenous rhodamine B-conjugated gelsolin or control peptide. Lastly, A/J mice were tracheotomized and control or gelsolin peptide was administered via nebulization, and the changes in central airway resistance were measured after inhaled methacholine using the forced oscillation technique via FlexiVent.

Results: Rhodamine B-conjugated gelsolin and control peptides were rapidly internalized in primary cultures of human ASM cells. Gelsolin peptide treated human ASM cells generated less IP3 under basal and bradykinin (Gq-coupled) conditions (n=3-6, $p<0.05$ for basal and $p<0.001$ for bradykinin). In ex vivo wire myograph studies, gelsolin peptide pretreated tracheal rings from both wild type and gelsolin null mice contracted less in response to acetylcholine, compared to control peptide treated rings (n=4-8, $p<0.05$ for wild type and $p<0.01$ for gelsolin null). In in vivo lung resistance measurement studies, gelsolin peptide nebulized A/J mice demonstrated attenuated increases in central airway resistance in response to inhaled methacholine challenges compared to control peptide nebulized mice (n=6-9, $p<0.05$).

Conclusion: The small PIP2-binding region of the actin capping and severing protein gelsolin modulated downstream IP3 synthesis and acetylcholine-induced contraction ex vivo. This peptide fragment delivered to the respiratory system of mice via nebulization was also able to attenuate subsequent methacholine-induced increase in airway resistance in vivo. This effect was likely due to the peptide binding to PIP2 rendering it a less available substrate for PLCβ-mediated hydrolysis of PIP2 to IP3 and diacylglycerol. The current study demonstrated that introduction of this small gelsolin peptide into the airway may be a novel therapeutic option in bronchoconstrictive diseases.

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TRSL/BS 72 (1331)
Sterile Lung Inflammation Augments Bacterial Clearance in Mice via NLRP3 Inflammasome

Arun Prakash, MD, PhD[1], Xiaoli Tian, PhD[1]; Judith Hellman, MD[1]

[1]*UCSF, San Francisco, CA*

Introduction:
Reperfusion injury following ischemia is believed to contribute to multiorgan failure and mortality in septic and severely injured trauma patients. The lungs, as part of a vital organ system at an interface between the host and environment, are very susceptible to injury and even temporary impairments can be life threatening. IL-1Î[2] and upstream NLRP3 inflammasome signaling complex have been reported to control other sterile inflammatory processes, such as ventilator-induced lung injury (VILI). We sought to understand whether this sterile inflammatory response (IR) utilizes the NLRP3 inflammasome and if it serves an adaptive or maladaptive function, especially in the context of bacterial infections.

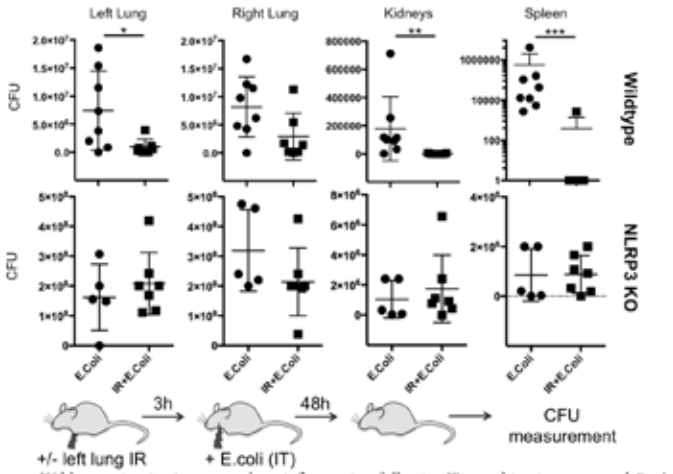

Figure. Wildtype mice (top) generate lung inflammation following IR, resulting in augmented *E.coli* clearance from lungs and peripheral organs unlike Inflammasome KO (NLRP3 KO, bottom) mice.

Methods: We used a mouse model of unilateral ischemia reperfusion (IR) to study IR-induced lung inflammation. By subjecting wild type, and NLRP3 inflammasome knockout mice (NLRP3 KO) to left lung IR, and using pharmacologic inhibitors to block caspase activation and IL-1R signaling, we examined role of the inflammasome and resulting IL-1Î[2] release in IR inflammation through the measurement of local and systemic IL-6 and other inflammatory cytokine levels. Finally, we studied whether preceding lung IR inflammation affected subsequent E.coli pneumonia resolution in both wild type and inflammasome KO mice by measuring CFU in blood and peripheral organs 48h after infection. Data from in vivo studies comparing two conditions were analyzed using 2-tailed nonparametric Mann-Whitney analyses.

Results: We found that NLRP3 KO mice did not display the 2-fold to 8-fold increase in inflammatory cytokines (IL-6, IL-12) and chemokines (CXCL1) over sham seen in wild type mice subjected to IR. Furthermore, inhibitors of caspase-1, and IL-1R blocking antibodies significantly blunted the IL-6 inflammatory response (about 2-fold reduction). Strikingly, mice subjected first to lung IR and then to an E.coli pneumonia had significantly reduced bacterial loads at the site of infection (left lung: 8-fold lower, right lung: 3-fold lower) and in peripheral organs (spleen: 1500-fold lower, kidney: 100-fold lower) (see Figure). Conversely, we observed an absence of this effect in NLRP3 KO mice (see Figure).

Conclusion: Our data support a beneficial role for IR injury induced lung inflammation. The early generation of inflammatory mediators and neutrophil recruitment may provide the lung with the capacity to contain and clear local or disseminated bacterial infections. Overall, this study suggests a potential protective role for IR inflammation in lung infection and raises the exciting possibility that the immune response elicited through IR, through the NLRP3 inflammasome and IL-1Î[2] signaling, could be exploited or harnessed to treat trauma patients with concomitant bacterial pneumonia.

References:
None

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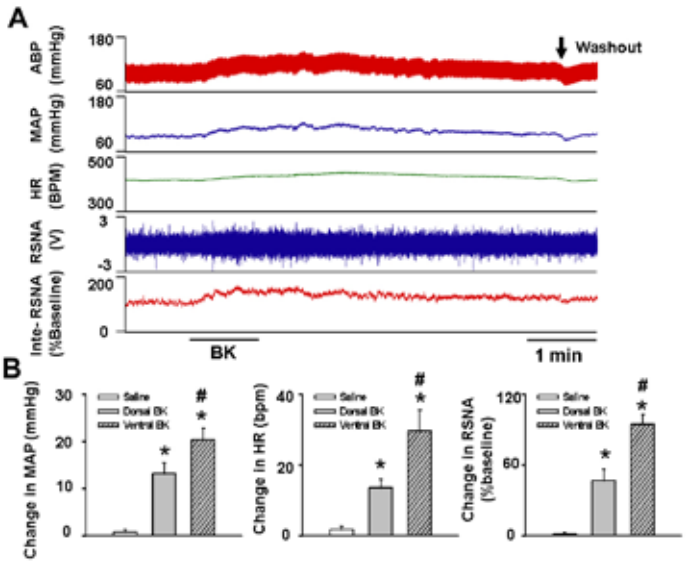
Poster Presentations, *continued from page 195*

TRSL/BS 73 (1109)
Identification of a New Pulmonary Spinal Sympathetic Afferent Reflex in Rodents

Hanjun Wang, MD[1], Irving H. Zucker, PhD[1]; Zhiqiu Xia, MD[1]; Julia Shanks, PhD[1]; George J. Rozanski, PhD[1]; Andrew J. Patterson, MD, PhD[1]; Steven J. Lisco, MD[1]

[1]University of Nebraska Medical Center, Omaha, NE

Introduction: Since the original work of Hering and Breuer in 1868 numerous studies have demonstrated that the lung vagal afferents are primarily involved in pulmonary reflex control of cardio-respiratory activities in normal and pathological conditions. In general, stimuli to pulmonary vagal afferents evokes a cardiovascular inhibitory effect. However, whether pulmonary spinal afferents are also involved in cardiovascular control remains unclear. Here, we provide novel evidence demonstrating that activation of pulmonary spinal afferents by bradykinin (BK) evokes a previously undocumented potent sympatho-excitatory reflex in anesthetized vagotomized rats.



Methods: These experiments were approved by the Institutional Animal Care and Use Committee and were carried out under the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. After bilateral section of the cervical vagal nerves in urethane- Î±-chloralose anesthetized rats, we applied a square of filter paper (3 Ã— 3 mm) saturated with BK (1 and 10 Î¼g/ml) to the dorsal or ventral surface of the left or right lung to stimulate regional pulmonary spinal afferents.

Results: We found that application of BK on both dorsal and ventral surfaces of the lungs resulted in tachycardia and pressor responses associated with increased renal sympathetic nerve activity (RSNA). However, compared to dorsal application, the sympatho-excitatory responses to BK on the ventral surface of lungs were more profound (change in mean blood pressure: +20.3 ±2.5 vs. 13.2 ±2.2 mmHg; Heart rate: +29.6 ±5.9 vs. 13.5 ±2.5 bpm; RSNA: +94.2 ±8.5 vs. 46.7 ±9.7%basal; n=6-8/each, P<0.05). The BK-induced sympatho-excitatory response in the lungs was dose-dependent whereas application of vehicle (saline) on any area of lungs had no cardiovascular effects. In order to further confirm the origin of this reflex, we used epidural application of a selective afferent neurotoxin (resiniferatoxin, RTX) to chronically ablate thoracic/cervical TRPV1-expressing afferent soma at the level of C6-T5 DRGs and repeated BK application 5-6 weeks post RTX. We found that this treatment almost completely abolished all sympatho-excitatory responses by lung application of BK (change in mean blood pressure: +2.6 ±0.8 mmHg; Heart rate: +3.4 ±1.4 bpm; RSNA: +9.3 ±4.2%basal; n=9).

Conclusion: These data strongly suggested a new pulmonary spinal sympathetic afferent reflex in rats. Further studies will be needed to confirm this newly identified reflex in large mammalian animals and humans.

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TRSL/BS 74 (1332)
A Novel GABA-A Receptor α-Subunit-Selective Ligand Relaxes Mouse and Human Airway Smooth Muscle

Gene Thomas Yocum, MD[1], Peter Yim, MD[1]; Yi Zhang, MD[1]; Jose Perez-Zoghbi, PhD[1]; Alexander Arnold, PhD[2]; James Cool, PhD[2]; Charles W. Emala, MD[1]

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

Introduction: The GABA-A receptor is expressed on airway smooth muscle (ASM), and pharmacologic activators of this receptor lead to direct ASM relaxation. However, the potential therapeutic use of GABA-A receptor ligands to relax ASM risks undesired activation of brain GABA-A receptors resulting in sedation. Compound S is a novel GABA-A receptor positive allosteric modulator selective for GABA-A receptors containing Î±5 subunits that does not penetrate the blood-brain barrier after systemic administration, thus limiting sedative side-effects. We hypothesized that this promising therapeutic would relax ASM across multiple species, including human, in response to different contractile ligands.

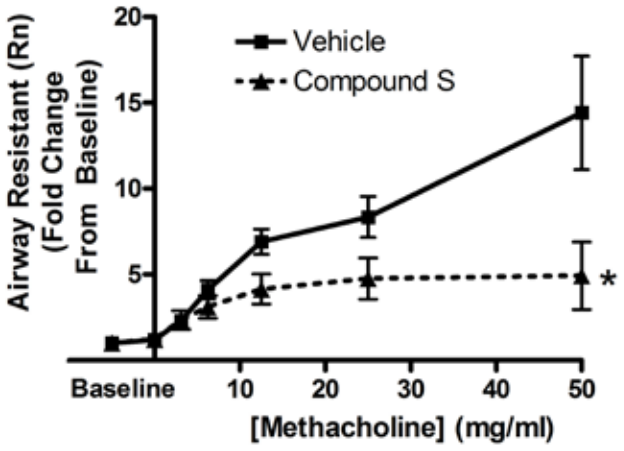

Figure 1: *In vivo* mouse airway resistance. Mice pretreated with inhaled compound S had significantly lower *in vivo* airway resistances during a graded methacholine challange than vehicle-treated mice. *p<0.05 AUC compared to vehicle. n=8

Methods: Human ASM strips were contracted with 20 nM leukotriene D4 (LTD4; a potent contractile agonist) and then exposed to 100 µM compound S or vehicle (0.2% ethanol) during continuous contraction force monitoring in organ baths. In mouse precision-cut lung slices (PCLS), airways were contracted with methacholine 300 nM and then exposed to 100 µM compound S or vehicle during measurements of peripheral airway luminal areas and ASM calcium oscillations. After pretreatment with inhaled Compound S (10 mM) or vehicle., increases in mouse in vivo airway resistance in response to inhaled, graded methacholine challenges (0-50 mg/ml) were measured by force oscillation technique (flexiVent).

Results: Compound S led to significant relaxation of LTD4-contracted human airway smooth muscle strips in organ bath preparations (56.8% of contraction remaining at 60 min versus 87.2% for vehicle control, n=3 human donors, p<0.05). In mouse PCLS experiments, 100 µM compound S led to potent airway relaxation and inhibited methacholine-induced calcium oscillations in ASM cells. Compound S pretreatment significantly inhibited methacholine-induced increases in in vivo mouse airway resistance (Rn) as measured by forced oscillation technique (p<0.05 compared to vehicle control; n=8).

Conclusion: Compound S is a promising therapeutic for bronchoconstrictive diseases given its favorable pharmacokinetic/dynamic profile (limiting side-effects) and potency in relaxing ASM from mouse and human in multiple clinically relevant experimental paradigms. This relaxation likely results from the inhibition of ASM cell calcium oscillations.

References:

None

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T 75 (1933)
Down-Regulation of Angiopoietin-1 Mediates Neuronal Cell Death Following Experimental Traumatic Brain Injury in Mice

Bogdan Stoica, MD[1], Boris Sabirzhanov, PhD[1]; Tarryn Aubrecht, PhD[1]; Rebecca Henry, PhD[1]; Alan Faden, MD[1]

[1]*University of Maryland School of Medicine, Baltimore, MD*

Introduction: Traumatic brain injury (TBI) initiates regulated neuronal death mechanisms that significantly contribute to neuronal loss and neurological dysfunction. Micro-RNAs (miRs) are short (20-23 nucleotide) noncoding RNAs that negatively regulate gene expression at the post-transcriptional level by binding to the 3 €²-untranslated region (UTR) of target mRNAs, leading to their degradation and/or translational inhibition. Although miRs have been implicated in the pathophysiology of central nervous system (CNS) disorders and may modulate neuronal cell death pathways, few have been directly evaluated at a mechanistic level in TBI. We have previously shown that increased brain levels of miR-711 are detected in the first 72 hours after TBI in mice, a period associated with maximal secondary tissue injury. Angiopoietin-1 (Ang-1) is a well-known endothelial growth factor but its effects on neurons have yet to be elucidated. Here we examine the modulation of Angiopoietin-1 by miR-711 as a secondary injury mechanisms following TBI.

Methods: Studies were performed using young adult (3 months old, 22–26 €‰g) male C57Bl/6 mice. Controlled cortical impact (CCI) is an experimental model of TBI. Rat cortical neurons (RCNs) were derived from rat embryonic cortices. Cell death, cell viability, and in-plate fluorometric caspase-3 activity were measured using the LDH, Calcein AM, and DEVD-AMC assays. Quantitative real-time PCR amplification was performed by using cDNA TaqMan Universal Master Mix II (Applied Biosystems). Statistical analysis was performed using the Prism version 6 for Windows (GraphPad Software) as indicated. If the data passed a normality test, further analysis involved one-way ANOVA followed by multiple pairwise comparisons using the Student-Newma-Keuls post hoc test.

Results: We show that Ang-1 is rapidly down-regulated in the brain after experimental traumatic brain injury (TBI) and in neuronal models of cell death such as etoposide-induced DNA damage. Ang-1 treatment inhibits etoposide-induced up-regulation of pro-apoptotic Bcl-2 family members Noxa, Puma, Bim, and Bax; reduces markers of caspase-dependent (cytochrome c release/caspase activation) and caspase-independent (apoptosis-inducing factor release) pathways; and limits neuronal cell death. Ang-1 treatment phosphorylates receptors Tie2 and Î²1-integrin and limits the etoposide-induced decrease in Akt activity. Blocking Tie2 and Î²1-integrin signaling reduces Ang-1 neuroprotective effects. After both TBI and etoposide treatment in vitro miR-711 are up-regulated, consistent with its putative role as a negative regulator of Ang-1. We show that miR-711 directly targets the Ang-1 mRNA 3' UTR, decreasing Ang-1 expression. Increased levels of miR-711 and Ang-1 mRNA are found in the RISC complex site of microRNA-mediated degradation of target mRNAs after etoposide treatment. Administration of a miR-711 mimic down-regulates Ang-1, whereas a miR-711 hairpin inhibitor reduces the Ang-1 decline after TBI. In addition, administration of Ang-1 increases Akt activation; reduces Puma, Noxa, Bim and Bax levels; and attenuates caspase-dependent and -independent neuronal apoptosis after TBI.

Conclusion: Thus, miR-711-dependent down-regulation of Ang-1 expression, followed by Akt pathway inhibition may play a role in neuronal cell death after neuronal injury in vitro and after experimental TBI. Based on these findings we suggest that miR-711 may be a potential therapeutic target for TBI.

References:

miR-711 upregulation induces neuronal cell death after traumatic brain injury. Cell Death Differ. 2016 Apr;23(4):654-68

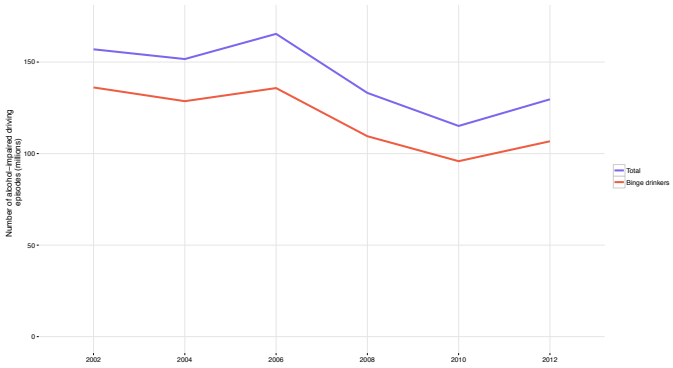
Poster Presentations, *continued from page 198*

T 76 (1277)
Alcohol-Impaired Driving in US Counties, 2002-2012

Jacob Sunshine, MD, MS[1], Laura Dwyer-Lindgren, PhD[2]; Alan Chen, BS[2]; Sam Sharar, MD[1]; Ali Mokdad, PhD[2]

[1]University of Washington, Seattle, WA, [2]Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA

Introduction: Alcohol-impaired driving remains a significant risk factor for trauma-related morbidity and mortality.(1) Although previous reports on alcohol-impaired driving provide national- and state-based estimates, most enforcement of impaired driving laws occurs at the municipal level; thus, county level information is needed to guide allocation of limited law enforcement and healthcare resources.(2)



Methods: We used a previously validated 'small area estimation' strategy to analyze data from the Behavioral Risk Factor Surveillance System (BRFSS), a state-based telephone survey conducted annually by state health departments and the Centers for Disease Control and Prevention; the BRFSS conducts approximately 400,000 interviews each year.(3)(4) Respondents were asked, 'During the past 30 days, how many times have you driven when you've had perhaps too much to drink?' We used small areas mixed effects models (integrating respondent demographic information from the BRFSS and county-level socioeconomic information from the US Census) to estimate the prevalence of alcohol-impaired driving in every US County from 2002 through 2012, the latest year for which county identifiers are available. We also calculated the total annual episodes of reported alcohol-impaired driving during the study period, including among the high-risk subset of adults who engage in binge drinking behavior.

Results: Approximately 998,500 individual BRFSS responses were used for this analysis. From 2002-2012 there were an estimated 1.56 billion episodes of reported alcohol-impaired driving in the United States. The estimated reported episodes of alcohol-impaired driving in 2012 (129.7 million) were decreased 17.4% from those in 2002 (160.0 million) (Figure 1). Men were more likely to engage in alcohol-impaired driving than women; in 2012, men had 102.6 million estimated reported episodes of alcohol-impaired driving (879 episodes per 1000 adult males) compared to 27.1 million episodes among women (219 episodes per 1000 adult females). There is considerable variation in the prevalence of alcohol-impaired driving at the county level, ranging from 2.0% (95% uncertainty interval, 0.89%–3.5%) in Sitka City Borough, Alaska to 9.3% (95% uncertainty interval, 6.6%–12.2%) in Nance County, Nebraska (Figure 2). Among the 50 most populous US counties, Kings County, New York had the lowest prevalence of alcohol-impaired driving (2.0%, 95% uncertainty interval, 1.5%–2.7%), whereas Milwaukee County, WI had the highest prevalence (5.5%, 95% uncertainty interval, 4.6%–6.6%) (Figure 3).

Conclusion: This study found guarded progress with respect to the number of reported episodes of alcohol-impaired driving in the United States from 2002-2012. However, while the age-standardized prevalence of this behavior has decreased slightly, there continue to be several million episodes of alcohol-impaired driving each month. Because these data rely on self-report, our results likely represent a significant underestimate of the true prevalence of alcohol-impaired driving in the United States. Nonetheless, our findings suggest high-priority counties that may benefit from targeted efforts to mitigate this high-risk behavior..

References:

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T 77 (1770)
Neuropathology and Behavioral Deficits in a Rat Model of Brain Injury to Occupants of Vehicles Targeted by Land Mines: Mitigation by Shock-Absorbing Hull Designs

Flaubert Tchantchou, PhD[1], Ulrich Leiste, PhD[2]; Adam Puche, PhD[1]; William Fourney, PhD[2]; Gary Fiskum, PhD[1]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]University of Maryland College Park, College Park, MD

Introduction: Exposure to blasts has resulted in traumatic brain injury (TBI) to over 200,000 U.S military personnel during the last 10 years [(1)]. Many of these victims were occupants within vehicles targeted by land mines. Using our novel rat model of under-vehicle blast-induced TBI [(2)], we found that blast-induced acceleration of approximately 2400G impaired hippocampus-dependent working memory and caused long term anxiety-like behavior. These behavioral deficits were associated with several neuropathological markers including hippocampal neuronal death, inflammation, and loss of synaptic proteins [(3)]. An increase in the G force to 2800G resulted in substantial, 67% mortality. This study tested different vehicle hull designs for their ability to reduce the force transferred to the animals and for their ability to reduce mortality and TBI.

Methods: Fully conscious male Sprague Dawley rats were placed within restraints secured on the top of an aluminum platform, representing the frame of a vehicle. A second platform representing the hull of a vehicle was located directly under the top platform. A small explosive was detonated under the hull resulting in peak vertical acceleration of 2800G. In an effort to reduce this force on the rats, five crushable aluminum cylinders were placed between the bottom and top platforms. In some experiments, the cylinders were coated with polyurea. Blast survivors and sham rats were tested to assess working memory and anxiety-like behavior. Animals were euthanized and brain tissue collected for histological and biochemical analyses. Statistical analysis was performed by one way ANOVA with Tukey-Kramer post-test analyses. There were 6-12 animals per group and the study was approved by the UMB IACUC committee..

Results: Vehicle designs that included polyurea coated cylinders between the hull and the frame reduced blast induced acceleration load on the rats from 2800G to 550G and completely prevented mortality. Blast with uncoated cylinders design generated accelerations of 2300G, with 29% mortality, emphasizing the importance of polyurea coating. Moreover, polyurea coated cylinders prevented the deficits in working memory ($p < 0.01$) and anxiety-like behavior ($p < 0.05$), that were observed in rats subjected to blast with uncoated cylinders. Histological analysis of rat brains revealed a significant increase in perivascular immunoglobulin G effusion (blood brain barrier disruption) and microglia/microphage infiltration in blast rats with uncoated cylinders. Furthermore, there was a substantial increase in the number of apoptotic hippocampal neurons ($p < 0.01$) and a decrease in the puncta density of pre- and post-synaptic markers Bassoon ($p < 0.05$) and Homer-1 ($p < 0.01$), in comparison with sham rats. Apoptotic cell loss was associated with decreased hippocampal expression of the anti-apoptotic protein Bcl-2 and of the activated cell survival promoting protein pERK ($p < 0.01$). These pathological alterations were attenuated by the presence of polyurea-coated cylinders in the model vehicle.

Conclusion: The current military 'Mine-Resistant Ambush Protected (MRAP)' vehicles that incorporate a V-hull design have dramatically reduced mortality following blasts but only modestly reduce the acceleration experienced by the occupants, resulting in ongoing TBI and other injuries. The addition of shock-absorbing cylinders between the frame and the hull of these vehicles may further reduce blast-induced casualties.

References:

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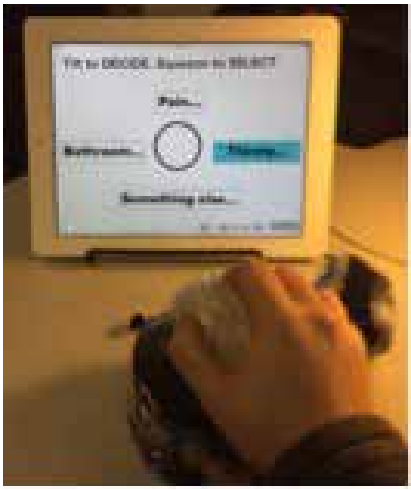
CC 78 (1713)
Testing a Novel Manual Communication System for Mechanically Ventilated ICU Patients

Miriam A. Goldberg, M.Eng[1], Leigh R. Hochberg, MD, PhD[2]; Dawn Carpenter, NP[1]; Johnny Isenberger, MSN[1]; Stephen Heard, MD[1]; J. Matthias Walz, MD[1]

[1]University of Massachusetts Medical School, Worcester, MA

Introduction: Available communication methods for intubated patients in the ICU are insufficient to meet patient needs. In addition to the psychological strain patients incur due to extended inability to communicate, both ICU patients and their care providers report broadly unsuccessful communication attempts, resulting in less effective medical care and undue stress.[1, 2] Use of existing methods — including letter boards, writing, and mouthing words — for mechanically ventilated (MV) patients has led to a consensus that new methods are required. [3] Novel technologies and approaches may be used, in conjunction with human-computer interface –centered design approaches, to create a more intuitive and useful method of patient communication. We report on the testing of a new system designed to address the communication needs of MV patients that is currently being tested in a low- to medium- acuity surgical ICU. [4]



Methods: We have developed several generations of prototypes designed to address patient communication needs. Design of this device has focused on ICU-specific communication needs, including ICU-specific content, infection control, simple design, and capitalizing on motor movements that can be easily performed by most ICU patients. Initial testing, starting with non-MV patients able to give more detailed feedback, has begun in a low- to medium-acuity surgical ICU. Recently developed prototypes (Figures 1, 2) combine custom-built tablet software, focusing on the needs that nurses believe patients wish to express in the ICU setting, with a newly designed manually operated access device. The system is intended to produce visual and auditory output in order to allow patients to answer basic questions and effectively convey information.

Results: Initial patient impressions are encouraging, particularly among patients who have recently experienced mechanical ventilation. The design decision to separate the access method from a visual output system (compared to usual tablet computer configurations, in which the access method is identical to the visual display) has been validated by observing patient needs. Many patients are unfamiliar with tablet software or struggle with manual dexterity required to access the tablet screen directly, further indicating the need for an external access method as part of the system. The content suggested by nurses via a previously conducted survey has been confirmed by patients as relevant to their experience.

Conclusion: A novel manually operated communication system has elicited both positive reviews and helpful feedback from patients. Ongoing iteration may yield a system that is particularly well adapted to the unique communication challenges of mechanically ventilated patients in the ICU.

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Poster Presentations, *continued from page 201*

TCSEM 79 (1719)
Principles of Augmentative & Alternative Communication System Design in the ICU Setting

Miriam Goldberg, M.Eng[1], Leigh R. Hochberg, MD, PhD[2]; Dawn Carpenter, NP[1]; Johnny Isenberger, MSN[1]; Stephen Heard, MD[1]; J. Matthias Walz, MD[1]

[1]University of Massachusetts Medical School, Worcester, MA, [2]Brown University, Providence, RI

Introduction: The ICU as a technology design setting requires specific and thoughtful awareness of patient-, caregiver-, and environment-related constraints. Designing an ICU-specific communication system, which involves additional layers of subjective impressions and user-specific preference compared to more technical medical interventions, involves an even deeper understanding of patient needs and desires, building on existing work exploring available technologies for use in this setting. [1, 2] We report our initial experience from a pilot study with a novel communication device engineered specifically to allow mechanically ventilated ICU patients to communicate with caregivers.[3]

Methods: We used a validated survey for nurses about communication purposes to explore the beliefs, attitudes, and desires of nurses with regard to the parameters of the technology design effort. [4] Many hours of observation and discussion were included in the conception and initial prototyping stages. Existing technologies available for communication assistance in the ICU – e.g, letter boards, writing on paper, and mouthing words – were both observed directly and asked about in discussions with nurses, and suggestions about the content for an eventual communication system were collected. ICU-specific design requirements were noted for incorporation into successive prototypes (Figures 1, 2). These requirements include adherence to infection control standards, accessibility to restrained patients, and availability to patients with motor weakness, contractures, edema, tremor, and/or neuropathy. In addition, the system must include a minimal learning curve, so that patients will be able to rapidly and intuitively understand how to use the system.

Results: Initial testing in the ICU has revealed additional considerations for technology design. For instance, many patients have visual impairments, necessitating that any images or text be large and high-contrast. Furthermore, patients benefit from a very short teaching/demo process due to their short attention span related to medication effects, fatigue, and underlying disease processes. Additionally, leveraging interfaces with significant similarities to what patients are already familiar with from everyday contexts appears to increase intuitiveness and reduce confusion. Nurses also mentioned that the system should, if at all possible, be accessible to at least some non-English-speaking patients. Finally, the wide variety of physical deficits that ICU patients experience requires that manually operated devices be as flexible as possible in terms of type of manipulation required, so that a large cross section of patients can participate.

Conclusion: ICU patients are in significant need of communication systems that meet their unique needs. Building such a system requires awareness of many different constraints, including both general heterogeneity of patient needs and capabilities and the constraints of the ICU setting itself.

References:

1. Journal of Pediatric Rehabilitation Medicine: An Interdisciplinary Approach 3 (2010) 289–301
2. Am J Crit Care, 2012, March; 21(2): e21–e32
3. Anesth Analg, 2016, 122(5S), S-470 [4] Anesth Analg, 2016, 122(5S), S-424

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Moderated Poster Discussion Sessions

Friday, May 5, 2017 • 1:00 pm – 2:30 pm

Category	Poster Board Number
Airway Management	1 – 4
Critical Care	5 – 8, 10 – 12
Cardiovascular Anesthesiology	13 – 18
Economics, Education and Policy	19 – 24
Neuroscience in Anesthesiology and Perioperative Medicine	25 – 34
Sleep Medicine	35
Obstetric Anesthesiology	36 – 37
Technology, Computing and Simulation, Equipment Monitoring	39 – 41
Pain Mechanisms	42 – 44
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Poster Presentation Schedule – Friday, May 5

Friday, May 5, 2017 • 1:00 pm – 2:30 pm

Airway Management and Critical Care: Group 1

Moderator: Wei Chao, MD, PhD, FAHA, University of Maryland School of Medicine, Baltimore, Maryland

AM 1 (1961)
Difficult Airway Algorithm and Rescue Cricothyrotomy (DAARC) Program, to Standardize the VA Team Approach to Non-OR Airways

Jessica L. Feinleib, MD, PhD[1]; Lynette Mark, MD[2]; Arthur French, MD, MS[3]; Viji Kurup, MD[4]; Paul Flint, MD[5]; Laeben Lester, MD[2]

[1]VACTHS, West Haven CT, New Haven , CT, [2]Johns Hopkins Hospital, Baltimore, MD, [3]Veterans Administration Puget Sound Healthcare System, Seattle, WA 98108, WA, [4]Yale University School of Medicine, New Haven, CT, [5]Oregon Healthh & Science University, Portland, OR

AM 2 (1059)
Nebulized Ketamine for an Elective Awake Intubation in a Known Difficult Airway

Adrian M. Fischl, MD[1]; Ana Costa, MD[1]

[1]SUNY Stony Brook, Stony Brook, NY

AM 3 (1818)
Use of Continuous Waveform Capnography in Out-of-Operating Room Airway Management Emergencies: An Ethnographic Research Approach to Impact System Based Practice

Anne Marie Walters, MD[1]; **Matthew Betz, DO**[1]; Laeben Lester, MD[1]; Alexi Bennink, BS[2]; Gitika Vijn, BS[2]; Jessica L. Feinleib, MD, PhD[3]; Lynette Mark, MD[1]

[1]Johns Hopkins Hospital, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]VACTHS, West Haven CT, New Haven , CT

AM 4 (1543)
Difficult Airway Response Team (DART) Program and ACE-Inhibitor Induced Angioedema: The Who, What, When, Where, Why and How of Management

Julie Wyrobek, MD[1]; Laeben Lester, MD[2]; Lynette Mark, MD[2]

[1]Brigham and Women's Hospital, Boston, MA, [2]Johns Hopkins Hospital, Baltimore, MD

CC 5 (1775)
Initiating an Evidence Based Extubation Protocol Reduced the Incidence of Unintended Postoperative Intubations (UPIs)

Neilson V. Tran, MD[1]; Phillip Boysen, MD[1]; Stuart Hart, MD[1]

[1]Ochsner Clinic Foundation, New Orleans, LA

CC 6 (2210)
Mechanical Ventilation Enhances Sepsis-Induced Lung Injury: Role of WISP1-$\alpha v\beta 5$ Integrin Pathway in TLR4 Mediated Inflammation and Injury

Li-Ming Zhang, MD[1]; Xibing Ding, MD[2]; Shuqing Jin, MD[2]; Tunliang Li, MD[3]; Timothy Billiar, MD[1]; Bruce Pitt, PhD[4]; Quan Li, MD, PhD[2]

[1]University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, [2]Tongji University School of Medicine, Shanghai, China, [3]Central South University, Changsha, Hunan, China, [4]University of Pittsburgh School of Public Health, Pittsburgh, PA

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Critical Care: Group 2

Moderator: Thomas Anthony Anderson, PhD, MD, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

CC 7 (2070)
Clinical Study of Non-Invasive Venous Waveform Analysis (NIVA) for Prediction of a High Pulmonary Capillary Wedge Pressure

Bret D. Alvis, MD[1]; Kyle M. Hocking, PhD[1]; Kelly Kohorst, MD[1]; Irida Nikolla, MD[1]; Colleen Brophy, MD[1]; Franz Baudenbacher, PhD[2]; Susan Eagle, MD[1]; James Blum, MD, FCCM[3]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University, Nashville, TN, [3]Emory University, Atlanta, GA

CC 8 (1347)
Tension Pneumothorax at the Completion of Thoracic Surgery: What Happened?

Elvera L. Baron, MD, PhD[1]; Elvis Umanzor-Velasquez, MD[2]

[1]Icahn Medical Center at Mount Sinai School of Medicine, New York, NY, [2]Icahn Medical Center at Mount Sinai School of Medicine, Elmhurst, NY

CC 10 (1754)
Motoric Subtype of Delirium and Global Cognition After Critical Illness

Christina J. Hayhurst, MD[1]; Mayur B. Patel, MD, MPH, FACS[1]; Jim Jackson, PsyD[2]; Annachiara Marra, MD[1]; Jennifer L. Thompson, MPH[2]; Rameela Chandrasekhar, PhD[2]; Christopher Hughes, MD[1]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University School of Medicine, Nashville, TN

CC 11 (2121)
The TLR4 Agonist Monophosphoryl Lipid a Induces Innate Immune Memory Characterized by Alterations to Macrophage Metabolism and Antimicrobial Function

Edward Sherwood[1]; Jaime Young, PhD[2]; Benjamin Fensterheim, BS[2]

[1]N/A, Nashville, United States of America, [2]Vanderbilt University Medical Center, Nashville, TN

CC 12 (1730)
Multiple Biomarkers Improve Prediction for Infection in the SICU

William M. White, MD[1]; Hussam Ghabra, MD[1]; Daniah Dhaifallah, MD[1]; Michael Townsend, MD[1]; Joshua Goldberg, MD[1]; Phillip Boysen, MD[1]; Bobby Nossaman, MD[1]

[1]Ochsner Clinic Foundation, New Orleans, LA

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Poster Presentation Schedule, *continued from page 205*

Cardiovascular Anesthesiology: Group 3

Moderator: Tomoki Hashimoto, MD, University of California, San Francisco, San Francisco, California; and Randall Schell, MD, MACM, University of Kentucky, Lexington, Kentucky

CA 13 (2056)
Relationship Between Baseline Cerebral Oximetry and Mixed Venous Oxygen Saturation in Cardiac Surgical Patients

Viachaslau Barodka, MD[1]; Yurie Obata, MD[2]; Trent Magruder, MD[1]; Daniel Berkowitz, MD[3]; Charles Hogue, MD[4]

[1]The Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Northwestern Feinberg School of Medicine, Chicago, IL

CA 14 (1749)
Paradoxical Negative Interaction of Heart Failure and Renal Failure Among Patients Undergoing Elective, Non-Cardiac Surgery: An Analysis of 121,812 Patients in the 2012 NSQIP Database

Aaron S. Hess, MD, PhD[1]; Heidi Lindroth, RN[1]; Robert D. Sanders[2], BSc PhD MBBS FRCA

[1]University of Wisconsin Hospital and Clinics, Madison, WI, [2]University of Wisconsin, Madison, Madison, WI

CA 15 (2083)
12-HETE as a Novel Biomarker of Endothelial Cell Dysfunction in Diabetes Mellitus and Hyperglycemia

Helen Heymann, MS[1]; Nana-Maria Wagner, MD, PhD[1]; Carl Hurt, MD, PhD[1]; Eric R. Gross, MD, PhD[1]

[1]Stanford University, Stanford, CA

CA 16 (2054)
Plasma Free Hemoglobin, Oxidative Damage, and Acute Kidney Injury in Cardiac Surgery

Marcos G. Lopez, MD, MS[1]; Mias Pretorius[1]; Frederic T. Billings, MD, Mac[1]

[1]Vanderbilt University Medical Center, Nashville, TN,

CA 17 (2025)
Targeting Matrix Remodeling in Pulmonary Arterial Hypertension

Jochen Steppan, MD, DESA[1]; Huilei Wang, BA[1]; Yohei Nomura, MD[2]; Sean Melucci, BS[2]; Daniel Berkowitz, MD[1]; Larissa Shimoda, MD[1]; Lakshmi Santhanam, PhD[2]

[1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD

CA 18 (2045)
Blood Pressure Management in Hypoplastic Left Heart Syndrome After Stage 1 Palliation: Is There an ST Instability-Dependent Optimal Blood Pressure?

Eric L. Vu, MD[1]; Craig G. Rusin, PhD[1]; Kathy K. Kibler, CCP[1]; R. B. Easley, MD[1]; Dean Andropoulos, MD[1]; Ken M. Brady, MD[1]

[1]Baylor College of Medicine / Texas Children's Hospital, Houston, TX

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Poster Presentation Schedule, *continued from page 206*

Economics, Education and Policy: Group 4

Moderators: Stephanie Jones, MD, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and Manuel Pardo, MD, University of California, San Francisco, San Francisco, California

EEP 19 (2248)
Compliance with Scheduled Times in the Operation Room: Influence of the Weekday on Adherence to Planned Case Durations

Claudius Balzer, MD, MSc[1]; Klaus Hahnenkamp, MD[1]; Konrad Meissner, MD, MSc[1]

[1]Department of Anesthesiology, University Hospital of Greifswald, Greifswald, Germany

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EEP 20 (2110)
The Impact of Institutional, Comprehensive Faculty Development on Resident Education: Building A Point-Of-Care Ultrasound Program

Elifce Cosar[1]; Tanya Lucas, MD[2]; J. Aaron Scott, DO[3]; Maksim Zayaruzny, MD[2]; Luanne Thorndyke, MD[2]; Shubjeet Kaur, MD[4]; J. Matthias Walz, MD[1]

[1]University of Massachusetts Medical School, Worcester, MA, [2]UMass Memorial Healthcare, Worcester, MA, [3]University Of Massachusetts, Worcester, MA, [4]UMass Memorial Medical Center, Worcester, MA

EEP 21 (2021)
Ultrasonic Examination of the Underwater Spine: A Learning Technique to Enhance Acquisition of Basic Skills to Place an Epidural Catheter

Michael C. Scarbrough, MD[1]; Laurie Daste, MD[1]; Jacquelyn Paetzold, DO[2]; Phillip Boysen, MD[1]

[1]Ochsner Clinic Foundation, New Orleans, LA, [2]Tulane University School of Medicine, New Orleans, LA

EEP 22 (2031)
CUSUM Analysis: An Application of Learning Curves to Ensure Basic Skills in Anesthetic Procedures

Michael C. Scarbrough, MD[1]; Laurie Daste, MD[1]; Jacquelyn Paetzold, DO[2]; Phillip Boysen, MD[1]

[1]Ochsner Clinic Foundation, New Orleans, LA, [2]Tulane University School of Medicine, New Orleans, LA

EEP 23 (2052)
No Significant Difference in Outcomes when Anesthesia Care is Provided by an Anesthesiologist Assistant or a Nurse Anesthetist: An Analysis of Medicare Data

Eric Sun, MD, PhD[1]; Thomas R. Miller, PhD, MBA[2]; **Jasmin Moshfegh**[1]; Laurence Baker, PhD[1]

[1]Stanford University, Stanford, CA, [2]American Society of Anesthesiologists, Schaumburg, IL

EEP 24 (2090)
Discrepancies Between Data from an Anesthesia Information Management System and Manual Case-Logging: An Enduring Threat to Data Quality and Resident Experience

Zachary A. Turnbull, MD[1]; Virginia Tangel, MA[2]; Dahniel Sastow, BA[2]; Bohdan Hawryluk, MS[2]; Kane O. Pryor, MB, BS[1]

[1]New York Presbyterian Hospital – Weill Cornell Medicine, New York, NY, [2]Weill Cornell Medicine, New York, NY

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Poster Presentation Schedule, *continued from page 207*

Neuroscience in Anesthesiology and Perioperative Medicine: Group 5

Moderators: Peter A. Goldstein, MD, Weill Cornell Medical College New York-Presbyterian Hospital, New York, New York; and Thomas Floyd, MD, Stony Brook University, Stony Brook, New York

NR 25 (1965)
Incidence, Mechanisms, and Hemodynamic Implications of Systolic Dysfunction Following Traumatic Brain Injury: A Cohort Study

Vijay Krishnamoorthy, MD, MPH[1]; Ali Rowhani-Rahbar, MD, MPH, PhD[1]; Edward Gibbons, MD[1]; Nophanan Chaikittisilpa, MD[1]; Kevin Luk, MD, MS[1]; Monica Vavilala, MD[2]

[1]University of Washington, Seattle, WA, [2]University of Washington, Seattle, WA

NR 26 (2202)
A Nighttime Dexmedetomidine Bolus Promotes N3 Sleep: A Pilot Study

Lei Gao, MD[1]; Lauren Hobbs, MS[1]; Kara Pavone, BS[1]; Emery N. Brown, MD, PhD[1]; Oluwaseun Akeju, MD[1]

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

NR 27 (2283)
Isoflurane Alters Neural Progenitor Cell Development Within Hippocampus

Christy Gray, MD, PhD[1]; Cyrus D. Mintz, MD, PhD[1]; Roger A. Johns, MD, PhD[1]

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

NR 28 (2189)
Is the Integrated Stress Response (ISR) Involved in the Development of Postoperative Cognitive Decline (PCD) in a Mouse Model?

Mervyn Maze[1]; Xiaomei Feng, MD, PhD[1]; Qin Shao, MD[1]; Susana Vacas, MD[1]; Yosuke Uchida, MD[1]; David Lutrin, MD[1]; Peter Walter, PhD[1]; George Gallos, MD[2]

[1]University of California, San Francisco, San Francisco, CA, [2]Columbia University Medical Center, New York, NY

NR 29 (2234)
Volatile Anesthetics Inhibit Neuronal Regeneration in C. Elegans

Vinod Singaram, MD, PhD[1]; Zilu Wu, PhD[2]; Meghna Mehta, BS[1]; Jan Schilling, MD[2]; Andrew Chisholm, PhD[1]; Hemal Patel, PhD[1]

[1]University of California, San Diego, San Diego, CA, [2]UCSD, San Diego, CA

NR 30 (2183)
Dbh -/- Mice Show Hypersensitivity to Isoflurane in Both Spontaneous Motor Activity and Electroencephalography

Andrew McKinstry-Wu, MD[1]; Andrezj Wasilczuk, BS[1]; Steven Thomas, MD, PhD[1]; Alex Proekt, MD, PhD[1]; Max Kelz, MD, PhD[1]

[1]University of Pennsylvania, Philadelphia, PA

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Poster Presentation Schedule, *continued from page 208*

Neuroscience in Anesthesiology and Perioperative Medicine and Sleep Medicine: Group 6

Moderators: Ines Koerner, MD, PhD, Oregon Health and Science University, Portland, Oregon; and Jeffrey Sall, PhD, MD, University of California, San Francisco, San Francisco, California

NR 31 (1922)
Atg5 Plays Important Role on Propofol Regulation of Autophagy and Cell Proliferation or Death

Huafeng Wei[1]; Zhendong Xu[1], Yong Wang[1], Ge Liang[1], Zhiqiang Liu[2], Wuhua Ma[3], Christopher Ward[4]

[1]University of Pennsylvania, Philadelphia, PA, [2]Tongji University School of Medicine, Shanghai, China, [3]Guangzhou University of Chinese Medicine, Guangzhou, China, [4]Children Hospital of Philadelphia, Philadelphia, PA

NR 32 (1923)
General Anesthetics Induced Neurotoxicity by Impairment of Lysosome and Autophagy Function via Intracellular Calcium Dysregulation in Alzheimer's Disease

Yan Wang, MD, PhD[1]; Meirong Yang, MD, PhD[1]; Ge Liang, MD[1]; Huafeng Wei[1], Saadet Inan, MD, PhD[1]; Zhendong Xu, MD, PhD[1]; Christopher Ward, MD[2]

[1]University of Pennsylvania, Philadelphia, PA, [2]Children Hospital of Philadelphia, Philadelphia, PA

NR 33 (2140)
The Association Between Hospitalization, Surgery, and Incident Dementia in Older Adults with Mild Cognitive Impairment

Huafeng Wei[1]; Meirong Yang[1], Yan Wang[1], Ge Liang[1], Saadet Inan[1], Zhendong Xu[1], Christopher Ward[2]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [3]University of Florida, Gainesville, FL, [4]Wake Forest University, Winston-Salem, NC

NR 34 (1996)
Reconstructing Consciousness and Cognition: Human Neurobehavioral Recovery Following Exposure to Isoflurane

Max Kelz, MD, PhD[1]; Michael S. Avidan, MBBCh[2]; George Mashour, MD, PhD[3]; Andrew McKinstry-Wu, MD[1]; Ben Palanca, MD, PhD[2]; Stefanie Blain-Moraes, PhD[4]; Mathias Basner, MD, PhD[1]

[1]University of Pennsylvania, Philadelphia, PA, [2]Washington University School of Medicine, St. Louis, MO, [3]University of Michigan, Ann Arbor, MI, [4]McGill, Montreal, Quebec

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SM 35 (1838)
A Novel Role for TIMELESS in Mammalian Circadian Clocks Using a Murine Model of Human Familial Advanced Sleep Phase

Philip Kurien, MD[1]; Pei Ken Hsu, PhD[1]; Guangsen Shi, PhD[1]; Ying Hui Fu, PhD[1]; Louis Ptacek, MD[1]

[1]UCSF, San Francisco, CA

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Poster Presentation Schedule, *continued from page 209*

Obstetric Anesthesiology and Technology, Computing and Simulation, Equipment Monitoring: Group 7

Moderators: George Gallos, MD, Columbia University, New York, New York; and Paul S. Garcia, MD, Emory University/ VAMC Atlanta, Decatur, Georgia

OB 36 (1422)
Comparative Potency of Calcium-Activated Chloride Channel Anoctamin 1 Antagonists on Human Uterine Smooth Muscle (USM) Contractility

Shunsuke Hyuga, MD[1]; Joelle H. Shosfy, MA[2]; Wen Fu, PhD[1]; Joy Vink, MD[1]; George Gallos, MD[1]

[1]Columbia University College of Physicians and Surgeons, New York, NY, [2]Columbia University College of Physicians and Surgeons, New York, NY

OB 37 (2011)
Ondansetron and Spinal Anesthesia-Associated Hypotension During Cesarean Section: Using Risk Difference to Assess Therapeutic Effectiveness

Courtney Masear, MD[1]; Sharon C. Reale, MD[1]; Sarabdeep Singh, PhD[1]; Karen Lindeman, MD[1]; George Gallos, MD[2]

[1]Johns Hopkins University, Baltimore, MD, [2]Columbia University, New York, NY

TCSEM 39 (1417)
Initiation of an Emulsion Microinfusion: Flow Direction Influences Onset Rate

Robert A. Peterfreund, MD, PhD[1]; Amy C. Tsao, BA[1]; Michael Parker, MD[2]; Mark A. Lovich, MD, PhD[3]; Hao Deng, MD[1]; Timothy Houle, PhD[1]

[1]Massachusetts General Hospital, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Steward St. Elizabeth's Medical Center, Boston, MA

TCSEM 40 (1523)
Effective Evaluation of Arterial Pulse Waveform Analysis: the Online Two-Dimensional Log^{10}(SVV)-SVI Plots

Teiji Sawa, MD, PhD[1]; Atsushi Kainuma, MD[2]; Koichi Akiyama, MD[2]; Saeko Hamaoka, MD[3]; Mao Kinoshita, MD, PhD[2]

[1]Kyoto Prefectural University of Medicine, Kyoto City, Kyoto Prefecture, [2]Kyoto Prefectural University of Medicine, Kyoto City, Kyoto Prefecture, [3]Kyoto Prefectural University of Medicine, Kyoto, Kyoto

TCSEM 41 (1739)
Automated Feedback System Improves Perioperative Outcome Awareness

Jonathan Wanderer, MD[1]; Leslie Fowler, Med[2]; Jesse Ehrenfeld, MD[1]; Teus Kappen, MD[3]; Warren Sandberg, MD, PhD[3]; Matthew D. McEvoy, MD[2]

[1]Vanderbilt University School of Medicine, Nashville, TN, [2]Vanderbilt University Medical Center, Nashville, TN

Pain Medicine and Pain Mechanisms: Group 8

Moderator: Lucy L. Chen, MD, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

PME 42 (1349)
CX_3CR1^+ Cells in the PNS Play a Key Role in Development of Neuropathic Pain in Mice

Jianguo Cheng, MD, PhD[1]; LiPing Liu, MD, PhD[1]; Yan Yin, MD[1]; Fei Li, MD[1]; Zhen Hua, MD, PhD[1]

[1]Cleveland Clinic, Cleveland, OH

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Poster Presentation Schedule, *continued from page 210*

Pain Medicine and Pain Mechanisms: Group 8, *continued*

PME 43 (2123)
Brain Mechanisms of Mood Treatment in Chronic Low Back Pain: Preliminary Analysis

James W. Ibinson, MD, PhD[1]; Andrea Gillman, PhD[1]; Claire Q. Paduano, BS[1]; Marco Loggia, PhD[2]; Vitaly Napadow, PhD[2]; Robert R. Edwards, PhD[3]; Ajay D. Wasan, MD[1]

[1]University of Pittsburgh, Pittsburgh, PA, [2]Harvard Medical School, Charlestown, MA, [3]Brigham and Women's Hospital, Boston, MA

PME 44 (2043)
Enabling TRPV1-Based Pre-Emptive Analgesia for Post-Surgical Pain in the Rat: Behavioral and Transcriptomic Analysis

Stephen Raithel[1]; Danielle LaPaglia, BA[2]; Matt Sapio, PhD[2]; Michael Ladarola, PhD[2]; Andrew Mannes, MD[2]

[1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, [2]National Institutes of Health, Clinical Center, Bethesda, MD

PM 45 (2027)
Development of ROS-Responsive Microspheres for Sustained Local Delivery of Therapeutics for the Treatment of Chronic Pain

Michael Chi, MD[1]; Taylor Kavanaugh, BS[2]; Jerod Denton, PhD[1]; Craig Duvall, PhD[2]

[1]Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University, Nashville, TN

PM 46 (1028)
Effect of Ultra Short Wave Irradiation on Stellate Ganglion on Brachial Blood Flow

Kazuaki Fukushima, PhD[1]; Kazumasa Fukushima, PhD[2]; Yuji Fukushima, MD, PhD[3]

[1]Home Care Clinic, Tokyo, Japan, [2]Rise City Clinic, Higashi Ikebukuro, Tokyo, [3]Tama Nanbu Hospital, Tama, Tokyo

Junior Faculty Travel Award in Perioperative Medicine

PM 47 (1723)
A Randomized Trial of Perioperative Gabapentin to Promote Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort

Jennifer Hah, MD, MS[1]; Sean Mackey, MD, PhD[1]; Bradley Efron, PhD[1]; Rebecca McCue, BS[1]; Stuart Goodman, MD, PhD[2]; Catherine Curtin, MD[2]; Ian Carroll, MD, MS[2]

[1]Stanford University, Stanford, CA, [2]Stanford University, Palo Alto, CA

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Pain Medicine: Group 9

Moderator: May Pian-Smith, MD, Massachusetts General Hospital, Boston, Massachusetts

PM 48 (1421)
First Literature Report of Ketamine Infusion for Treatment of Refractory Postherpetic Neuralgia

Ayesha Hameed, MD[1]; Judith Aronsohn, MD[1]; Jaspreet Toor, DO[2]

[1]Northwell Health System, New Hyde Park, NY, [2]Hofstra Northwell School of Medicine, New Hyde Park, NY

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Pain Medicine: Group 9, *continued*

PM 49 (2240)
Chiari Malformation Type 1 and Pain Management of Chronic Headache: A Literature Review

Ayesha Hameed, MD[1]; Michelle Kars, MD[1]

[1]Northwell Health System, New Hyde Park, NY

PM 50 (1750)
Dezocine for Opioid Addiction in a Rat Morphine Dependence Model

Renyu Liu, MD, PhD[1]; Hasan Babazada, PhD[1]; Feixiang Wu, MD, PhD[1]; Xiping Huang, PhD[2]; Weifeng Yu, MD, PhD[3]

[1]University of Pennsyvania, Philadelphia, PA, [2]University of North Carolina, Chapel Hill, NC, [3]Jiaotong University, Shanghai , Shanghai

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PM 51 (1722)
Longitudinal Pain Sensitivity Phenotyping Using Portable, Brief Bedside QST in Mastectomy Patients for Prediction of Persistent Postsurgical Pain

Kristin Schreiber, MD, PhD[1]; Natt Zinboonyahgoon, MD[1]; Gauri Vasudevan, BS[1]; Robert R. Edwards, PhD[1]

[1]Brigham and Women's Hospital, Boston, MA

PM 52 (2013)
DREADDs Activation of Periaqueductal Gray Dopamine Neurons Produces Gender Specific Analgesic Responses

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

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

PM 53 (1440)
Corticostriatal Circuit Regulates Acute and Chronic Pain in Rodents

Jing Wang, MD, PhD[1]; Michelle Lee, BA[1]; Toby Manders, BA[1]; Hau Lin, BA[1]; Erik Martinez, BA[1]; Chen Su, MD[1]; Runtao Yang, BA[1]

[1]New York University School of Medicine, New York, NY

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Patient Safety: Group 10

Moderator: Manuel C. Vallejo, MD, D.MD, West Virginia University, Morgantown, West Virginia; and Jesse Ehrenfeld, MD, MPH, Vanderbilt University Medical Center, Nashville, Tennessee

PS 54 (1970)
A Pilot Study on Critical Event Debriefing at an Academic Medical Center

Alexander Arriaga[1]; Rachel Sweeney, BA[1]; Justin Clapp, PhD[1]; Emily Gordon, MD, MSEd[1]; Scott Falk, MD[1]; Dimitry Baranov, MD[1]; Lee Fleisher, MD[1]

[1]Hospital of the University of Pennsylvania, Philadelphia, PA, [2]Mayo Clinic, Jacksonville, FL

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Poster Presentation Schedule, *continued from page 212*

Patient Safety: Group 10, *continued*

PS 55 (1387)
How Can We Safely Reduce 50% of Patient Monitor Alarms in the Surgical Intensive Care Unit?

Peter Hu[1]; Hsiao-chi Li, PhD[1]; Shiming Yang, PhD[1]; Samuel Galvagno, MD[1]; Samuel Tisherman, MD[1]; Peter Rock, MD[1]

[1]University of Maryland Baltimore, Baltimore, MD

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PS 56 (2000)
Predicting Need for Intubation in the Field: Comparison of Glasgow Coma Scale To Vital Signs

Peter Hu[1]; Lichien Li, MS[1]; Shiming Yang, PhD[1]; Yao Li, PhD[1]; Peter Rock, MD[1]

[1]University of Maryland Baltimore, Baltimore, MD

PS 57 (2036)
What are the Characteristics of Patients Who Want Perioperative Music Therapy?

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PS 58 (1228)
A Qualitative Study of the Teaching and Learning of Internal Jugular Vein Cannulation

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PS 59 (1547)
Trends of Intraoperative Opioid and Non-Opioid Analgesic Use and Associated Postoperative Pain Scores at an Academic Tertiary Care Hospital Over A Four-Year Period

Gregory A. Smith, MD[1]; Marcel Durieux, MD, PhD[1]; Bhiken Naik, MBBCh[1]

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Pediatric Anesthesiology: Group 11

Moderator: Christina M. Pabelick, MD, Mayo Clinic, Rochester, Minnesota

PED 60 (1556)
Transfusion Thresholds and Adverse Outcomes in Pediatric Cardiac Surgery Patients With and Without Cyanotic Disease

Branden M. Engorn, MD[1]; William W. Yang, BS[1]; Mereze A. Visagie[2]; Joshua A. Wetzler[2]; Luca M. Vricella, MD[1]; Steven Frank, MD[1]; Dheeraj Goswami, MD[1]

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Pediatric Anesthesiology: Group 11, *continued*

Junior Faculty Travel Award in Pediatric Anesthesia

PED 61 (1287)
Age at Exposure to Anesthesia in Children and Mental Disorder Diagnosis

Caleb Ing, MD, MS[1]; Ming Sun, MS[1]; Mark Olfson, MD, MPH[1]; Charles DiMaggio, PhD, MPH, PA-C[2]; Lena Sun, MD, MPH[1]; Melanie Wall, PhD[1]; Guohua Li, MD, DrPH[1]

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PED 62 (1535)
The Under Accounted for Role of Hypercarbia & Hypoxia in the Neonatal Rodent Models of Anesthesia-Related Developmental Delay

Kseniya Khmara[1]; Ryan Lamm, BA1; Thomas Floyd, MD1

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PED 63 (1120)
Mitochondrial cAMP-dependent Phosphorylation in the Developing Murine Brain

Richard J. Levy, MD, FAAP[1]; Yang Long, MD[1]; Aili Wang, MD[1]

[1]Columbia University, New York, NY

PED 64 (1092)
Reduced Hemorrhage with ε-Aminocaproic Acid in Pediatric Craniofacial Reconstruction

Srijaya K. Reddy[1]; Taylor Mann, MD[2]; Heather Gordish-Dressman, PhD[1]; Robert F. Keating, MD[1]; Richard J. Levy, MD, FAAP[3]

[1]Children's National Health System, Washington, DC, [2]The Johns Hopkins University, Baltimore, MD, [3]Columbia University, New York, NY

PED 65 (1508)
Rhesus Macaques Exposed to Isoflurane Anesthesia as Infants Display Disrupted Functional Connectivity as Juveniles

Katie J. Schenning, MD, MPH[1]; Oscar Miranda-Dominguez, PhD[1]; Lauren D. Martin, DVM[2]; Gregory A. Dissen, PhD[2]; Damien Fair, PA-C, PhD[1]

[1]Oregon Health & Science University, Portland, OR, [2]Oregon National Primate Research Center, Beaverton, OR

Perioperative Anesthesia: Group 12

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

PA 66 (1194)
Postoperative Pulmonary Complications Not Increased with Combined Regional + General Anesthesia Compared to General Anesthesia Alone: A Sub-Analysis of The Perioperative Research Network Study

Kristina Coger, MD[1]; Gyorgy Frendl, MD, PhD[2]; Juraj Sprung, MD, PhD[3]; Daryl J. Kor, MD[3]; Bala Subramaniam, MD[4]; Ricardo Martinez Ruiz, MD[5]; Ana Fernandez-Bustamante, MD, PhD[1]

[1]University of Colorado School of Medicine, Aurora, CO, [2]Brigham and Women's Hospital, Boston, MA, [3]Mayo Clinic, Rochester, MN, [4]Beth Israel Deaconess Medical Center, Boston, MA, [5]University of Miami, Miami, FL

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Perioperative Anesthesia: Group 12, *continued*

PA 67 (1708)
Postoperative Complications Affecting Survival after Cardiac Arrest in General Surgery Patients

Minjae Kim, MD, MS[1]; Guohua Li, MD, DrPH[1]

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

PA 68 (1631)
Postoperative Acute Kidney Injury and Renal Recovery: A Report from the Multicenter Perioperative Outcomes Group

Michael Mathis, MD[1]; Amy M. Shanks, PhD[1]; Milo Engoren, MD[1]; Leif Saager, MD, MMM, FCCM[1]; Sachin Kheterpal, MD, MBA[1]

[1]University of Michigan, Ann Arbor, MI

PA 69 (1647)
An Evidence-Based Opioid Sparing Anesthetic Technique: Preliminary Data

Jacquelyn Paetzold, DO[1]; Phillip Boysen, MD[2]

[1]Tulane University School of Medicine, New Orleans, LA, [2]Ochsner Clinic Foundation, New Orleans, LA

PA 70 (1781)
Identification of Barriers to Implementation of Lung Protective Ventilation in the Operating Room

Jamie Privratsky, MD, PhD[1]; Nawar Al Rawas, MD[1]; Matthew D. Read, MD[1]; Thomas Christiansen, MD[1]; Benjamin Dunne, MD[1]; Erica Harris, MSN, CRNA[1]; Atilio Barbeito, MD[1]

[1]Duke University Medical Center, Durham, NC

PA 71 (1606)
Perioperative Decline in High Density Lipoprotein Particles is Associated with Increased Risk of AKI After Cardiac Surgery

Loren Smith, MD, PhD[1]; Derek K. Smith, DDS, PhD[1]; Alan T. Remaley, MD, PhD[2]; MacRae F. Linton, MD[1]; Frederic T. Billings, MD, Mac[1]

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Translational / Bench Science: Group 13

Moderator: Matthew McEvoy, MD, Vanderbilt University Medical Center, Nashville, Tennessee

TRSL/BS 72 (1522)
Cerebral Vascular Thrombospondin-1 Associates with the Epsilon 4 Allele of Apolipoprotein E in Alzheimer's Disease

Jessica Cassavaugh, MD, PhD[1]; Caitlin Czajka, PhD[2]; Grace Lee, B[2]; Caterina Rosano, MD, MPH[1]; Julia Kofler, MD[1]; Eric McDade, DO[4]; Jeffery Isenberg, MD, MPH

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Translational / Bench Science: Group 13, *continued*

TRSL/BS 73 (1709)
An Antagonist of the Anoctamin-1 Calcium-Activated Chloride Channel Relaxes Mouse Airway Smooth Muscle Despite β-Adrenoceptor Desensitization and Attenuates MUC5AC Production

Jennifer Danielsson, MD[1]; Yi Zhang, MD[1]; Charles W. Emala, MD[1]

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TRSL/BS 74 (1771)
Murine Cardiac Arrest and Cardiopulmonary Resuscitation Exposes the Glomerular Filtrate to Cardiac Protein and Leads to Chronic Kidney Disease

Michael Hutchens, MD, MA[1]; Rumie Wakasaki, MD, PhD[1]; Paul Piehowski, PhD[2]

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TRSL/BS 75 (1692)
The Immortalisation of Primary Human Myoblasts Derived from Patients Susceptible to Malignant Hyperthermia and their Non-Susceptible Relatives

Vikas Kaura, MSc, FRCA[1]; Marie-Anne Shaw, PhD[1]; Paul D. Allen, MD, PhD[1]; Philip M. Hopkins, MD, FRCA[1]

[1]Leeds Institute of Biomedical and Clinical Sciences, Leeds, Yorkshire

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TRSL/BS 76 (1629)
IL-β-Mediated Disruption of the Tight Junction Permeability Barrier of Human Dermal Microvascular Endothelial Cells

Richard K.Kim, MD MSc[1]; Martin Kluger, PhD[2]; Jordan S. Pober, MD, PhD[2]

[1]Yale-New Haven Hospital, New Haven, CT, [2]Yale School of Medicine, New Haven, CT

Translational / Bench Science: Group 14

Moderators: Holger Eltzschig, MD, PhD, The University of Texas Health Science Center at Houston, Texas; and Warren Sandberg, MD, PhD, Vanderbilt University, Nashville, Tennessee

TRSL/BS 77 (1650)
NOX2 Deficiency Alters Macrophage Phenotype through an IL-10/STAT3 Dependent Mechanism: Implications for Traumatic Brain Injury

David Loane, PhD[1]; James Barrett, PhD[1]; Rebecca Henry, PhD[1]; Sonia Villapol, PhD[2]; Bogdan Stoica, MD[1]; Mark Burns, PhD[2]; Alan Faden, MD[1]

[1]University of Maryland School of Medicine, Baltimore, MD, [2]Georgetown University, Washington, DC

TRSL/BS 78 (1997)
The Human Metabolite of a Bioactive Ginger Phytochemical Relaxes Human Airway Smooth Muscle: Potential Novel Therapeutics for Bronchoconstriction

Elvedin Lukovic, MD, PhD[1]; Yingdong Zhu, PhD[2]; Jennifer Danielsson, MD[1]; Shengmin Sang, PhD[2]; Charles W. Emala, MD[1]

[1]Columbia University, New York, NY, [2]North Carolina Agricultural and Technical State University, Kannapolis, NC

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Translational / Bench Science: Group 14, *continued*

TRSL/BS 79 (1779)
Idebenone Bypasses Impaired Mitochondrial Respiration in Primary Rat Cortical Neurons or Astrocytes Only When it is Enzymatically or Chemically Reduced

Brian M. Polster, PhD[1]; Sausan M. Jaber, BS[1]; Brian A. Roelofs, PhD[1]; Shealinna X. Ge, BA[1]; Joshua L. Milstein, BA[1]

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TRSL/BS 80 (2257)
Fatty Acid Metabolism is Pivotal for Maintained Post-Ischemic Cardiac Function in Arctic Ground Squirrel Isolated Heart

Matthias Riess[1]; Hunter F. Douglas, BS[2]; Michele M. Salzman, BS[2]

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TRSL/BS 81 (1210)
Isoflurane Effects on Pro-Inflammatory Interleukin-23 Activity in Mice

Lindsay Stollings, MD[1]; Li-Jie Jia, MD[2]; Pei Tang, PhD[1]; Huanyu Dou, MD[3]; Binfeng Lu, PhD[1]; Yan Xu, PhD[1]

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TRSL/BS 82 (1612)
Plasma Exosome miRNAs Mediate Inflammation in a Mouse Model of Sepsis

Lin Zou, MD, PhD[1]; **Jinjin Xu, PhD**; Yan Feng, MD, PhD; Olivia Conn, BS[1]; Wei Chao, MD, PhD[1]

[1]University of Maryland School of Medicine, Baltimore, MD

AM 1 (1961)
Difficult Airway Algorithm and Rescue Cricothyrotomy (DAARC) Program, to Standardize the VA Team Approach to Non-OR Airways

Jessica L. Feinleib, MD, PhD[1], Lynette Mark, MD[2]; Arthur French, MD, MS[3]; Viji Kurup, MD[4]; Paul Flint, MD[5]; Laeben Lester, MD[2]

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Introduction: In an effort to reduce VHA patient morbidity and mortality associated with failed airways, VHA SimLEARN undertook the production of an educational program addressing the Difficult Airway Algorithm and Rescue Cricothyrotomy (DAARC) (1). The goal of this educational system is to provide mastery based medical education delivered remotely to the ~150 hospitals in the VHA system. Many have proposed the importance of mandatory post certification airway education (2). We opted for a novel composite educational tool and blended learning curriculum, incorporating serious gaming, called the DAARC educational program Figure 1. This program is centered on the Vortex system cognitive aid that is in alignment with the most recent with DAS and ASA airway guidelines (3) Figure 2. The DAARC educational system consist of video didactics, podcasts, a formative serious game and a summative round of the DAARC serious game Figure 3-5. The target audience for this multi-million-dollar project includes all airway team members e.g. anesthesiologists, surgeons, emergency and critical care physicians as well as respiratory therapists and critical care nurses.

Methods: In January 2017 the DAARC game won 'Best in Show' for Games and Virtual Environments at the International Meeting on Simulation in Healthcare. The VHA is now engaging in a collaborative validation process with academic medical centers for the DAARC program. A pilot study on difficult airway management is underway at multiple sites comparing the DAARC serious game curriculum to similar content from traditional educational materials, textbook, etc. This will then be followed by traditional simulation, in a flipped classroom format. We will randomly assign subjects to these different educational groups and then follow their clinical behavior during simulation airway management. Simulation outcomes that will be recorded are the use of the cognitive aid(Vortex), time to obtain a successful airway, number of attempts in each technique, number of attempts with an optimization of each technique, time interval from failure of non-surgical interventions until cricothyrotomy i.e. time from recognition of need surgical rescue to front of neck access.

Results: Our results are forthcoming this spring.

Conclusion: After 3 years of design, programing, production, and editing the DAARC program is currently live in the VHA learning management system and awaiting validation of it's training effectiveness. As DAARC is an innovative training program that relies on serious gaming in place of traditional live simulation for complex and dynamic clinical decision making (4). We wish to determine if this educational modality is effective and based on that information make recommendations to the national VHA service chiefs on the potential use of the DAARC program. Additionally, the 2012 VHA Out-of-Operating Room Airway Management (OORAM) directive is scheduled for a revision and we are aiming to provide data that will give guidance on the use of DAARC in the VHA credentialing system. If proven effective the use of the DAARC program could provide the 150 VHA hospital system with a mastery based airway educational system for the maintenance of credentialing. Additionally, DAARC would then standardize and align all VHA airway management practice with current ASA and DAS guidelines and thereby, improve veteran airway safety.

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2. Is it time for airway management education to be mandatory? BJA, June, 1-4, 2016
3. The Vortex: striving for simplicity, context independence and teamwork in an airway cognitive tool. BJA, Jul;115(1):148-9, 2015
4. Effect of simulation training on compliance with difficult airway management algorithms, technical ability, and skills retention for emergency cricothyrotomy. Anesthesiology, 120:999-1008, 2014

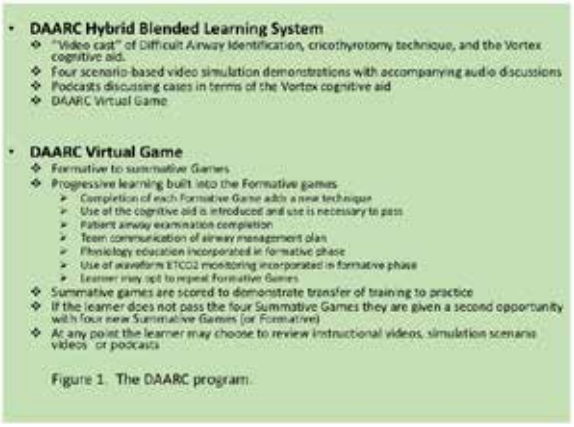

Figure 1. The DAARC program.

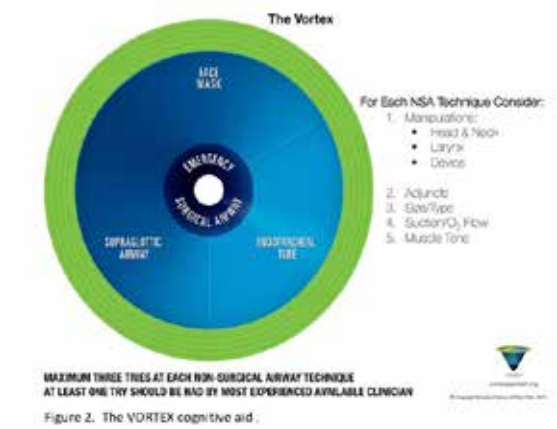

Figure 2. The VORTEX cognitive aid.


Figure 3. The DAARC game environment with the avatar RN, MD and RT.

Figure 4. DAARC game airway exam.

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Figure 5. The DAARC game cricothyrotomy technique.
Please note in the lower left corner the Vortex cognitive aid.

AM 2 (1059)
Nebulized Ketamine for an Elective Awake Intubation in a Known Difficult Airway

Adrian M. Fischl, MD[1], Ana Costa, MD[1]

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Introduction: Despite being available for clinical use since the 1970s, there are very few studies describing inhalational ketamine in the anesthesia literature.

Methods: The aim of this investigation was to evaluate whether nebulized ketamine could provide effective and safe intubating conditions for an awake intubation in a patient with a known difficult airway. Ketamine has a favorable pharmacologic profile including sedation, bronchodilation, somatic analgesia, amnesia, local anesthetic properties, and dissociation from the environment. Here we describe the use of nebulized ketamine as an adjunct for an awake fiberoptic intubation.

Results: A 60 year-old male with a past medical history of alcohol and tobacco abuse, coronary artery disease, aortic stenosis requiring aortic valve replacement, and metastatic squamous cell carcinoma of the neck presented for elective surgery. The patient had a prior history of a neck dissection with subsequent radiation therapy, which was complicated by post-operative bleeding, requiring emergent tracheostomy placement following a failed intubation attempt. His tracheostomy was reversed prior to his current presentation for further neck dissection. During our encounter, he presented for further resection of cancer in the left neck with skin and hyoid bone resection, along with revision and advancement of a right scapular free flap on the neck. Due to the patient's surgical history, worrisome airway exam, history of a difficult endotracheal intubation, and history of radiation to the neck, an extensive discussion was held regarding airway management. The patient agreed to an awake fiberoptic intubation with the otolaryngologist present in the room in case the airway could not be secured. Upon entering the operating room, the patient was placed on standard ASA monitors, given 2 mg of midazolam for anxiolysis, and was instructed to breathe through a nebulizer containing 100 mg of ketamine. This dose was chosen based on previous reports of 2 mg/kg of nebulized ketamine given for pediatric dental procedures. The patient was also placed on a dexmedetomidine infusion to ameliorate the cardiostimulatory effects of the aerosolized ketamine. Once nystagmus was apparent, an ovassapian airway with lidocaine ointment was placed into the oropharynx, and an 8 cm endotracheal tube was guided into the trachea using a Storz fiberoptic scope on the first attempt. The patient remained spontaneously breathing, responsive, and cooperative throughout the procedure. Post-operatively, the patient stated that he had no recollection of the awake endotracheal intubation, and did not feel any discomfort during the procedure.

Conclusion: This is the first case report on the use of nebulized ketamine as an adjunct in an awake fiberoptic intubation. Nebulized ketamine may play a role in the management of awake intubation for a known difficult airway due to its favorable pharmacologic properties. In the future, the authors' goal is to refine this technique and develop it as a case series.

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Nebulized ketamine decreases incidence and severity of post-operative sore throat. Indian Journal of Anaesthesia. 2015;59(1):37-42. Ketamine: Current applications in anesthesia, pain, and critical care. Anesthesia, Essays and Researches. 2014;8(3):283-290. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. Anesth Analg. 2015;121:167

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AM 3 (1818)
Use of Continuous Waveform Capnography in Out-of-Operating Room Airway Management Emergencies: an Ethnographic Research Approach to Impact System Based Practice

Anne Marie Walters, MD[1], **Matthew Betz, DO**[1]; Laeben Lester, MD[1]; Alexi Bennink, BS[2]; Gitika Vijn, BS[2]; Jessica L. Feinleib, MD, PhD[3]; Lynette Mark, MD[1]

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Introduction: Continuous waveform capnography (PETCO2: patient end-tidal carbon dioxide) is superior to colorimetric capnography to assess for adequate mask ventilation, confirm intubation, monitor ventilation after intubation, and ensure effectiveness of chest compressions during ongoing CPR. See Figure 1. To accommodate PETCO2 in all potential out of operating room airway management (OORAM) locations, The Johns Hopkins Hospital replaced all AEDs with the ZOLL S Series with PETCO2 capability in 2014. The Department of Anesthesiology & Critical Care Medicine (ACCM) introduced a Residency Program system based practice (SBP) that included: mandatory in-services for all clinical staff, hands-on simulations, Grand Rounds and resident conference presentations. Despite efforts, the practice has not been widely adopted. The aim of our study is to apply an ethnographic research approach to identify obstacles to use of PETCO2 in OORAM locations and use this information to design and implement a campaign to increase penetration of PETCO2.

Methods: Ethnographic research is the systematic investigation of a culture or system, integrating human factors and systems analysis. Our Residency Program consulted with Masters in Science Engineering Management Students enrolled in an Ethnographic Research Tutorial. The Team made observations, formulated a hypothesis and created a survey for ACCM clinicians to assess current usage pattern for PETCO2 during OORAM, and ethnographic obstacles to use. The survey was supplemented by focus group interviews with ICU and ward nurses to obtain qualitative data. Following data collection and analyses, the Team made recommendations to improve the ongoing SBP Program.

Results: There was a response of 83 voluntary respondents: 36 attendings, 24 CRNAs, 15 residents and 8 fellows. Only 13% of respondents use PETCO2 before, during and after OORAM. Use of PETCO2 was most common for verification of proper intubation - 76% used colorimetric capnography and 36% used PETCO2. The survey results reveal that the ethnographic challenges contributing to lack of use of PETCO2 can be subdivided into three categories: supply chain, training and operational issues. See Figure 2. Focus Groups with ICU and ward nurses for qualitative data revealed that nurse certifications are both BLS and ACLS, with only ACLS providers being trained in PETCO2.

Conclusion: Ethnographic researchers bring valuable perspective to patient safety problems through their training background in human factors and systems analysis. Findings of this study included a low utilization of PETCO2 in OORAM due to perceptions regarding lack of access to equipment, delay in procedure, and knowledge deficits about use and benefit. Recommendations for improvement of our SBP initiative included: addressing supply chain for PETCO2 disposables and cable with daily maintenance ZOLL rounds; partnering with ACLS Committees to reinforce AHA recommended best practices for all stages of airway management and codes; multimodal education targeted to clinical trainees and attending providers to include an instructional video for assembly of the ZOLL with PETCO2; and teamwork with nurse managers and respiratory therapists to recruit their expertise with ZOLL and PETCO2 set up when the emergency response teams arrive to the patient bedside. These findings and recommendations are actively being addressed in a comprehensive program to increase PETCO2 utilization that will be rolled out over the coming months.

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Anesthesiology 2013; 118: 192-201 Br J Anaesth 2011; 106:632-"42 Anaesthesia 2011; 66:544-"9 Best Pract Res Clin Anaesthesiol 2011; 25:277-"90

Figure 1: Advantages and Disadvantages of Colorimetric versus Continuous Waveform Capnography

	COLORIMETRIC	CONTINUOUS WAVEFORM
READOUT	SEMI QUANTITATIVE: Uses indicator paper that changes color based on amount of CO2 in the breath. The color ranges from purple (ETCO2 < 0.5%) to yellow (ETCO2 > 2%). This causes issues when physicians need exact readings, especially those higher than 2%.	QUANTITATIVE: Requires multiple components including insert with a sensor, AED and a wire to connect to AED
RELIABILITY	SEMI RELIABLE: Several situations where device is rendered unusable. If the capnograph comes into contact with any acidic or basic substance, or into contact with bodily fluids, it will stop working.	RELIABLE: Includes a digital sensor that displays an exact, numerical output. Also includes waveform pattern instead of simply presence/absence.
AVAILABILITY	UBIQUITOUS: Device is available in every Ambu bag.	REDUNDANTLY STOCKED: Components can be found in emergency "crash" cart and in a pouch attached to the back of the AED

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AM 4 (1543)
Difficult Airway Response Team (DART) Program and ACE-Inhibitor Induced Angioedema: The Who, What, When, Where, Why and How of Management

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Introduction: With the increasing popularity of ACE inhibitors (ACE-I) there has been a corresponding increase in ACE-I Associated Angioedema (AIIA). AIIA is a life threatening complication of ACE-I use primarily because the edema of the tongue and oropharynx can lead to airway obstruction in severe cases. Thus AIIA is a difficult airway scenario that requires prompt recognition and management, with accurate differentiation from anaphylaxis. At our institution, the Difficult Airway Response Team (DART) Program is comprised of a multidisciplinary team, available 24/7, to identify, risk stratify and mobilize resources for patients with a suspected difficult airway. The aim of our study is to analyze and describe the presentation and intervention of patients who present with severe AIIA triggering DART activation.

Methods: We performed a single center retrospective analysis of our DART program data from 2008-2015. The DART is comprised of attending and senior resident anesthesiologists, otolaryngologists, trauma surgeons, emergency medicine physicians and designated personnel to bring a DART cart, which is comprised of emergency airway equipment. DART can be activated by any level of provider. Data for patients including demographics, presentation, location, risk factors, response time, and interventions were collected prospectively. Descriptive data are reported as percentages and means, as appropriate.

Results: We identified 45 patients with angioedema for which a DART was activated from 2008-2015. Eighteen (37%) of these were confirmed to have AIIA. Average DART response time was 5.17 minutes. Sixteen (89%) of patients with AIIA were African American and 50% (N=9) were obese. Average age was 54 years old and 44% were female. The ED was the most common site of presentation. Fourteen (78%) patients with AIIA were had stage III Angioedema or higher. Fifteen (83%) patients with AIIA triggering DART activation were intubated and 3 (17%) were monitored in the ICU with serial nasal endoscopic evaluation and did not require intubation. Of patients requiring intubation, 60% (N=9) were brought to the OR, 3 were intubated in the ICU, 2 were intubated on the floor unit and 1 was intubated in the ED. The most successful first-time method of intubation was via an awake nasal fiberoptic intubation. Patients were assessed for an awake surgical airway, anatomy marked and local anesthesia injected when deemed appropriate. However, no patients required a surgical airway. There were no morbidities or mortalities associated with airway interventions.

Conclusion: Anesthesiologists and providers involved with airway management must readily distinguish anaphylaxis from angioedema as the medical treatment and airway intervention can be significantly different. They must risk stratify, manage, and appropriately triage patients that present with AIIA. Based on our DART Program experience, patients with Stage III and IV angioedema should be evaluated carefully and either intubated or monitored with serial airway examinations in the ICU. When airway intervention is necessary, we prefer to manage these patients in the OR with awake nasal FBI. We conclude that a DART Program or equivalent multidisciplinary airway team, with expertise in awake nasal flexible bronchoscopic intubation and awake surgical airway, are important to safely manage patients with emergent presentation of ACE-1 induced angioedema.

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CC 5 (1775)
Initiating an Evidence Based Extubation Protocol Reduced the Incidence of Unintended Postoperative Intubations (UPIs)

Neilson V. Tran, MD[1], Phillip Boysen, MD[2]; Stuart Hart, MD[1]

[1]Ochsner Clinic Foundation, New Orleans, LA, [2]University of Maryland, Baltimore, Maryland

Introduction: UPIs are defined by any unplanned intubation and ventilator support within 30 days of the principal operative procedure. UPIs are one component of postoperative pulmonary complications (PPCs), which are the leading cause of death and increase in healthcare expenditure in surgery. The UPI rate is determined by the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). The ACS NSQIP semiannual report demonstrated that our institution had a yearly UPI rate 50% higher than the national benchmark at 30 days. This prompted a quality improvement (QI) initiative to reduce our institution's UPI rate. This involved determining the causation of every UPI during that year and subsequently implementing an appropriate extubation protocol based on the findings.

Methods: The ACS NSQIP collects and analyzes 135 variables to generate benchmarks and incidence rates for a multitude of conditions. The methodologies have been validated, but the data set is limited in that it is a small sampling of rare events. The data is given in terms of rates (not actual cases) and must be extrapolated to reflect the total patients involved, which could limit one's ability to determine causation. Several methods were used to elucidate details from the NSQIP report which included: ventilator usage in the post-anesthesia care unit, billing/coding information, manual electronic medical record review, and ventilator usage in the surgical intensive care unit (SICU).

Results: Using the aforementioned methods, it was determined that every reported incidence of UPI during that year occurred in the SICU. A standardized extubation protocol (detailed in the Discussion section) was subsequently developed and promptly instituted in the SICU. During that time, the UPI rates had improved by 50% for the 24 and 48 hour timeframes (Figure 1).

Conclusion: UPIs are a major source of morbidity and mortality for surgical patients. The optimal rate of UPIs is debatable, but national benchmarks from quality programs (such as the ACS NSQIP) are an essential part of QI for determining where issues exist and the efficacy of interventions. Use of weaning protocols have demonstrated the reduction of the duration of mechanical ventilation by 25%, weaning duration by 78%, and length of stay in the ICU by 10%. First, the patient needs to be assessed 'readiness to wean.' If the patient meets the inclusion criteria, a spontaneous breathing trial should be performed at the outlined settings. The patient should be assessed every hour as tolerated and weaning parameters should be obtained. If the patient passes the spontaneous breathing trial, proceed with extubation (Figure 2). Post-surgical patients requiring admission into the intensive care unit and ventilator support present a unique challenge in regards to UPIs. Post-operative ventilator requirements can typically be attributed to the acute surgical intervention performed (versus intrinsic chronic pathology). This presents the opportunity for aggressive weaning from mechanical ventilation as the patients recover from surgery. Our institution demonstrated a 50% reduction in the UPI rate over the last year after implementing a standardized extubation protocol. Improvements in this area will directly affect patient outcomes, healthcare costs, and institutional performance (Figure 3).

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CC 6 (2210)

Mechanical Ventilation Enhances Sepsis-Induced Lung Injury: Role of WISP1-αvβ5 Integrin Pathway in TLR4 Mediated Inflammation and Injury

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Introduction: Mechanical ventilation is a common requisite component of intraoperative care for adequate gas exchange and the delivery of anesthetics in patients with sepsis, whereas sepsis is the most common predisposing factor for ARDS/ALI and many of these patients require mechanical ventilation. High tidal volume ventilation (HTV) of normal lungs and exacerbation of existing acute lung injury (ALI) by more moderate mechanical ventilation (e.g. two-hit model) cause an iatrogenic syndrome of ventilator induced lung injury (VILI). It is less clear if extrapulmonary systemic sepsis sensitizes the lung to moderate tidal volume ventilation (MTV) and its underlying pathways.

Methods: We used 8-10 week old male C57BL/6 and TLR4-/- mice and peritoneal macrophages (PM) and animal protocols were approved by the Animal Care and Use Committee of the University of Pittsburgh and experiments were performed in strict adherence to the National Institutes of Health Guidelines for the Use of Laboratory Animals. We used a mouse two-hit model of cecal ligation and puncture (CLP) followed 12 h later by moderate tidal volume ventilation (MTV; 10 ml/kg, 6 h) and focused on WNT1 inducible secreted protein (WISP1) - integrin β5 pathway of TLR4 mediated pulmonary inflammation and injury in intact mice and isolated peritoneal macrophages.

Results: Six h of MTV, that in itself did not cause ALI, exacerbated increases in alveolar capillary permeability (as measured by Evans blue albumin), histopathologic scoring of ALI and indices of pulmonary inflammation (cytokines, chemokines, neutrophil influx and activation of MAPK) in wild type mice that previously (12 h) underwent CLP; the effects of this two-hit model were completely abrogated in TLR4 null mutants. Attendant with these findings was a significant increase in intrapulmonary WISP1 and integrin β5 in two-hit model and the latter was sensitive to TLR4 ablation. Intratracheal administration of neutralizing antibodies to either WISP1 or integrin β5 partially inhibited the two hit phenotype. In PM, activation of TLR4 (with LPS) led to a time- and concentration-dependent increase in integrin β5 expression that was MyD88 (and NF-ÎºB but not TRIF) dependent. Recombinant WISP1 increased LPS induced cytokine release in PM that could be inhibited by silencing either TLR4 or integrin β5.

Conclusion: This two-hit model provides relevant new information regarding unresolved issues of most common risk factor for ARDS/ALI (systemic sepsis) and sensitization to oftentimes used moderate tidal volume ventilation (to support gas exchange and rest respiratory muscles). Collectively, these data show an important positive feedback role for WISP1-integrin β5 pathway in TLR4 mediated exacerbations of ALI to systemic sepsis by moderate tidal ventilation.

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CC 7 (2070)
Clinical Study of Non-Invasive Venous Waveform Analysis (NIVA) for Prediction of a High Pulmonary Capillary Wedge Pressure

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Introduction: Acute decompensated heart failure is the leading cause of hospitalization in patients over the age of 65.[1] Pulmonary capillary wedge pressures (PCWP) have been considered the gold standard for assessing volume overload.[2] PCWP have also been used to gauge the severity of heart failure and confirm the diagnosis of heart failure with preserved ejection fractions.[3] When continuous pulmonary artery pressure readings are available to clinicians, a reduction in heart failure hospitalizations and an improvement in quality of life have been demonstrated.[3] Limitations to pulmonary capillary wedge pressures are that they require an invasive placement of a pulmonary artery catheter, and, in some cases, the placement of an expensive invasive permanent device.[1,4] Vascular harmonics have been shown to correlate with volume status.[5] We hypothesize that non-invasive venous waveform analysis (NIVA) that utilizes piezoelectric sensors to detect vascular harmonics can predict high (>20 mmHg) pulmonary capillary wedge pressures without the need for an invasive procedure.

Methods: Patients (n=43) undergoing cardiac catheterization were enrolled in this Vanderbilt University Institutional Review Board approved protocol. Prior to the patient undergoing their cardiac catheterization, the NIVA device was placed over the median antebrachial vein (Figure 1). Over the course of the procedure, continuous, non-invasive, real-time data of the vascular harmonics were obtained (Figure 2). Upon completion of the procedure, the piezoelectric sensors were removed from the patient and the data were imported into LabChart software (ADInstruments, Colorado Springs, Co, USA). The data were transformed into the frequency domain using Fourier transformations to display the patient signal as a function of sin waves and their corresponding power. The peaks corresponding to the patients' heart rate (f1-f8) were measured as a function of power and inputted into our 'NIVA signal' algorithm. The PCWP was obatined from the pulmonary artery catheter used during the cardiac catheterization, per routine. To determine NIVA signal's ability to predict an elevated PCWP (above 20 mmHg) a receiver operator characteristic (ROC) curve was used.

Results: The ROC curve comparing the NIVA signal against the PCWP revealed an area under the curve of 0.805, demonstrating NIVA's ability to detect a wedge pressure above 20 mmHg (Figure 3).

Conclusion: In patients undergoing cardiac catheterization, their NIVA signal was able to detect a high pulmonary capillary wedge pressure. This non-invasive method could provide a real-time assessment of a patient's cardiac condition by informing a clinician when the pulmonary capillary wedge pressure is high. Funded by The National Science Foundation Award (NSF) ID: 154576

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CC 8 (1347)
Tension Pneumothorax at the Completion of Thoracic Surgery: What Happened?

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Introduction: A 60 year old female, active smoker, with a history of hypertension, HIV/AIDS medication non-adherent (CD4 count 263), hepatitis C, former intravenous drug user currently on methadone, presented with recurrent episodes of pneumonia, complicated by loculated exudative pleural effusion of unknown etiology. She was scheduled for therapeutic thoracocentesis, pleural biopsy, and chemical pleurodesis via left thoracoscopy. Intraoperatively, patient was hemodynamically unstable secondary to difficult-to-control lung parenchymal bleeding, necessitating conversion to thoracotomy. After control of bleeding, decortication and pleurodesis were performed. Postoperatively, after repositioning the patient supine, and prior to extubation, the patient developed high peak airway pressures, hypoxemia, and hypotension, consistent with tension pneumothorax [(1,2)]. Chest tube, although present, was found to be non-functional. The patient was treated supportively, while chest tube malfunction was corrected [(3,4)]. She was transferred to the ICU intubated and sedated, then successfully extubated on post-operative day one. She was discharged home on post-operative day five without further complications.

Etiologies of Pneumothorax[1,2]

Outside OR and ICU	In Critically-Ill Ventilated Patients
Most Common: - Chronic obstructive pulmonary disease (COPD) - Bullous lung disease - Cystic fibrosis - Asthma	Disease Processes: - ARDS - Pneumonia - Trauma - COPD/Asthma
Less common: - Necrotizing pneumonias - Sarcoidosis - Connective tissue disease - Idiopathic pulmonary fibrosis - Marfan' Syndrome - Lung cancer - Sarcoma	Iatrogenic Procedures: - Positive pressure ventilation - Central venous catheterization - Surgical procedures in the thorax or neck - Tracheostomy - Thoracoscopy - Laparoscopy

Methods: n/a

Results: n/a

Conclusion: Tension pneumothorax after decortication and pleurodesis is a not a common phenomenon, though thoracic surgery and positive pressure ventilation are known risk factors for development of pneumothorax. Here we review signs, symptoms, pathophysiology, and management of tension pneumothorax in patients undergoing non-cardiac thoracic surgery. This case demonstrates that continuous communication between anesthesiologist, surgeons, and nursing staff is critical in patient safety and appropriate clinical management.

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Poster Presentations, *continued from page 227*

CC 10 (1754)
Motoric Subtype of Delirium and Global Cognition after Critical Illness

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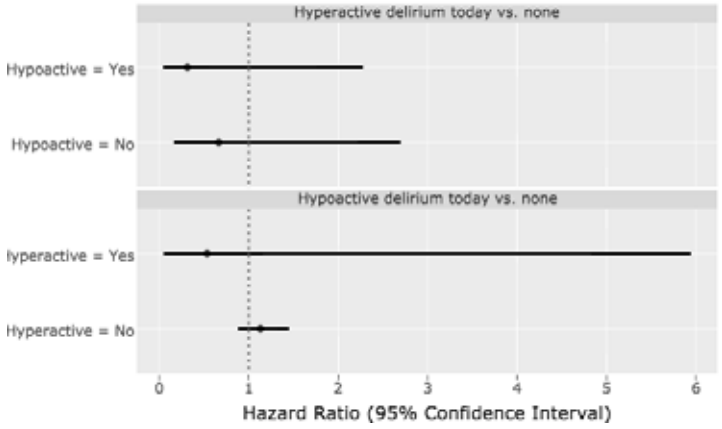
Introduction: Delirium is associated with worse long-term global cognition after critical illness.(1) Hypoactive delirium has been associated with worse outcomes in ICU patients compared to hyperactive delirium (2), but the association of delirium motoric subtype with global cognition is unknown. We hypothesized that hypoactive compared to hyperactive delirium would be associated with worse global cognition.

Figure 1: Hazard Ratios (95% CIs) for Motoric Subtypes, 12m Mortality among All Patients



Methods: In a multicenter prospective cohort of adult ICU patients, we assessed level of consciousness and delirium twice daily with the RASS (3) and CAM-ICU.(4) We considered a day to have hypoactive delirium if one or more CAM-ICU assessments were positive with corresponding RASS ‰¤ 0 and to have hyperactive delirium if one or more CAM-ICU assessments were positive with corresponding RASS > 0. We assessed global cognition with Repeatable Battery for the Assessment of Neurological Status (RBANS)(5) 3 and 12 months after discharge. We used multivariable linear regression to examine the independent association of days with hypoactive delirium and days with hyperactive delirium with global cognition. We allowed for interaction between hypoactive and hyperactive delirium and adjusted for baseline and ICU course covariates.

Results: We included 465 patients with a median age of 59 years, APACHE II score of 24, and ICU length of stay of 4.9 days, 91% of whom required mechanical ventilation. 74% of patients experienced hypoactive delirium (median 3 days), and 16% experienced hyperactive delirium (median 1 day). Increased number of days with hypoactive delirium was significantly associated with worse global cognition at 3 months (p=0.03) and 12 months (p=0.03) and was not modified by hyperactive delirium. There was no significant association between number of days with hyperactive delirium and global cognition at 3 months (p=0.09) and 12 months (p=0.16).

Conclusion: Hypoactive delirium but not hyperactive delirium is an independent risk factor for worse global cognition up to 12 months after hospital discharge.

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CC 11 (2121)

The TLR4 Agonist Monophosphoryl Lipid a Induces Innate Immune Memory Characterized by Alterations to Macrophage Metabolism and Antimicrobial Function

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Introduction: Monophosphoryl lipid A (MPLA) is a toll-like receptor 4 (TLR4) ligand that protects animals from infection with common nosocomial pathogens. Our data show that MPLA-conferred protection is independent of the adaptive immune system, yet dependent on augmentation of neutrophil and macrophage functions[1,2]. However, it is unclear how MPLA changes phagocyte physiology to achieve the protective memory phenotype. We explored the impact of MPLA on macrophage metabolism and function.

Methods: Mouse bone marrow derived macrophages (BMDMs) were primed with MPLA (1ug/mL) for 24 hours, washed and rested for 3 days. Metabolic function was assessed by performing glycolytic and mitochondrial stress tests using the Seahorse XFe96 Extracellular Flux Analyzer. Glucose utilization was assessed by 1,2-13C glucose metabolic flux analysis. Cytokine secretion, phagocytosis and respiratory burst were assessed as functional endpoints. Hexokinase II, succinate dehydrogenase and HIF-1Î± expression were measured by Western blotting.

Results: During the priming period, MPLA induced significant cytokine secretion and increased macrophage glycolytic rate. However, 3 days following the removal of MPLA, BMDMs became refractory to LPS-induced cytokine secretion yet sustained an elevated glycolytic rate. MPLA exposure initially induced a 'broken' TCA cycle corresponding to decreased oxygen consumption, but at 3 days following MPLA removal the TCA cycle corrected and glucose-derived carbon was shuttled into the mitochondria promoting TCA cycle function as indicated by increased glucose-derived succinate generation, increased oxygen consumption, and elevated mitochondrial ATP production. Elevations in glycolysis and TCA cycle function were further confirmed by increased expression of hexokinase II and succinate dehydrogenase. The phenotype was not significantly altered in BMDM from MyD88 or TRIF knockout mice, but was lost in BMDMs isolated from TLR4 knockout and MyD88-TRIF double knockout mice. Functionally, MPLA-primed macrophages displayed elevated phagocytosis and respiratory burst functions. Priming of macrophages with MPLA induced accumulation of HIF-1Î±, which appears to be functionally important since MPLA-primed HIF-1Î± KO macrophages were unable to fully induce MPLA-mediated glucose consumption and demonstrated a reduced capacity for phagocytosis compared to MPLA-primed wild type macrophages.

Conclusion: MPLA initially induces aerobic glycolysis with a 'broken' TCA cycle that facilitates cytokine secretion, but this phenotype then switches to one with elevated glycolysis and a functioning TCA cycle that facilitates key antimicrobial functions. The memory phenotype can be induced through redundant actions of the MyD88- and TRIF-dependent signaling pathways and is dependent, in part, on stabilization of HIF-1Î±.

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Poster Presentations, *continued from page 229*

CC 12 (1730)
Multiple Biomarkers Improve Prediction for Infection in the SICU

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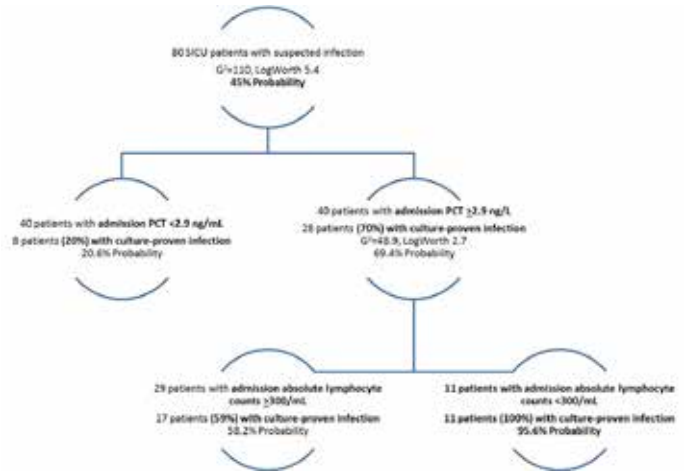
Introduction: Recent studies have shown that one or more admission biomarkers, such as procalcitonin, may improve prediction for culture-proven infection in the medical ICU. However, less is known in the post-surgical setting. This prospective observational study examined admission procalcitonin with other classical measures for suspected infection and the association of culture-proven infection in the surgical ICU.

Methods: Following IRB approval, admission procalcitonin levels, body temperature, white blood cell counts, absolute and percentage lymphocyte counts were obtained in 80 consecutive post-surgical patients admitted for suspected infection. Data were measured and expressed as counts (%) or medians [25-75% interquartile range: IQR] with analysis utilizing Wilcoxon rank sum test with statistical significance, set at P<.01, to reduce the incidence of false discovery rates. A decision tree with 5-fold internal cross-validation was generated for these admission variables with LogWorth values ‰¥2.0 to indicate statistical significance when P<.01. The diagnostic sensitivity of the recursive partitioning model was analyzed with c-index statistics.



Results: The admission incidence of culture-proven infection was 45%. Postoperative infection increased SICU length of stay from 3 [2-6] days to 5 [2-11] days, P=.0954, and hospital length of stay from 12 [7-22] days to 19 [8-25] days, P=.1804. When admission procalcitonin values were ‰¥2.9 ng/mL (LogWorth=5.4) and admission lymphocyte counts were <300/mL (LogWorth=2.7), all patients developed culture-proven infection (C-index = 0.79). Admission variables such as body temperature, WBC counts, and percentage lymphocyte counts were not predictive for culture-proven infection in this analysis.

Conclusion: This study suggests both admission procalcitonin levels and absolute lymphocyte counts provide important decision information in predicting culture-proven infection in the surgical ICU. This association, if confirmed by future studies, may improve antibiotic stewardship in the surgical ICU.

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Poster Presentations, *continued from page 230*

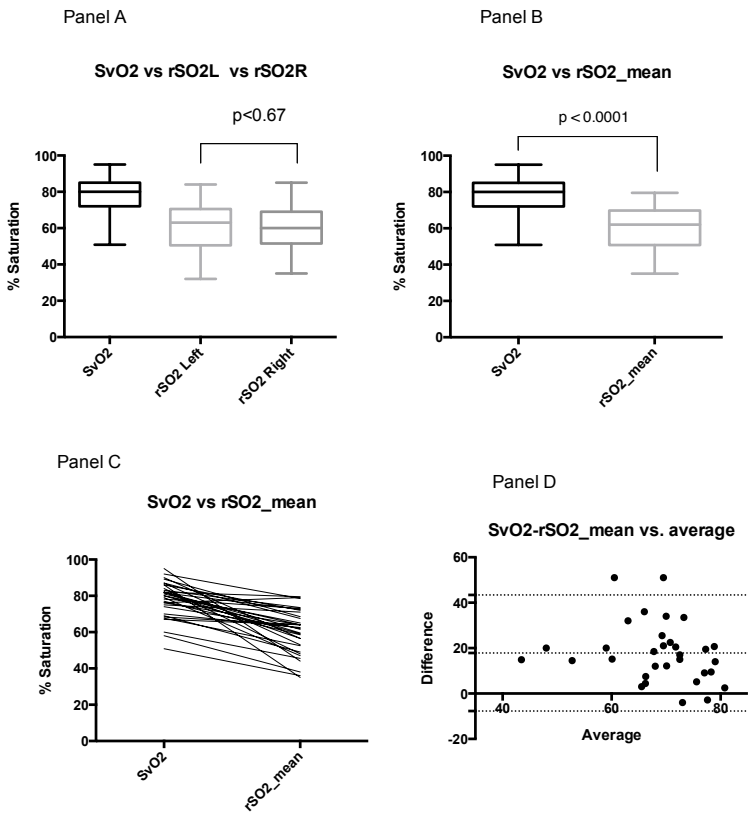
CA 13 (2056)
Relationship Between Baseline Cerebral Oximetry and Mixed Venous Oxygen Saturation in Cardiac Surgical Patients

Viachaslau Barodka, MD[1], Yurie Obata, MD[2]; Trent Magruder, MD[1]; Daniel Berkowitz, MD[3]; Charles Hogue, MD[4]

[1]The Johns Hopkins University, Baltimore, MD, [2]The Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD, [4]Northwestern Feinberg School of Medicine, Chicago, IL

Introduction: Clinically, mixed venous oxygen saturations (SvO2) a marker of adequate perfusion is measured via a pulmonary artery catheter (PAC), but their placement is invasive and may be associated with patient harm. We tested the hypothesis that values of cerebral oximetry (rScO2), as measured by NIRS, predict SvO2 exceeding clinically relevant thresholds of 60% and 70%.

Methods: Mixed venous blood samples were drawn from pulmonary channel of Swang Ganz catheter in cardiac surgical patients prior to cardiopulmonary bypass (N=33). Cerebral oximetry rScO2 values were recorded simultaneously. Linear regression, Bland-Altman plots, and receiver-operating characteristic curve analysis was utilized to select values of rScO2 with high specificity for predicting SvO2 below the predefined thresholds of 60% or 70%.

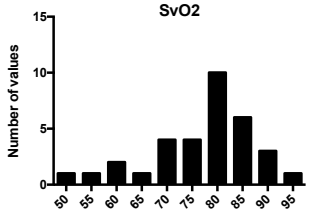


Results: A significant correlation was observed between rScO2 and SvO2 (coefficient 1.03, 95% confidence interval (CI) 0.88-1.18, p < 0.001; R2 = 0.86). Median SvO2 values were consistently higher than median rScO2 (bias +17.83, standard deviation 13.04, upper/lower limits of agreement 43.49/-7.72). Based on ROC analysis, rScO2 ‰¥45% was 96% sensitive and 100% specific for predicting SvO2>60% threshold (AUC 0.97), but only three patients studied had SvO2 values ‰¤ 60%. A rScO2 value >65% was associated with an SvO2 > 70% in all patients. A mean rScO2 value > 53% had 85% sensitivity and 71% specificity for detecting SvO2>70% (AUC 0.78).

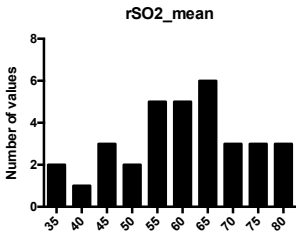
Conclusion: We found that rScO2 ‰¥65% has 100% specificity for assuring a SvO2>70%.

continued on page 231

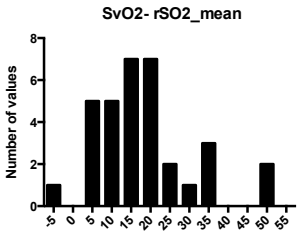
Panel A



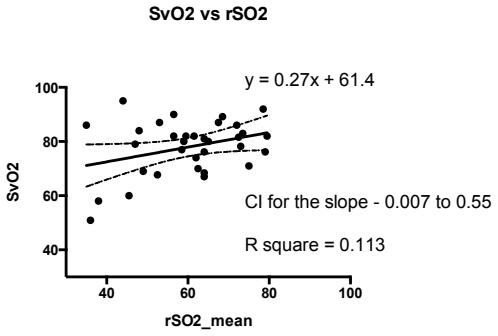
Panel B



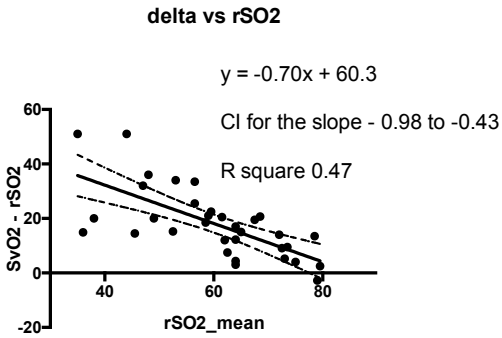
Panel C



Panel A



Panel B



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CA 14 (1749)

Paradoxical Negative Interaction of Heart Failure and Renal Failure Among Patients Undergoing Elective, Non-Cardiac Surgery: An Analysis of 121,812 Patients in the 2012 NSQIP Database

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Introduction: Heart failure (HF) and renal failure (RF) are common diseases in non-cardiac surgical patients and are associated with excess mortality[1,2]. Patients with coexisting HF and RF, termed cardiorenal syndrome (CRS) have approximately twice the hazard of 180-day mortality as those with HF alone[3,4]. Evidence that HF therapy improves RF in patients with CRS and vice versa suggests that there is an important interaction between these disease states5-8. To our knowledge, the interaction between HF and RF in CRS has not been analyzed in a non-cardiac surgical population.

Methods: We conducted a retrospective cohort analysis of all patients included in the 2012 National Surgical Quality Improvement Project (NSQIP) database undergoing elective, non-cardiac surgery (n = 485,529). Patients were included in the final analysis if complete comorbidity data was available. Bivariate analyses were performed using Pearson's Ï‡2 test or Student's t-test. Mortality at 30 days was modeled using logistic regression. All variables significant at the bivariate level were included in the initial multivariable model. First-order interactions between ischemic heart disease, renal failure, and congestive heart failure were tested a priori, with no more than one interaction term per model.

Results: We analyzed 485,529 patients undergoing elective, non-cardiac surgery of whom 121,812 (25%) had complete comorbidity data and were included in the final analysis. There was no statistically significant difference in mortality between patients with complete and incomplete data (988 vs 2851, 1% vs 1%, p = 0.353). In a multivariable logistic regression model there was statistically significant effect modification between HF and RF: RF in the absence of HF (OR 1.50, 95% CI 1.28 – 1.76), HF in the absence of RF (OR 1.75, 95% CI 1.49 – 2.05) and CRS (HF x RF, OR 2.04, 95% 1.37 – 3.03, p = 0.002 for the interaction) were all associated with increased 30-day mortality. No other tested interactions were statistically significant. In the same model, male sex (OR 1.26, 95% CI 1.10 – 1.43), increasing age (OR 1.06 95% CI 1.05 – 1.07) African American race (OR 1.55 95% CI 1.29 – 1.86), lower BMI (OR 0.96, 95% CI 0.95 – 0.97), history of severe COPD (OR 2.25, 95% CI 1.89 – 2.67), cerebrovascular disease (OR 1.49, 95% CI 1.26 – 1.77), ischemic heart disease (OR 1.27, 95% CI 1.08 – 1.46), peripheral vascular disease (OR 1.43, 95% CI 1.19 – 1.74), diabetes mellitus (OR 1.20, 95% CI 1.03 – 1.40), and hepatobiliary disease with ascites (OR 8.84, 95% CI 6.03 – 12.97) were also significantly associated with increased 30-day mortality.

Conclusion: In a model of 30-day mortality among 121,812 patients undergoing elective, non-cardiac surgery we found a significant, negative interaction between HF and RF in patients with CRS. While the OR for CRS was higher than either comorbidity alone, it is less than expected (1.50 x 1.75 = 2.6). Based on current evidence and opinion it might be expected that CRS would lead to worse outcomes than product of HF and RF separately, i.e., a positive interaction, because of the challenges in managing volume status in these patients. Our findings may represent a previously hidden protective mechanism, however, significant selection bias among patients included in the NSQIP is a more plausible hypothesis. Published estimators of surgical risk likely significantly misrepresent the risk of death among patients with CRS.

References:

Paradoxical negative interaction of heart failure and renal failure among patients undergoing elective, non-cardiac surgery: an analysis of 121,812 patients in the 2012 NSQIP database.

Poster Presentations, *continued from page 233*

CA 15 (2083)
12-HETE as a Novel Biomarker of Endothelial Cell Dysfunction in Diabetes Mellitus and Hyperglycemia

Helen Heymann, MS[1], Nana-Maria Wagner, MD, PhD[1]; Carl Hurt, MD, PhD[1]; Eric R. Gross, MD, PhD[1]

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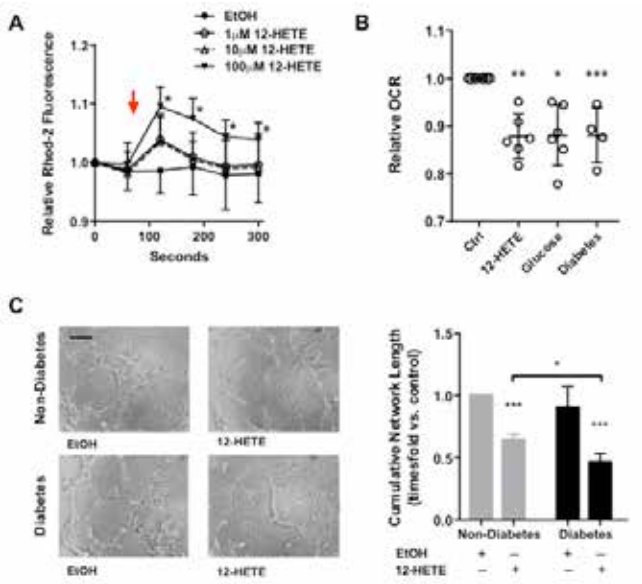
Introduction: Diabetes mellitus and hyperglycemia-induced endothelial dysfunction is associated with an increased risk of perioperative complications [1,2]. In a type 1 diabetes mellitus rat model, we previously detected increased plasma concentration of the fatty acid peroxidation product 12-hydroxyeicosatetraenoic acid (12-HETE). Here, we hypothesize that 12-HETE-induced mitochondrial calcium influx mediates endothelial cell dysfunction in diabetes mellitus and hyperglycemia.



Methods: Human umbilical vein endothelial cells (HUVECs) were exposed to 12-HETE (1, 10, and 100 μM) or the 12-HETE vehicle ethanol (EtOH) while measuring mitochondrial calcium influx by flow cytometry of rhodamine-2AM. Mitochondrial membrane potential was assessed in HUVECs by JC-10 fluorescence following 12-HETE exposure. Further, mitochondrial respiration of HUVECs exposed to 1 μM 12-HETE was compared to respiration of either HUVECs incubated for 48 hours with 25mM glucose or mannitol, or human aortic endothelial cells (HAECs) from type 1 diabetic patients. To assess endothelial cell function, in vitro capillary formation after 1 μM 12-HETE was analyzed in HAECs of diabetics compared to HAECs of non-diabetics matched by age and ethnicity. Data is presented as mean ±SD and statistical analysis was performed using two-way ANOVA/ Bonferroni or Students t-test.

Results: 12-HETE caused mitochondrial calcium influx in HUVECs (Fig A, rhodamine-2 AM fluorescence intensity vs. EtOH, n=6, *P<0.05). 12-HETE also decreased mitochondrial membrane potential (0.84 ±0.4 JC-10 emission vs. EtOH, n=5, *P<0.05) and mitochondrial respiration (Fig B, oxygen consumption rate [OCR] vs. EtOH, n=6, **P<0.01). The effects of 12-HETE at the mitochondria measured by OCR were comparable to those caused by hyperglycemia (Fig B, vs. mannitol, n=6, **P<0.01) and HAECs of diabetics (Fig B, vs. HAECs of non-diabetics, n=4, *P<0.05). In HUVECs, HAECs of non-diabetics, and HAECs of diabetics, 1 μM 12-HETE resulted in endothelial cell dysfunction (Fig C, 0.66 ±0.1, 0.65 ±0.05 and 0.46 ±0.07, respectively, vs. EtOH, n=2-6, ***P<0.001). Interestingly, the effects of 12-HETE were particularly pronounced in HAECs of diabetics compared to non-diabetics (*P<0.05).

Conclusion: We demonstrate how 12-HETE, produced during diabetes and hyperglycemia, causes changes in mitochondrial calcium influx and results in endothelial cell dysfunction. Although more studies are needed, 12-HETE could serve as a biomarker reflecting vascular disease severity in diabetic patients. Further, a therapeutic intervention targeting 12-HETE's effects at the mitochondria may potentially mitigate endothelial dysfunction in diabetic patients.

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CA 16 (2054)
Plasma Free Hemoglobin, Oxidative Damage, and Acute Kidney Injury in Cardiac Surgery

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Introduction: Acute kidney injury (AKI) occurs in up to 30% of patients who undergo cardiopulmonary bypass (CPB) during surgery.[1,2] CPB lyses erythrocytes, and free hemoglobin (Hb), similar to other hemeproteins, is nephrotoxic.[3,4] In a rat model, hemeprotein-induced AKI was mediated by oxidative damage, and we have recently demonstrated that increased oxidative damage is an independent predictor of AKI following cardiac surgery.[5,6] We tested the hypothesis that increased plasma free Hb concentrations in patients undergoing cardiac surgery are associated with AKI and that this association is mediated by oxidative damage.

Methods: We measured plasma free Hb 30-minutes into CPB, immediately after CPB, and at ICU admission in Statin AKI cardiac surgery RCT participants. We measured plasma concentrations of isofurans, stable products of arachidonic acid peroxidation, at ICU admission to quantify intraoperative oxidative damage. AKI was defined using Acute Kidney Injury Network criteria. To isolate the association between peak free Hb and AKI we performed multiple logistic regression adjusted for age, estimated glomerular filtration rate, statin treatment, and baseline hematocrit ($\hat{I}^2$Hb1, model 1, Figure 1). To assess any mediation by oxidative damage, we added isofurans to the model and examined $\hat{I}^2$Hb and the independent association between isofurans and AKI ($\hat{I}^2$Hb2 and $\hat{I}^2$isofuran, model 2), and we measured the association between peak free Hb and isofurans, adjusted for the same covariates ($\hat{I}^2$Hb3, model 3). A decrease in the association between free Hb and AKI in model 2, an association between isofurans and AKI, and an association between free Hb and isofurans are required to demonstrate any evidence of oxidative damage mediating an association between intraoperative plasma free Hb and postoperative AKI.

Results: Sixty-five of 259 patients (25.1%) developed AKI within 72 hours of cardiac surgery. The median (10th, 90th percentile) free Hb concentration was 0.0 mg/dl (0.0, 75.0) 30 minutes into CPB, 69.8 mg/dl (0.0 to 295.0) immediately following CPB, and 60.0 mg/dl (0.0, 234.8) at ICU admission. Median isofurans concentration at ICU admission was 65.4 pg/ml (33.4, 141.6). The peak median plasma free Hb concentration in AKI patients was 48.6 mg/dl higher than in non-AKI patients, and in adjusted analyses, a 50 mg/dl increase in peak free Hb was independently associated with a 16% increase in the odds of AKI ($\hat{I}^2$Hb1 OR, 1.16 [95% CI, 1.02 to 1.33]; P=0.02; Figure 2). When isofurans were added to the model, this association was reduced ($\hat{I}^2$Hb2 OR, 1.13 [95% CI 0.99 to 1.30) and no longer significant (P=0.06). A 25 pg/ml increase in peak isofurans was independently associated with an 18% increase in the odds of AKI ($\hat{I}^2$isofuran OR, 1.18 [95% CI, 1.03 to 1.33]; P=0.03, Figure 3), and a 50 mg/dl increase in peak plasma free Hb was independently associated with a 4.8 pg/ml [95% CI, 2.0 to 7.5; P=0.001] increase in plasma isofurans (Figure 4).

Conclusion: Intraoperative plasma free Hb concentrations were independently associated with AKI following cardiac surgery, and this association may be partially mediated by increased oxidative damage. Increased free Hb was associated with increased oxidative damage, and increased oxidative damage was independently associated with AKI. Interventions to decrease intraoperative hemolysis, scavenge plasma free Hb, and decrease oxidative damage during cardiac surgery should be studied to decrease AKI and subsequent patient morbidity.

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continued on page 236

Poster Presentations, *continued from page 235*

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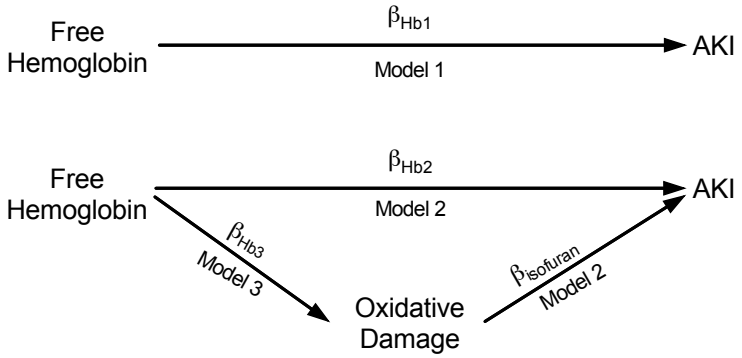

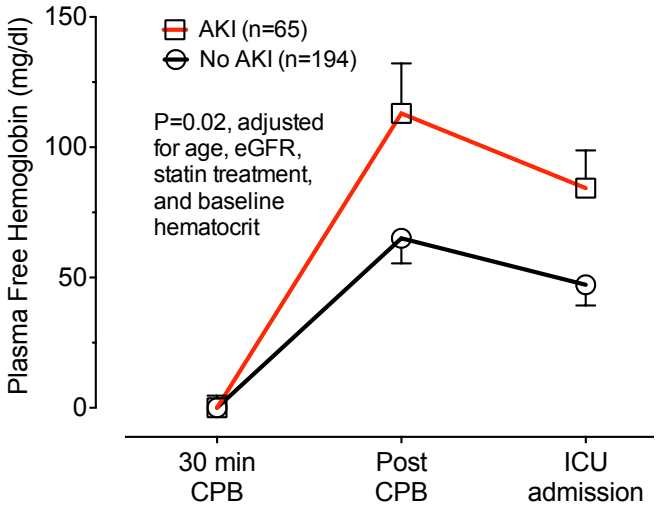

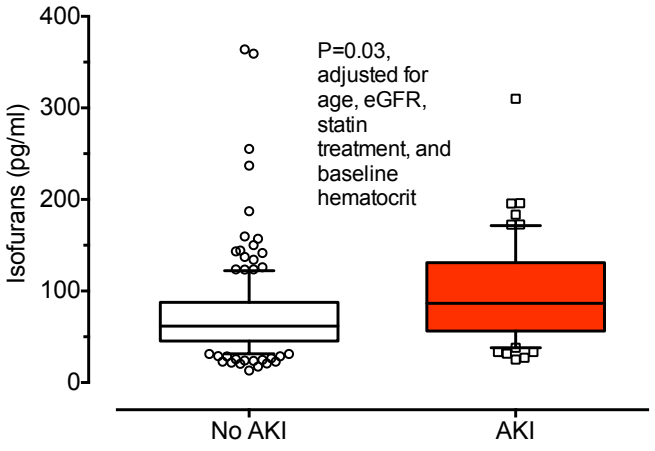

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CA 17 (2025)
Targeting Matrix Remodeling in Pulmonary Arterial Hypertension

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Introduction: Pulmonary arterial hypertension is characterized by increased pulmonary arterial pressures resulting in right ventricular strain and heart failure. The underlying pathology is not completely understood with most disease models focusing on either endothelial dysfunction, reactive smooth muscle cell hyperplasia, or matrix remodeling. Given the emerging role of the collagen crosslinking enzyme lysyl oxidase like-2 in the systemic vasculature we evaluated its role in the pulmonary vasculature.

Methods: We measured LOXL2 abundance in the media and the cytosol of human pulmonary artery smooth muscle cells (HPASMC) in the presence and absence of hypoxia. We then subjected a group of rats to three weeks of Sugen 5416 hypoxia, harvested the pulmonary arteries, tested vasoreactivity (wire myography), and stress strain relationships (electromechanical puller). Lastly we subjected LOXL2 +/- mice and their littermate controls to three weeks of Sugen 5416 hypoxia and evaluated pulmonary physiology using invasive pressure/volume loops.

Results: HPASMC subjected to hypoxia show increased levels of LOXL2 abundance and mRNA levels. Pulmonary arteries isolated from rats that were exposed to Sugen 5416 hypoxia show decreased maximal contractility in hypoxic animals. There is a marked increase in vessel stiffness evidenced by a leftward shift of the stress strain relationship in animals exposed to hypoxia. Right heart catheterization of LOXL2 +/- and WT mice exposed to hypoxia showed no change in cardiac function (EF%, CO, SV, dp/dt), but increased maximal power generated by the animals with high level of LOXL2 (PowMax). This might be due to the increased pulmonary artery pressure that is more pronounced those animals (Pmax, Pmean, Pes, Ped), as well as higher elastance (Ea) and increased stiffness (Tau).

Conclusion: At a cellular level, hypoxia results in increased LOXL2 secretion. This coincides with decreased smooth muscle cell contractility, and increased passive vessel stiffness. Furthermore, mice with high LOXL2 levels demonstrate higher pulmonary artery pressures, increased right ventricular elastance, and impaired cardiac relaxation when exposed to hypoxia.

References:

n/a

CA 18 (2045)

Blood Pressure Management in Hypoplastic Left Heart Syndrome After Stage 1 Palliation: Is there an ST Instability-Dependent Optimal Blood Pressure?

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Introduction: Posing a challenge in the perioperative management of hemodynamics, hypoplastic left heart syndrome (HLHS) infants are a high risk population with an interstage mortality risk of 11-15% [(1)]. A new measure of 3-dimensional ST-segment vector instability has been described with increased instability associated with interstage cardiopulmonary arrest [(2)]. The objective of this study was to correlate ST-segment vector instability with blood pressure to evaluate if there are optimal blood pressure parameters which minimize instability. In addition, a subgroup analysis examined if there was a difference in response to blood pressure based on shunt type utilized for pulmonary blood flow: Blalock-Taussig (BT) vs. Sano.

Methods: In this retrospective observational study at a tertiary children's hospital, all infants with a diagnosis of HLHS from January 2013 to January 2015 were queried from a physiological database system: recordings (240 Hz) of electrocardiogram (ECG), arterial line blood pressure (ABP), central venous pressure (CVP), common atrial pressure (CAP), and coronary perfusion pressure (CPP) were obtained in the 12 hours after Norwood procedure. ECG processing of the ST segments in leads II, aVL, and V5 was performed to quantify ST instability as previously described (2) and instability was correlated with systolic (SBP), DBP, CVP, and CPP over the 12-hour period (ICM+ Software, Cambridge; UK). A generalized estimating equation approach [(3)] for regression was utilized to account for repeated measurements (Stata 14 Software, College Station, TX; USA). Spearman's rank correlation was calculated for each relationship.

Results: A total of 27 HLHS infants were included in the study: 10 with BT and 17 with Sano shunts (table 1). There was no overall difference in ST instability between BT and Sano groups in the 12 hours postoperatively. All relationships between ST instability and blood pressures are presented in figure 1. There was a significant trend for increased instability with increased SBP in the BT shunt group which was not observed in the Sano group. No significant trends in ST instability were observed with DBP, MAP, or CVP. There was a significant trend in increased ST instability ($p = 0.05$) with low (<20 mmHg) and high (38-40 mmHg) CPP in the BT shunt group. The optimal CPP was 27.8 ± 6.7 mmHg which correlated with ST instability of 0.34 ± 0.24 mm / 20min. In the Sano group, there was trend in increased ST instability ($p = 0.06$) at low CPP (<26 mmHg). The optimal CPP was 29.8 ± 3.0 mmHg which correlated with ST instability of 0.28 ± 0.09 mm / 20 min.

Conclusion: In HLHS subjects with BT shunts, elevated instability is noted with higher SBP whereas this relationship is not observed in patients who have received Sano shunts. This may be a reflection of how the shunt type affects cardiac strain in light of elevated SBP. When CPP was derived, increased instability was noted at extremes in CPP.Future studies examining larger time periods, particularly the peri-arrest period may lead to improved blood pressure management goals during the HLHS interstage and reduce cardiopulmonary arrests.

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Table 1. Characteristics of study population.

Characteristic	Overall (n = 27)	BT (n = 10)	Sano (n = 17)	p
Age (days)	6 [4 – 8]	7.5 [4 – 8]	5 [4 – 8]	0.46
Male sex	14 (52%)	5 (50%)	9 (53%)	1.0
Weight (kg)	3.2 [2.8 – 3.6]	3.3 [3.0 – 3.3]	3.0 [2.7 – 3.6]	0.50
Gestational age at birth (weeks)	38.9 [37.6 – 39.1]	38.9 [37.6 – 39.0]	38.9 [37.7 – 39.2]	0.85
Anatomy:				0.85
MA/AA	9	3	6	
MA/AS	1	0	1	
MS/AA	10	4	6	
MS/AS	7	3	4	
Interstage (days)	100 [94 – 118]	94 [89 – 97]	116 [98 – 128]	0.002*
Interstage Arrest	10 (37%)	5 (50%)	5 (29.4%)	0.42
Survival	24 (89%)	9 (90%)	15 (88%)	1.0

Values are median [IQR_{25} – IQR_{75}] or number (percentage) reported when applicable. BT = Blalock-Taussig. MA = mitral atresia. MS = mitral stenosis. AA = aortic atresia. AS = aortic stenosis. p-values comparing BT and Sano shunt group population values. *Statistically significant ($p < 0.05$).

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EEP 19 (2248)
Compliance with Scheduled Times in the Operation Room: Influence of the Weekday on Adherence to Planned Case Durations

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Introduction: The operation room is usually the most cost-extensive part of a hospital. For an efficient OR utilization, precise scheduling of and adherence to planned case durations is crucial. We know from previous studies that deviations of planned case durations and lack of timeliness of start times are quite variable. The aim of subsequent analyses was therefore to identify potential reasons for this variability, with the present study focusing on the influence of the weekday on case durations.

Methods: The study was performed in an academic medical center in Germany with over 900 beds and 22 operating rooms, which performs about 20,000 surgical procedures per year. The analysis of OR scheduling was based on the operating room management software and database. Scheduled surgery cases on regular working days were screened for weekend and non-elective daytime status. Data were analyzed with standard software.

Results: A total of 14,014 surgery cases between September 2015 and August 2016 underwent screening for elective status. After appropriate screening, 13,547 cases were included in the final analysis. The average difference of duration vs. plan was 7 ± 48 minutes. The longest deviation from plan (12 ± 52 minutes) was found on Mondays. On successive days, this difference decreased, with the shortest deviation (2 ± 45 minutes) being found on Fridays.

Conclusion: The assumption that the performance of operating rooms would not be fundamentally influenced by weekdays was proven wrong. OR-Managers should continue to identify reasons for the variability of prolonged cases.

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Poster Presentations, *continued from page 240*

EEP 20 (2110)
The Impact of Institutional, Comprehensive Faculty Development on Resident Education: Building a Point-Of-Care Ultrasound Program

Elifce Cosar, MD[1], Tanya Lucas, MD[2]; J. Aaron Scott, DO[3]; Maksim Zayaruzny, MD[2]; Luanne Thorndyke, MD[2]; Shubjeet Kaur, MD[4]; J. Matth Walz, MD[1]

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Introduction: The benefits of Faculty development include increased vitality, as well as increased rates of retention. In 2012, the UMass Medical School Office of Faculty Affairs (OFA) was awarded an educational grant by the American Council on Education, and the Alfred P. Sloan Foundation in support of initiatives to support career flexibility for academic faculty. We describe the impact of Faculty development on Resident education through the creation of a point-of-care ultrasound (PoC-US) training program, funded by a Grant awarded to two mid-career Faculty in our Department.

Methods: The two Faculty supported by OFA underwent training in basic lung US, and basic-, and advanced Focused Assessed Transthoracic Echocardiography (FATE). Licenses for a comprehensive online e-learning portal on basic US physics, basic lung US, and FATE were then acquired for Residents (Ca-2 and CA-3), and core teaching Faculty in 2015.The portal includes pre-, and post-testing for each module, and allows for modification of content after acquisition of the learner licenses. Regular lectures on topics relevant to perioperative ultrasound were added to the core curriculum. An annual CME-approved two-day hands-on-training (HOT) course was hosted in 2015, and 2016 (basic lung US, basic-, and advanced FATE). All clinical providers were offered participation in HOT in 2016. Additional US equipment for all clinical sites was acquired through partial matching with departmental funds. We used the Kirkpatrick 4 level model to evaluate the effectiveness of the. Statistical analysis of exam scores and group comparisons was performed using the t-test for dependent, and independent samples. A post-HOT satisfaction survey was performed using a 4-point Likert scale.

Results: 25 Residents, 16 Faculty, two CRNAs, and one Fellow completed the HOT courses in 2015, and 2016. Among CA-2 Residents, there was a significant increase from pre-, to post test exam scores across all e-learning modules (Level 2 outcome, Table 1). When comparing the 2015 and 2016 CA-2 Resident cohort exam scores, no significant increase was found. Ninety percent of all course participants ranked the quality of the HOT, and relevance to their practice as excellent (Level 1 outcome). Of 10 instructors participating in the 2016 HOT, the two Faculty members awarded the Vitality grant received the highest effectiveness ratings by course participants.

Conclusion: The quick implementation of the program, and high ratings of effectiveness as educators for the supported Faculty shows the impact comprehensive development can have on Faculty vitality, and Resident education. While still in its early stages, the incorporation of surface US teaching into US Anesthesiology Residency Programs has been suggested. Three factors allowed for the successful inception, and rapid scaling of the initiative: The starter grant by OFA, the combination of e-learning modules with HOT courses, and collaboration with other Departments with expertise in PoC-US education (Cardiology, Emergency Medicine). Future efforts will be directed at demonstrating the effectiveness of the program through assessment of skills acquired by the learners (Level 2), utilization of PoC-US by learners in the clinical environment (Level 3), and the establishment of a robust research infrastructure to determine impact on patient outcomes (Level 4). Lastly, building a robust quality control program and training of all Faculty in the Department will ensure long term success and sustainability of the effort

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Table 1: CA-2 Resident intra- group test comparison for the 2016 cohort (pre-, to post test for basics of US physics, and basic FATE module). Data are expressed as means, ± standard deviations.

	Pre Test	**Post Test**	**P-value**
Basic US Physics (% means ± SD)	53.5±27.6	89.7±5.6	0.008
Basic FATE (% means ± SD)	51.3±20.1	87.3±5.2	0.0002

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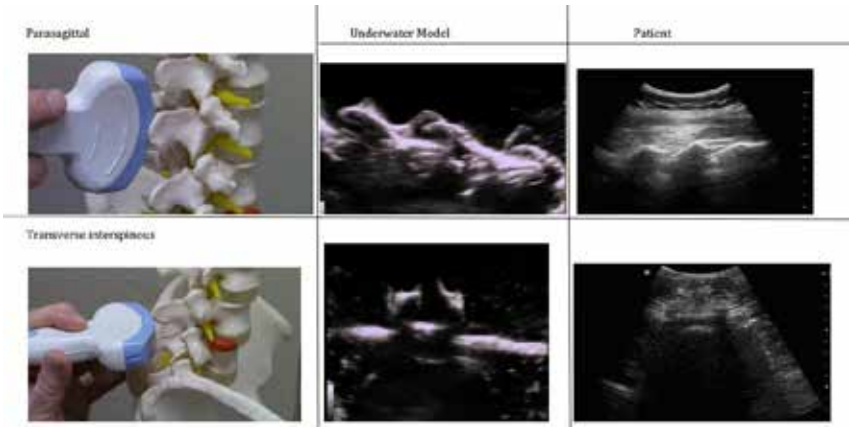
EEP 21 (2021)
Ultrasonic Examination of the Underwater Spine: A Learning Technique to Enhance Acquisition of Basic Skills to Place an Epidural Catheter

Michael C. Scarbrough, MD[1], Laurie Daste, MD[1]; Jacquelyn Paetzold, DO[2]; Phillip Boysen, MD[1]

[1]Ochsner Clinic Foundation, New Orleans, LA, [2]Tulane University School of Medicine, New Orleans, LA

Introduction: We used a sequential analysis technique (CUSUM) to assess individual learner acquisition of the skill to place an epidural catheter. We observed that anatomic assessment of the back and spine by palpating landmarks was the most difficult step for the learner, often due to obesity or difficulty establishing the midline of the spine. We separated this initial skill to provide a learning technique which depended on the combination of ultrasonic examination of a submersed model of the human spine, proceeding to ultrasound examination of patient anatomy.



Methods: We employed a GE Venue 50 Ultrasound device, with a low frequency curvilinear probe, and depth set to 8 – 10 cm. We submerged an acrylic model of the human spine to an appropriate depth and ran the probe over the surface of the water to obtain an image. A longitudinal paramedian approach was used to examine the sacrum, moving cephalad to examine each interspace and to ascertain the approximate position of the ligamentum flavum and posterior dura. Switching to the transverse plane the bony structures including the spinous processes, articular and transverse processes, and vertebral bodies are identified. An ultrasound examination of a patient is then performed, and in addition to spinal anatomy, the dorsal dura mater, ligamentum flavum, ventral dura mater, and posterior longitudinal ligament are imaged. The ideal insertion point is determined, depth to the epidural space is measured, and best angle of approach is noted. The image is frozen, captured, and printed, and the learner is asked to mark each anatomical entity on the print.

Results: Skilled anesthesiologists can complete the spinal ultrasound examination in 2 – 3 minutes, including verbal confirmation of the anatomy. Using our checklist, 10 learners were able to reach this target after 10 – 12 patient examinations.

Conclusion: We conclude that using our underwater spine simulation enhances transition to the actual patient examination. It identifies the best interspace for access, the angle of needle introduction, and the distance from skin to epidural space. It will identify spinal abnormalities such as scoliosis, and establish the midline when often not appreciated by palpation of the back. As an approach to the assessment of learning this skill we can shorten the overall time to epidural placement, increasing patient safety and comfort.

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EEP 22 (2031)
CUSUM Analysis: An Application of Learning Curves to Ensure Basic Skills in Anesthetic Procedures

Michael C. Scarbrough, MD[1], Laurie Daste, MD[1]; Jacquelyn Paetzold, DO[2]; Phillip Boysen, MD[1]

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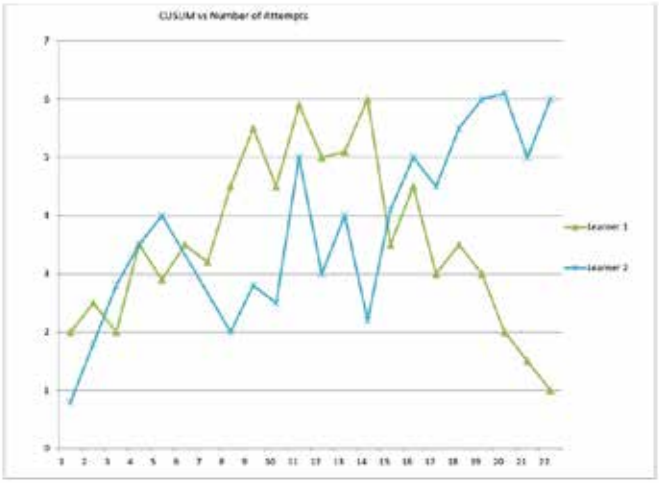
Introduction: The cumulative sum control chart (CUSUM) is a sequential analysis technique developed to monitor change detection. It is a process control chart that identifies deviation from an expected or standardized mean. It has been used to monitor acquisition of clinical skills as a formative and summative evaluation [(1,2)]. We concentrated on formative skills for a learner to place labor epidurals, with the aim of identifying and intervening to assist a struggling learner.



Control range +/- 10%. Graph rises by value of 0.9 (1-f) with failure and declines by 0.1 (f) with success. Graph falls to "control" or within for given boundaries[3].

Methods: We followed six learners over a six month period. All learners underwent an initial didactic and simulation curriculum which involved video presentations, lectures, and introduction to spinal anatomy with ultrasonic examination of an underwater spine model, culminating in observing a staff anesthesiologist placing an epidural. We defined epidural placement as successful if placement resulted in effective analgesia without the assistance of a staff anesthesiologist. Failed epidural placement was recorded if dural puncture occurred or if physical assistance from a staff anesthesiologist was necessary. We further determined that once the skill of ultrasound examination of spinal anatomy was mastered, residents and staff anesthesiologists could complete successful epidural insertion in 18 – 20 minutes. We recorded CUSUM statistics vs. number of attempts at insertion and plotted the results. We arbitrarily set the control limits as +/- 10% of the mean.

Results: In all six learners movement toward process control occurred at approximately 10 attempts. In 5/6 learners, they achieved process control in 25 – 30 attempts. Figure 1 shows two resident CUSUM charts, one with the desired continued movement toward the desired process control range, and one showing erratic deviation and stagnation in process improvement. This resident required intervention and focused instruction.

Conclusion: Individuals learn skills at a different rate. Formative instruction can avoid failure when summative evaluation is conducted with a pass/fail rating. Check-off lists, which only identify the number of procedures attempted without actually analyzing the desired skill set, are commonly reported. Process control charts and CUSUM evaluation can be used for a variety of anesthetic procedures including peripheral venous cannulation, central venous cannulation, tracheal intubation, spinal and epidural anesthesia. Learning curves provide a graphic display of the educational process.

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EEP 23 (2052)
No Significant Difference in Outcomes when Anesthesia Care is Provided by aAn Anesthesiologist Assistant or a Nurse Anesthetist: An Analysis of Medicare Data

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Introduction: Expanding the use of midlevel providers could reduce medical spending and increase access to health care. In the United States, anesthesia care can be provided by two types of midlevel providers: nurse anesthetists (NAs) and certified anesthesiologist assistants (CAAs). While NAs can practice in all 50 states, CAAs have authority to practice in only 16 states and the District of Columbia. Understanding whether CAAs are associated with differences in outcomes could guide efforts to expand the scope of CAA practice.

Methods: Our dataset consisted of administrative health insurance claims for patients covered by Medicare, the United States public insurer for the elderly and some disabled persons. We constructed an initial sample of 1,064,591 inpatient surgeries occurring between January 1, 2004 and December 31, 2011. We then applied several exclusion criteria. First, we excluded patients under 65 or over 89 years of age (n=223,884). Second, we excluded cases with a missing surgical procedure code (n=25,863). Third, we excluded cases with missing data on patient or hospital zip code (n=14,247), as well as cases where patient race or sex was unknown (n=2,355). Fourth, since our goal was to compare outcomes between midlevel providers, we excluded cases where neither a NA or CAA provided care (n=291,236), as well as a small number of cases where both provided care (n=82). Finally, we excluded any surgeries for which we had fewer than 100 observations (n=32,267) as well as any hospitals with fewer than 100 observations (n=22,152), resulting in a final sample of 452,502 cases comprising of 356 surgery types and 889 hospitals. We then examined whether outcomes were different when care was provided by a CAA compared to a NA. We considered three outcomes: inpatient mortality, inpatient length of stay, and inpatient medical spending. Our approach incorporated an extensive set of adjustments for potential confounders (e.g. patient comorbidities); in addition, we also utilized quasi-randomization method known as instrumental variables to further minimize confounding (Chetty et al., 2014). Specifically, this approach exploited daily variation in the number of CAAs that are available to do cases-which is likely due to state regulations or scheduling decisions as opposed to patient or hospital characteristics that could affect outcomes—to quasi-randomize patients to CAA versus NA care.

Results: The adjusted mortality for cases where a CAA provided care was 1.53% (95%CI 1.31 to 1.75), compared to 1.65% for cases where a NA provided care (95%CCI 1.64 to 1.66; p=0.115 for the difference; Figure 1). Compared to NA care, CAA care was associated with an insignificant 0.109 day decrease in length of stay (95%CI -0.128 to 0.109, p=0.879; Figure 2) and an insignificant $74 reduction in medical spending (95%CI -354 to 206, p=0.606; Figure 3).

Conclusion: We found no differences in outcomes between cases where a CAA provided care compared to a NA. Crucially, the estimated differences between CAA and NA care, as well as the upper limits of our confidence intervals, suggest effects that are small in magnitude and of little practical value. Thus, our results are more likely to reflect a precise estimate of no effect, as opposed to a lack of statistical power. These results suggest that expanding the number of states where CAAs can practice is unlikely to be associated with worse patient outcomes.

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Figure 1 : Unadjusted and Adjusted Inpatient Mortality, Stratified by Anesthesiologist Assistant Utilization

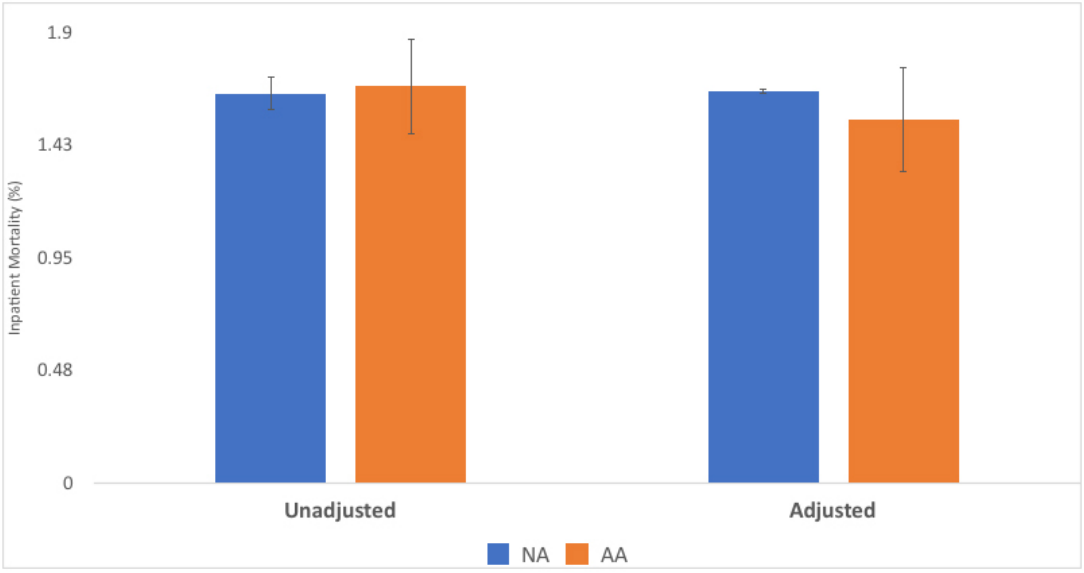

Figure 1 presents unadjusted and adjusted inpatient mortality rates, stratified by whether the patient received care from an anesthesiologist assistant (AA) or nurse anesthetist (NA). "Adjusted" refers to analyses that adjust for differences in surgery types, the patient characteristics listed in Table 1, and hospital characteristics, using the instrumental variables analysis described in the methods section. 95% confidence intervals are shown in parentheses and were calculated using standard errors that were clustered at the hospital level.

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EEP 24 (2090)

Discrepancies Between Data from an Anesthesia Information Management System and Manual Case-Logging: An Enduring Threat to Data Quality and Resident Experience

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Introduction: US anesthesiology residents are required to self-report their training experiences to the Accreditation Council for Graduate Medical Education (ACGME)1 via an online portal. ACGME case log data is used in assessing residents' procedural competencies, which informs operating room assignments.2 However, a recent study concluded >50% of residents over or under reported their total cases by at least 5%, and case details were similarly subject to misreporting.3 In light of these potential shortcomings, the reliability of ACGME data as a measure of procedural experience has been questioned.4 The aim of the present study was to replicate and extend on these prior findings.

Methods: We compared 2014-2015 ACGME case log data to AIMS data, treating AIMS as the reference standard. In accordance with current ACGME guidelines,5 only one resident was given credit for each case, which in our model was assumed to be the resident starting the case. Paper records account for less than 1% of our practice, and were excluded from analysis. A one-sample sign test to assess if the median discrepancies in resident case volume, days between procedure and submission to ACGME, reported ASA status, and reported age values significantly differed from 0. Unless otherwise indicated, all tests were two-sided with significance evaluated at the 0.05 alpha level.

Results: From 2014-2015, 81 residents completed a total of 24,276 cases, with 21,086 cases submitted to ACGME. Nearly two-thirds of residents (58%) underreported case volume by at least 5%, and another 26% overreported by at least 5%. For the 81 residents, the median value of case discrepancies between AIMS and ACGME was a surplus of 27 cases in AIMS [IQR: -11 to 91], and the median absolute deviation was 50 cases. The median difference in the number of days between the procedure and case logging was 9 days [IQR: 2 to 88]; both significantly differed from 0 ($p < 0.01$; the latter test was one-sided). Only 6% and 1% of residents had discordant median values of ASA status and age, respectively; the overall median discrepancies did not significantly differ from 0 ($p = 0.06$ and $p = 1.0$, respectively).

Conclusion: We identified significant, heterogeneous discrepancy between ACGME case logs and reference AIMS data, in a sample substantially larger than previously reported. Although no inference can be drawn on causality, recall bias, satisficing, and misinterpretation of ACGME reporting guidelines represent potential sources of error. Continued misreporting in ACGME case logs underscores the need for alternate methods with higher fidelity. The integration of existing AIMS technology can be leveraged to increase case log accuracy and allow for improved resident assessment.

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NR 25 (1965)
Incidence, Mechanisms, and Hemodynamic Implications of Systolic Dysfunction Following Traumatic Brain Injury: A Cohort Study

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Introduction: Traumatic brain injury (TBI) is a major public health problem±. While systolic cardiac dysfunction after subarachnoid hemorrhage has been observed [(3)], the effects of TBI on systolic function are not known. Furthermore, the hemodynamic implications and underlying mechanisms of TBI-induced systolic dysfunction have not been evaluated [(4)]. Our study's aims were to: 1.) Determine the incidence and longitudinal trajectory of systolic dysfunction, 2.) Evaluate the relationship between early hemodynamics and systolic dysfunction, and 3.) Examine the association between the early systemic inflammatory response syndrome (SIRS) and systolic dysfunction following moderate-severe TBI.

Methods: We conducted a prospective cohort study among isolated TBI patients under 65 years old, without cardiac comorbidities. Transthoracic echocardiography was performed within the first day, at 3 days, and at 7 days following injury in 32 patients with moderate-severe TBI and within the first day following injury in 32 patients with mild TBI (control group). Hemodynamic parameters, clinical systemic inflammatory response syndrome (SIRS) parameters (leukocyte count, temperature, respiratory rate, and heart rate), and confounding clinical variables (sedatives, fluid balance, vasopressors, osmotherapy, etc €¦) were collected. Systolic dysfunction was defined as a fractional shortening < 25%, and admission SIRS was defined as the presence of > 2 SIRS criteria. Descriptive statistics were used to compare demographic, clinical, and cardiac functional parameters in patients with moderate-severe TBI versus mild TBI. Among moderate-severe TBI patients, multivariable linear mixed models were used to assess the early hemodynamic profile in patients who developed systolic dysfunction; and multivariable Poisson regression models (with robust standard errors) were used to examine the association of admission SIRS with the development of systolic dysfunction.

Results: Sixty-four patients were included in the study, 32 with moderate-severe TBI and 32 with mild TBI (control group). Demographic, clinical, and echocardiographic characteristics of the cohort are summarized in Tables 1 and 2. Seven (22%) moderate-severe TBI patients, compared to 0 (0%) mild TBI patients, had systolic dysfunction within the first day after injury ($p<0.01$). In moderate-severe TBI patients with systolic dysfunction, the early adjusted hemodynamic profile involved elevated systolic blood pressure (SBP), mean arterial pressure (MAP), and heart rate (Figure 1, $p<0.01$ for all comparisons), with SBP and MAP decreasing significantly after 12 hours from admission in the group with systolic dysfunction, compared to the group without systolic dysfunction ($p<0.001$). The presence of SIRS on admission was associated with an increased risk of developing systolic dysfunction in moderate-severe TBI patients (Table 3, RR 4.01; 95% 1.16-13.79, $p = 0.03$). All patients with early systolic dysfunction recovered within the first week of hospitalization (Figure 2).

Conclusion: Systolic dysfunction can occur in previously healthy patients with moderate-severe TBI, and it is reversible over the first week of hospitalization. Patients with systolic dysfunction have greater hemodynamic instability and more SIRS criteria, suggesting an underlying mechanism mediated by catecholamine-excess and inflammation. Echocardiography may aid clinicians with hemodynamic management following TBI.

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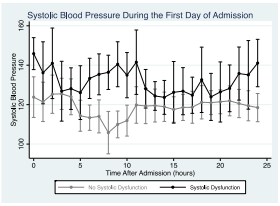
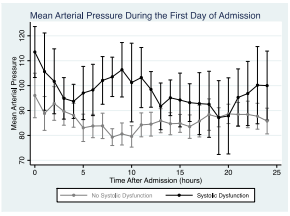
Figure 1a: Adjusted Systolic Blood Pressure Trajectory Over 24 Hours Following Admission for Moderate-Severe Traumatic Brain Injury[a,b]



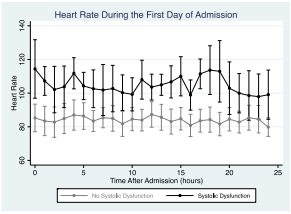
[a]In above figure, circles represent mean values of adjusted systolic blood pressure and whiskers represent the 95% confidence interval
[b]Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

Figure 1b: Adjusted Mean Arterial Pressure Trajectory Over 24 Hours Following Admission for Moderate-Severe Traumatic Brain Injury[a,b]



[a]In above figure, circles represent mean values of adjusted mean arterial pressure and whiskers represent the 95% confidence interval
[b]Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

Figure 1c: Adjusted Heart Rate Trajectory Over 24 Hours Following Admission for Moderate-Severe TBI[a,b]



[a]In above figure, circles represent mean values of adjusted heart rate and whiskers represent the 95% confidence interval

[b]Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

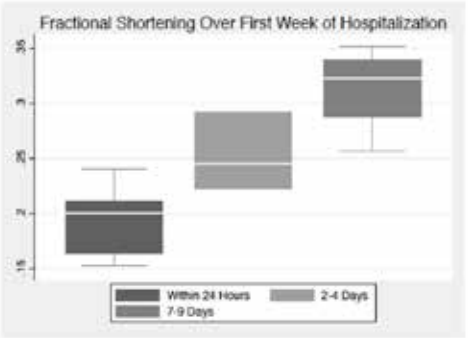


Table 1: Demographic and Clinical Characteristics in Mild and Moderate-Severe Traumatic Brain Injury Patients[a]

Variable	Mild TBI (n=32)	Moderate-Severe TBI (n=32)
Age (years)	36.2 (11.0)	36.5 (13.3)
Race		
White	18 (56%)	21 (66%)
Black	6 (19%)	3 (9%)
Hispanic	5 (16%)	3 (9%)
Asian / Pacific Islander	3 (9%)	2 (6%)
Native American	0 (0%)	3 (9%)
Male Gender	22 (69%)	27 (84%)
Medical Co-morbidities		
Pulmonary	0 (0%)	0 (0%)
Hypertension	1 (3%)	1 (3%)
Diabetes	0 (0%)	2 (6%)
Renal Disease	0 (0%)	0 (0%)
Injury Mechanism		
Fall	6 (19%)	10 (31%)
Motor vehicle crash	11 (34%)	10 (31%)
Vehicle vs. pedestrian	3 (9%)	5 (16%)
Bicycle crash	3 (9%)	1 (3%)
Gunshot to head	0 (0%)	1 (3%)
Assault	6 (19%)	3 (9%)
Other	3 (9%)	2 (6%)
Initial Head CT Findings[b]		
Epidural hemorrhage	4 (13%)	5 (16%)
Subdural hemorrhage	7 (22%)	24 (75%)
Subarachnoid hemorrhage	2 (6%)	23 (72%)
Intraparenchymal hemorrhage	4 (13%)	15 (47%)
Glasgow Coma Scale		
Admission GCS	14.8 (0.4)	5.2 (2.5)
Highest GCS (within 24 hours)	15.0 (0.2)	9.0 (3.0)
Lowest GCS (within 24 hours)	14.5 (0.8)	4.8 (2.4)
Admission Hematocrit (%)	40.6 (4.5)	38.0 (5.3)

[a]Values are mean(SD) for continuous variables and n(%) for categorical variables.
[b]Some patients had multiple head CT findings.
CT=Computed Tomography; GCS=Glasgow Coma Scale; bpm=beats per minute; MAP=mean arterial pressure

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Table 2: Early Echocardiographic Findings in Mild and Moderate-Severe Traumatic Brain Injury[a]

Cardiac Functional Parameters	Mild TBI (n=32)	Moderate-Severe TBI (n=32)	p
Systolic Function[b,c]			
Left Ventricle Area End-Diastole (cm^2)	16.15 (3.68)	18.60 (4.88)	**0.04**
Left Ventricle Area End-Systole (cm^2)	6.99 (1.93)	8.90 (3.39)	**0.01**
Fractional Area Change (cm^2)	0.57 (0.06)	0.53 (0.11)	0.10
Left Ventricle Internal Diameter End-Diastole (cm)	4.55 (0.45)	4.64 (0.61)	0.47
Left Ventricle Internal Diameter End-Systole (cm)	3.02 (0.43)	3.28 (0.60)	**0.05**
Fractional Shortening	0.34 (0.06)	0.30 (0.07)	**0.01**
Mitral Annular Septal Tissue Velocity [S'(s) (cm/s)]	8.21 (1.92)	9.49 (2.36)	**0.05**
Mitral Annular Septal Tissue Velocity [S'(s)] < 6 cm/s	3 (9%)	2 (6%)	0.42
Systolic Dysfunction (Fractional Shortening < 0.25)	**0 (0%)**	**7 (22%)**	**<0.01**
Diastolic Function[d,e]			
Mitral Inflow Peak Early Filling [E wave (cm/s)]	69.65 (12.53)	67.44 (19.64)	0.62
Mitral Inflow Peak Late Filling [A wave (cm/s)]	52.01 (14.08)	46.52 (12.83)	0.17
E-wave to A-wave Ratio	1.43 (0.42)	1.55 (0.57)	0.41
E-wave to A-wave Ratio < 1	4 (13%)	5 (16%)	0.47
E-wave to A-wave Ratio > 2	3 (9%)	5 (16%)	0.33
Mitral Inflow E-wave Deceleration Time (msec)	162.59 (39.18)	122.5 (43.51)	**<0.01**
Mitral Annular Septal Tissue Velocity [e'(s) (cm/s)]	10.28 (2.46)	9.46 (2.74)	0.28
E-wave to e'(s) Ratio	7.05 (1.85)	7.33 (2.01)	0.62
E-wave to e'(s) Ratio > 8	6 (19%)	11 (34%)	0.22
Mitral Annular Septal Tissue Velocity [e'(s)] < 8 cm/s	5 (16%)	9 (28%)	0.31

[a]Values are mean(SD) for continuous variables and n(%) for categorical variables

[b]Systolic area, diastolic area, and fractional area change from data available in 28 subjects mild TBI and 26 with moderate-severe TBI

[c]Mitral annular tissue Doppler velocities from data available in 21 subjects with mild TBI and 26 with moderate-severe TBI

Table 3. Univariate and multivariable analysis of the association between admission SIRS and individual admission SIRS criteria and systolic dysfunction in moderate-severe TBI

		Univariate		Multivariable*	
Admission variables	**n (%)**	**Relative risk (95% CI)**	**p**	**Relative risk (95% CI)**	**p**
SIRS	7 (22%)	4.76 (1.35-16.79)	**0.02**	4.01 (1.16-13.79)	**0.03**
Body temperature < 36 or > 38ºc	7 (22%)	1.05 (0.25-4.47)	0.95	0.68 (0.20-2.32)	0.54
Heart rate > 90 beats per minute	10 (31%)	2.93 (0.79-10.96)	0.11	3.35 (0.95-11.78)	0.06
Respiratory rate > 20 per minute	2 (6%)	2.50 (0.51-12.19)	0.26	1.00 (0.28-3.63)	0.10
White blood cell count <4 or >$12x10^3$ /mm^3	18 (56%)	1.94 (0.43-8.78)	0.39	1.62 (0.45-5.86)	0.46

*The final model adjusted for age, gender and highest Glasgow Coma Scale score within 24 hours after admission

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NR 26 (2202)
A Nighttime Dexmedetomidine Bolus Promotes N3 Sleep: A Pilot Study

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Introduction: Refinements to current sedation strategies, such as the neurophysiological approximation of sleep, may fundamentally benefit the brain health of patients. The electroencephalogram (EEG) spindle (12-16 Hz) oscillations observed during an intravenous infusion of dexmedetomidine shares features with non-rapid eye movement (NREM) stage 2 (N2) sleep spindles [1]. This suggests that dexmedetomidine engages endogenous N2 sleep mechanisms. This close approximation to normal physiology been suggested to explain, in part, the delirium sparing benefits of dexmedetomidine [2]. NREM stage 3 (N3) sleep is associated with improved cognition and synaptic plasticity [3]. However, it is unclear whether dexmedetomidine may be administered to promote N3 sleep.

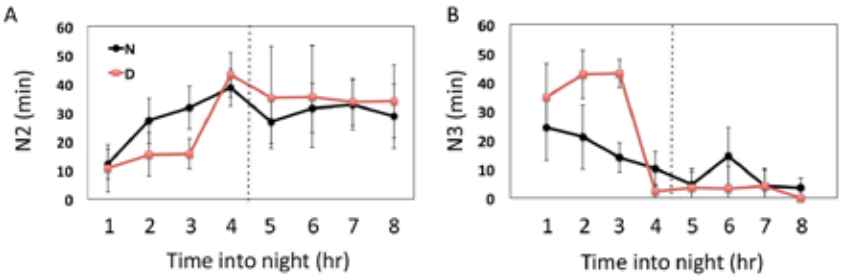

Figure 1. Dexmedetomidine increases N3 sleep during the first half of the night. Stage durations (minutes) versus time into study night, from 1st to 8th hours. Results represent mean ± standard deviation. N = natural sleep (n = 10); D = dexmedetomidine-induced sleep (n = 7). Horizontal dashed line divides first half (0-4h) and second half (4-8h) of night. N2 = non-rapid eye movement stage 2; N3 = non-rapid eye movement stage 2; min = minutes; hr = hour.

Methods: We performed a prospective, single-site, three-arm, randomized-controlled, crossover polysomnography pilot study (n = 10) comparing natural, intravenous dexmedetomidine- (1-Î¼g/kg over 10 minutes [n = 7] or 0.5-Î¼g/kg over 10 minutes [n = 3]), and zolpidem-induced (Ambien CR) sleep in healthy volunteers. Lights out occurred at 22:00 hours and volunteers were awoken approximately 8 hours later. We compared the technician scored sleep stages during the first half (0-4 hours) and second half (4-8 hours) of the night for the dexmedetomidine 1-Î¼g/kg group and the natural sleep group. We also computed and compared multitaper spectral estimates from a 1-minute period (midpoint of sleep stage) of N2 (first and second half) and N3 sleep from F3-F4 and O1-O2 bipolar electrodes.

Results: A single nighttime bolus of dexmedetomidine preserved normal sleep architecture but biased sleep architecture toward N3 sleep during the first half of the night (123 vs 69.6 minutes; t-test, Bonferroni-adjusted p = 0.0009, Fig. 1B and Table 1), but not in the second half (9.5 vs. 26.5 minutes; t-test, Bonferroni-adjusted p = 0.37, Fig. 1B and Table 1). Data from the zolpidem-induced sleep night, which was similar to the natural sleep night, is not shown. During the first N2, dexmedetomidine-induced sleep exhibited increased power predominantly in the sleep spindle band (confidence interval of difference in bootstrap means; 9.4–15.6 Hz, Fig. 3A). This increase in spindle power was not sustained during the second half of the night (Fig. 3B). Dexmedetomidine-induced N3 sleep oscillations were similar to natural N3 sleep oscillations (Fig. 3C).

Conclusion: We conclude that dexmedetomidine may be administered in bolus form to promote N3 sleep. Furthermore, increased spindle power during dexmedetomidine-induced N2 sleep suggests that this oscillatory dynamic reflects increasing thalamic and cortical hyperpolarization that favors N3 sleep.

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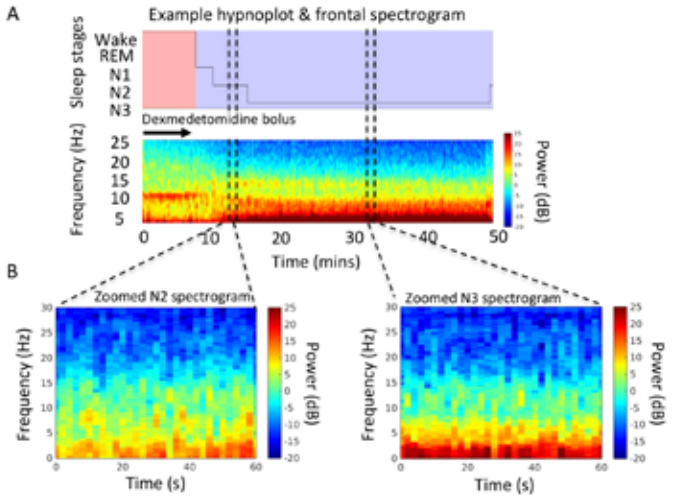

Figure 2. Illustrative hypnograms and spectrogram showing that dexmedetmodine preserves NREM sleep architecture. Fig. 2A represents first hour hypnogram showing scored sleep stages (top) with corresponding frontal channel multitaper spectrogram (bottom). Fig. 2B represents zoomed N2 (left) and N3 (right) spectrograms in the middle 60 seconds of each corresponding stag. NREM = non-rapid eye movement, REM = rapid eye movement, N1-3 = stages 1-3 of NREM sleep, mins = minutes, Hz = Hertz, s = seconds, dB = decibels.

Table 1. Dexmedetomidine-induced sleep compared to Natural sleep stage durations for first and second halves of the night

	First half (0-4h)							Second half (4-8h)						
	N	D		uncorrected 95% CI				N	D		uncorrected 95% CI			
Sleep Stage	n = 10	n = 7	Diff	Lower	Upper	*p*-value	*p*-value*	n = 10	n = 7	Diff	Lower	Upper	*p*-value	*p*-value*
N1	12.8	7.1	5.7	-1.5	12.7	0.1	N/A	15.4	16.4	-1.0	-17.8	10.6	0.9	N/A
N2	110.0	85.1	24.9	5.6	44.5	0.02	0.12	120.0	138.7	-18.7	-52.8	6.5	0.2	N/A
N3	69.6	123.0	-53.4	-75.4	-31.4	0.0001	**0.0009***	26.5	9.2	17.3	0.3	34.3	0.047	0.37
REM	15.7	0.0	15.7	3.9	27.6	0.01	0.1	57.8	37.6	20.2	11.1	38.2	0.006	**0.04***

First (0-4 hours) and second (4-8 hours) halves of study night. Mean sleep stage durations (minutes) for Natural (N) and Dexmedetomidine (D) patients with mean difference (Diff) and uncorrected 95% confidence intervals (CI) of the mean difference using the Independent Samples T-test. Bonferroni-corrected *p*-values less than 0.05 marked with *.

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NR 27 (2283)
Isoflurane Alters Neural Progenitor Cell Development within Hippocampus

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Introduction: Epidemiologic and pre-clinical animal studies raise concern that early exposure to anesthesia may have a lasting impact on neural development and cognition, particularly after repeated and/or prolonged anesthetic exposures. These data recently led the FDA to issue a safety announcement on the use of anesthetics in young children and add warnings to the labels of all general anesthetic drugs. The Pediatric Anesthesia NeuroDevelopmental Assessment (PANDA) study published in 2016 found that a single, brief general anesthetic exposure had no lasting effect on cognition in relatively healthy children[1]. While this study was reassuring, it did not evaluate the effects of prolonged or repeated anesthetic exposures, or assess more vulnerable patient populations. Further, it may not have been sufficiently powered to detect differences in secondary neurodevelopmental outcomes. In this study, we are investigating the effects of neonatal isoflurane exposure on neural progenitor cell (NPC) development within rodent hippocampus and the mechanisms underlying pediatric anesthetic neurotoxicity.

Methods: Post-natal day 7 (PND 7) mice were exposed to oxygen or approximately 1 MAC isoflurane for 4h. Hippocampal NPC proliferation and differentiation were assessed by immunostaining and confocal imaging at two weeks and six to eight weeks.

Results: Exposure of PND 7 mice to isoflurane alters hippocampal NPC development by reducing and/or delaying neurogenesis, as seen by a reduction in several neural markers at two weeks and a persistence of immature neuronal marker doublecortin (DCx) at six-eight weeks (versus control animals). There appears to be no compensatory increase in the number of NPCs choosing an alternative, glial fate.

Conclusion: Our data support and extend prior work suggesting that isoflurane impairs hippocampal neural development and the architecture of the developing brain, both acutely and chronically. Additional tests are underway to examine the impact of anesthetics directly on NPCs and the role of NMDA receptor-PSD95 signaling in this process.

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NR 28 (2189)
Is the Integrated Stress Response (ISR) Involved in the Development of Postoperative Cognitive Decline (PCD) in a Mouse Model?

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Introduction: The elderly's ability to stay mentally sharpis threatened in the surgical setting as both postoperative delirium and postoperative cognitive dysfunction (hereafter referred to as postoperative cognitive decline [PCD]), may complicate a surgical intervention. Among plausible biological explanations for PCD is the engagement of the innate immune response by the alarmin, high mobility group box protein 1 (HMGB1), released by aseptic surgical trauma, that initiates a peripheral- and subsequently a neuro-inflammatory response [(1)];thus HMGB1 can be used as a surrogate for surgery. Inflammation in the hippocampus is capable of interfering with synaptic plasticity that is required for learning and memory [(2)]. The integrated stress response (ISR) is a cellular adaptation to protein unfolding in the secretory pathway and leads to the phosphorylation of the Î±-subunit of the eukaryotic initiation factor 2 (eIF2Î±). High levels of p-eIF2Î± inhibit protein synthesis, possibly including IÎºB, the negative regulator that serves to retain NFÎºB in the cytosol. In its non-repressed form NFÎºB translocates into the nucleus where it upregulates genes for the pro-inflammatory cytokines of the innate immune response required for cognitive decline [(3)]. We wondered whether ISR is directly involved in PCD and whether targeting the ISR with a potent ISRInhiBitor (ISRIB) can block the development of PCD [(4)].

Methods: Following IRB approval, we investigated whether the ISR can be induced by either surgery or HMGB1 by assaying downstream markers of p-eIF2Î±. Next we assessed the effect of preoperatively, or pre-HMGB1, administered ISRIB on inflammation (ELISA, qPCR) and cognitive function (trace-fear conditioning [TFC]) in a mouse (C57BL/6) model; surgery involved aseptic trauma to the tibia with intramedullary fixation.

We next studied the effect of ISRIB on HMGB1-induced activation of NFïµ«B, and release of proinflammatory cytokines in a murine macrophage cell line (RAW 264.7).

Results: In peripheral blood mononuclear cells both surgery and HMGB1 induced ISR that was blocked by pre-treatment with ISRIB (Figure 1). Both surgery and HMGB1 induced inflammation and cognitive decline; again these changes were blocked by pre-treatment, but not post-treatment (DNS), with ISRIB (Figure 2). HMGB1-induced activation of NFïµ«B and release of pro-inflammatory cytokines in RAW cells was blocked by ISRIB (Figure 3).

Conclusion: These data indicate that the ISR is pivotally involved in PCD. Since ISRIB does not affect trauma-induced release of HMGB1 and can attenuate activation of NFÎºB through more than one pattern recognition receptor (DNS), we posit that the ISR is sited in circulating CCR2-expressing bone marrow-derived monocytes where it derepresses NFÎºB. Possible clinical utility of ISRIB for PCD and other inflammation-based postoperative complications is likely to be confined to pre-emptive strategies for pre-operatively identified vulnerable surgical patients.

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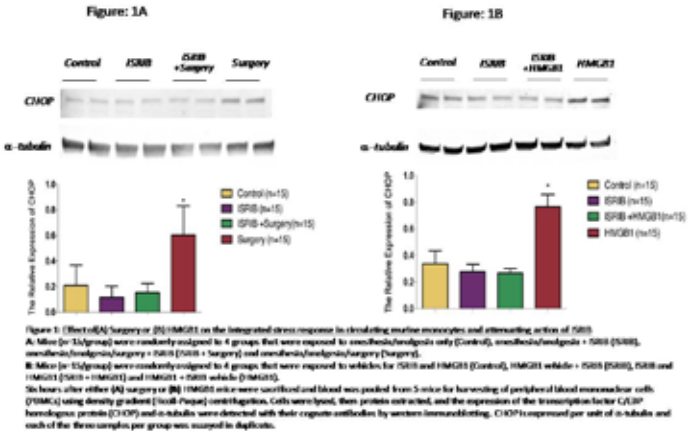

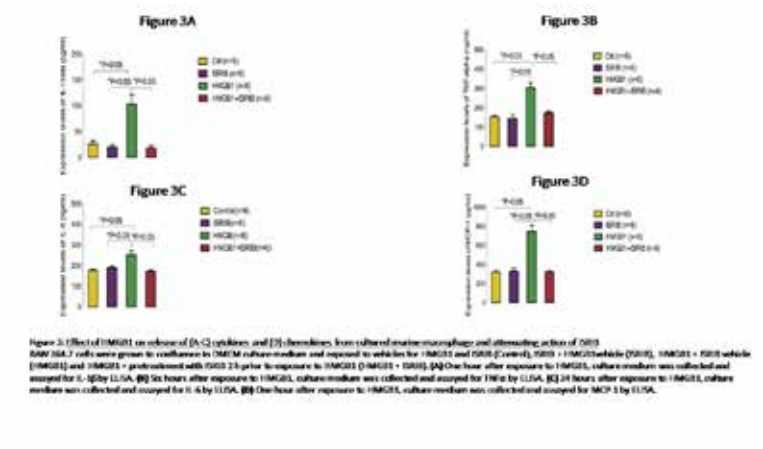

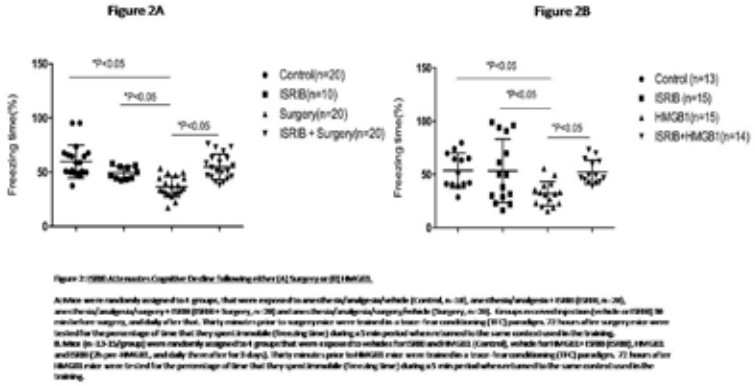

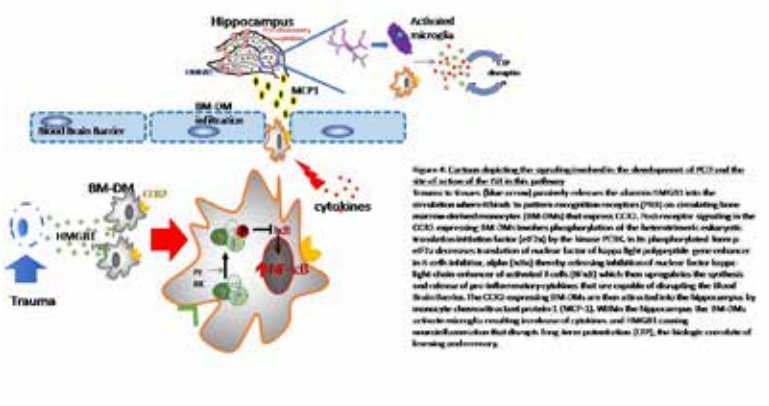

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NR 29 (2234)
Volatile Anesthetics Inhibit Neuronal Regeneration in C. Elegans

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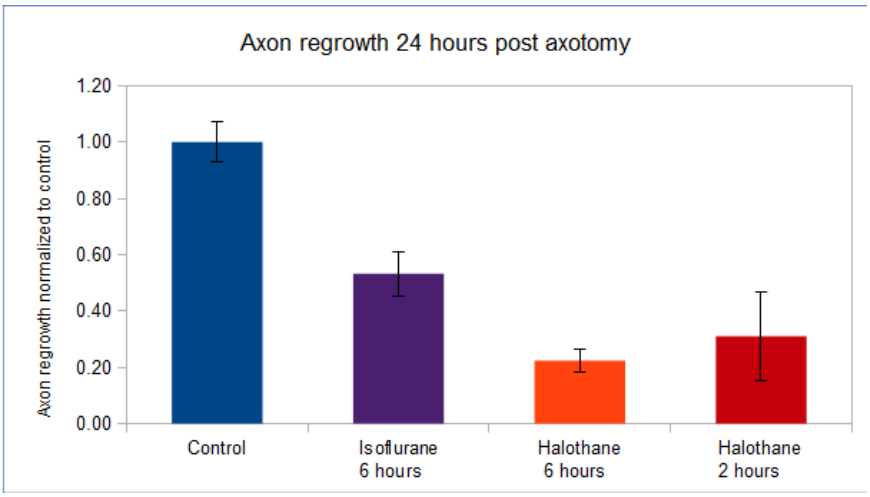
Introduction: Axonal regeneration is an evolutionarily conserved mechanism. Details of the processes underlying repair and regeneration are not well defined and still being elucidated in model organisms such as the nematode, C. elegans(1). Immediate surgical repair of injured peripheral nerves increases the likelihood of functional recovery in humans(2). Surgical repair of course necessitates exposure to anesthetics. While the mechanism of action of volatile anesthetics remains undetermined, they have been shown to be neurotoxic in developing neurons. It is unclear what effects anesthetics may have on the ability of an injured peripheral neuron to regenerate. Here we examined the effects of halothane and isoflurane on injured sensory neurons in C. elegans.



Methods: Laser axotomy of a mechanosensory neuron (Posterior Lateral Microtubule or PLM neuron) was performed on mechanically immobilized C. elegans using a femtosecond laser as described previously(3). After axotomy, worms were exposed to immobilizing concentrations(4) of halothane and isoflurane for 2 or 6 hours in a sealed chamber (anesthetic concentrations were determined at beginning and end of exposure)(5). Axon regrowth was measured 24 hours post axotomy.

Results: PLM axon regrowth after anesthetic exposure was normalized against control animals axotomized on the same day. Worms immobilized under halothane showed reduced axon regrowth by 69% (p=0.009) and 78% (p=0.0001) with 2 and 6 hour exposure respectively. The difference between the two exposure groups is not statistically significant. Isoflurane exposure for 6 hours reduced axon regrowth by 47% (p=0.002). Preliminary data from 2 hour exposure to isoflurane shows a similar reduction.

Conclusion: Axon regrowth was significantly limited by both halothane and isoflurane exposure after axotomy. Interestingly, longer anesthetic exposure did not reduce axon regrowth any further. However, halothane inhibited regrowth much more severely than isoflurane. These data indicate not only that volatile anesthetics affect axon regrowth, but that the choice of anesthetic could make a significant difference. Ongoing experiments include examination of axon regrowth with sevoflurane and with different anesthetic doses and defining potential mechanisms activated to determine potential therapeutic targets.

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NR 30 (2183)
Dbh -/- Mice Show Hypersensitivity to Isoflurane in Both Spontaneous Motor Activity and Electroencephalography

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Introduction: Previous behavioral studies have shown that mice lacking adrenergic ligands due to a genetic knockout of dopamine-Î²-hydroxylase (dbh -/-) are hypersensitive on induction to volatile anesthetics and dexmedetomidine, as measured by loss of righting reflex, and emerge at disproportionately lower concentrations of inhaled anesthetic than littermate controls.(1) Here, we examine stepwise anesthetic induction and emergence in dbh -/- mice and heterozygous littermate controls while monitoring spontaneous motor activity and continuous electroencephalography (EEG), to augment previously described behavioral evoked vestibular response of the righting reflex.

Methods: Mice: Adult female dbh -/- mice (n=6) and littermate homozygous and heterozygous controls (n=8) aged 10-14 months were chronically implanted with 26 extradural electrodes, along with 2 cervical and 2 thoracic silver EMG electrodes (fig 1). Exposure: Mice were placed within an 8L airtight, temperature-controlled chamber. Isoflurane was ramped from 0.0% to 1.0% and back to 0.0% in 0.2% increments, with 50 minutes per step under continuous EEG/EMG acquisition via 32-channel headstages (Intan) and open-ephys hardware and software. Motor Activity and EEG Analysis: All analyses were conducted on data from minutes 10-40 of an anesthetic step exposure, ensuring 5 volume turnovers and steady-state inhalation. After manual artifact rejection, the root-mean-square of non-overlapping 1 minute bins of EMG signal were normalized to baseline EMG activity. A mean of the fast Fourier transform of EEG data was similarly normalized to baseline EEG activity.

Results: Dbh -/- mice showed a loss of spontaneous activity at significantly lower concentrations than littermate heterozygote or wild-type controls, as well as delayed recovery ($p < 0.0001$) (fig 2, emergence arm shaded yellow). These behavioral patterns were reflected in the EEG spectra, where there were significant differences on induction and emergence arms. (fig 3, 4).

Conclusion: Dbh -/- mice show hypersensitivity to isoflurane not only through the previously described evoked vestibular response that is the righting reflex test, but also exhibit hypersensitivity in spontaneous movement, as measured by motor activity. These movement/motor endpoints reflect true hypersensitivity, rather than a primary motor phenomenon, as dbh -/- show increased delta power in their EEG spectrum, both absolutely and when normalized to their baseline power, at concentrations where they appear behaviorally less responsive than littermate controls.

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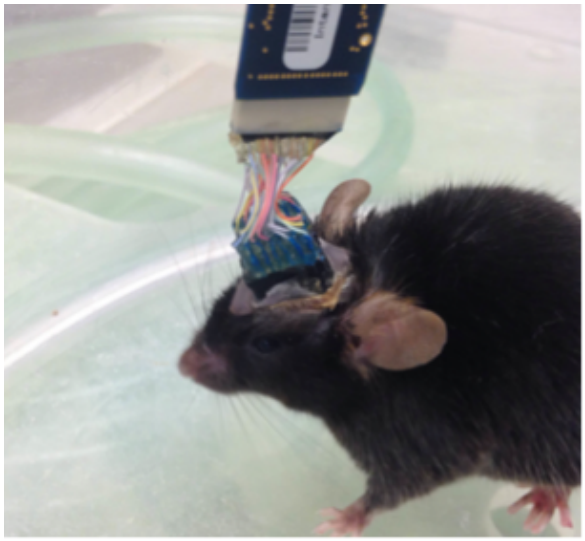

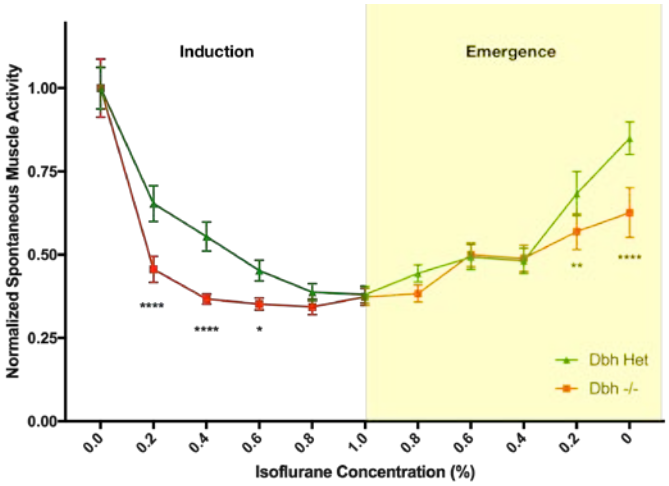

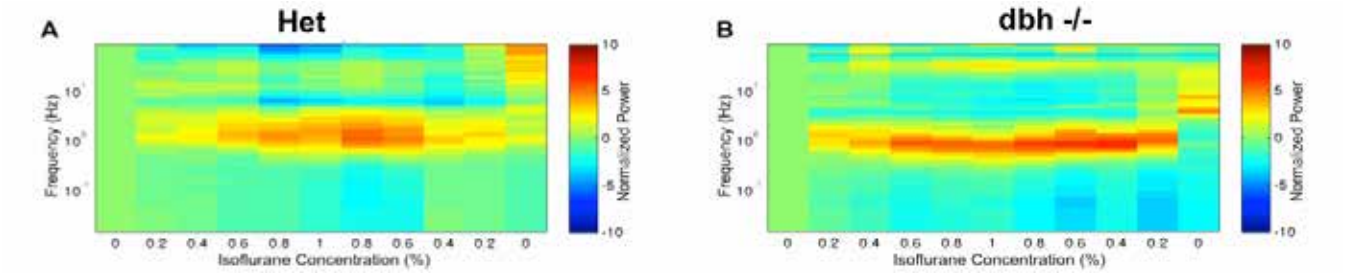

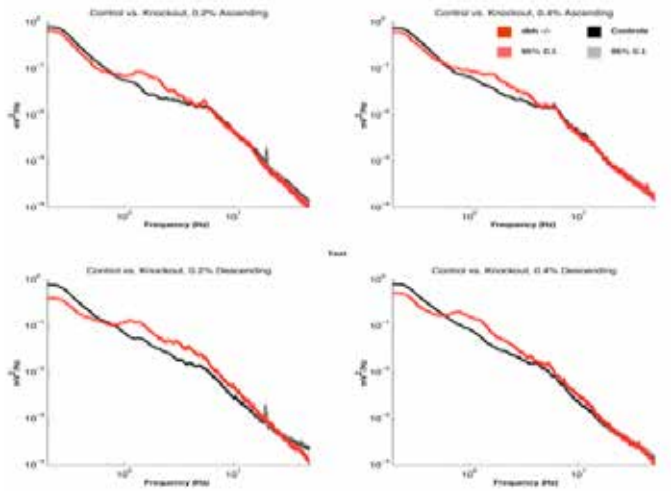

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NR 31 (1922)
Atg5 Plays Important Role on Propofol Regulation of Autophagy and Cell Proliferation or Death

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Introduction: Propofol has been demonstrated to affect autophagy and cell survival through unclear mechanisms[1,2]. Atg 5 is one of the key proteins to regulate autophagy but its role in regards to the propofol effects on autophagy is unknown. Using a cell line with total knock out of Atg 5 (ATG5-/-), we studied the role of Atg5 on the effects of propofol on autophagy and associated cell proliferation and survival.

Methods: ATG5-/- and WT fibroblasts were cultured and exposed to propofol at various concentrations and durations. Cell viability and toxicity were measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction and lactate dehydrogenase (LDH) release assays. Cell proliferation was determined by cell number counts with trypan blue exclusion and Bromodeoxyuridine (Brdu) incorporation. Autophagy activity was determined by measuring LC3 II protein levels using Western Blot. The autophagy flux inhibitor Bafilamycin was used to differentiate the induction of autophagy from the impairment of autophagy flux. The cytosolic calcium concentrations ([Ca2+] c were measured using dye Fura-2, in the presence or absence of the selective antagonist of InsP3 receptor (xestospongin C) or ryanodine receptor (dantrolene).

Results: Propofol dose-, -time and Atg5-dependently affected cell proliferation and death. Propofol up to concentrations of 200 μM for 6 or 12 hours did not affect cell viability in either type of cells. However, a 24 hour treatment of propofol at clinically relevant concentrations (10 μM) significantly increased MTT. Whereas high pharmacological concentrations of propofol (200 μM) decreased MTT in the ATG5-/-but not WT cells. Propofol at high pharmacological concentrations (100 and 200 μM) induced cell death as determined by LDH assay more significantly in ATG5-/- cells. Furthermore, propofol at 10 μM significantly increased proliferation determined by Brdu and trypan blue exclusion assays, while propofol at 200 μM significantly decreased cell proliferation only in ATG5-/-cells. Propofol dose-dependently increased the autophagy biomarker LC3 II when potentiated by bafilamycin, in WT but not ATG5-/- cells. Propofol increased [Ca2+]c in both types of cells, which could be inhibited by dantrolene and Xc.

Conclusion: Our results suggest that Atg5 plays a crucial role in propofol regulation of autophagy and associated cell survival and proliferation, which may be associated to its ability to cause calcium release from the endoplasmic reticulum via InsP3 and or ryanodine receptors. Propofol induced cell death only at extremely high pharmacological concentrations, and was associated with autophagy functional impairment.

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NR 32 (1923)

General Anesthetics Induced Neurotoxicity by Impairment of Lysosome and Autophagy Function via Intracellular Calcium Dysregulation in Alzheimer's Disease

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Introduction: General anesthetics (GAs) have been shown to worsen pathology and cognitive dysfunction in various types of Alzheimer's disease (AD) animal models[1], but the mechanisms are still unclear. Our previous works suggested that isoflurane causes neurotoxicity in PC12 cells with knocked-in Familiar Alzheimer Disease (FAD) presenilin 1 mutation through abnormal calcium release from the endoplasmic reticulum (ER)[2,3]. We hypothesize in this study, that the general anesthetics propofol and isoflurane, induce cell death through impairment of lysosome and autophagy function via disruption of intracellular calcium homeostasis in Alzheimer's disease.

Methods: PC12 cells transfected with wild type (WT) or mutated presenilin-1 (L286V) were treated with different concentrations of propofol for 6 or 12 hr or 2.4% isoflurane for 24 hr. The effects of propofol or isoflurane on cell survival, cytosolic calcium concentration ([Ca2+]c) and autophagy induction and flux were investigated. A stable and sensitive cell counting kit-8 were employed to measure cell viability. Changes with [Ca2+]c were determined by Fura-2 AM dye. We evaluated [Ca2+]c after exposing both cells to propofol in the presence or absence of the ryanodine receptor (RYR) antagonist (dantrolene), the inositol 1,4,5-trisphosphate (InsP3) receptor antagonist, (xestospongin C, Xc), and intracellular calcium chelator (BAPTA-AM). We used LysoTracker probes to determine the effects of propofol on lysosome acidification in WT and L286V cells. We examined the effects of isoflurane on autophagy induction and flux using a mRFP-GFP-LC3 construct and transfection procedure in the presence or absence of Xc.

Results: Propofol dose- and time- dependently induced cytotoxicity in both L286V and WT PC12 cells, while bafilomycin, an inhibitor of autophagy flux, significantly aggravated the propofol-mediated cell death only in L286V but not WT cells. BAPTA-AM, dantrolene and Xc significantly inhibited propofol-induced elevation of [Ca2+]c and cell damage. However, combined use of dantrolene and Xc, paradoxically and abnormally increased [Ca2+]c by calcium influx from the extracellular space and potentiated propofol induced cell damage. Compared to WT cells, L286V cells demonstrated significantly impaired lysosome acidification. Isoflurane significantly impaired the turnover of autolysosome in an InsP3R activity dependent manner, in L286V but not WT PC12 cells.

Conclusion: Our results show that propofol and isoflurane induce neurotoxicity in an FAD cell model with PS1 mutation through autophagy flux or functional impairment via excessive calcium release from the ER through over-activation of RYR or InsP3R, and associated with lysosome and autophagsome dysfunction.

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NR 33 (2140)
The Association Between Hospitalization, Surgery, and Incident Dementia in Older Adults with Mild Cognitive Impairment

Youn-Hoa Jung, MD[1], Gayane Yenokyan, PhD[2]; Alden Gross, PhD[2]; Steven DeKosky, MD[3]; Jeff Williamson, MD[4]; Michelle Carlson, PhD[2]; Charles Brown, MD[1]

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Introduction: Hospitalization and/or exposure to surgery/anesthesia may increase the risk of dementia. Because patients with mild cognitive impairment (MCI) are at high risk of dementia, it is critical to characterize how hospitalization and surgery/anesthesia affect these patients. We conducted a secondary analysis of data from the Ginkgo Evaluation in Memory (GEM) study[1] to determine if hospitalization, and in particular surgery/anesthesia, would be associated with incident dementia in patients with MCI.

Methods: The GEM study was a randomized, controlled trial of ginkgo biloba in community volunteers that found no effect on incident dementia risk. Significant inclusion criteria were age >75 years old without dementia. MCI was diagnosed at baseline in 482 participants based on Clinical Dementia Rating score of 0.5 and impairment on neuropsychological testing. Participants were assessed every 6 months over a median of 6.1 years for incident dementia by an expert committee using a neuropsychological battery and clinical evaluation. Hospitalization and ICD-9 codes were recorded prospectively. Chi-squared tests and Cox proportional hazard models were used to examine the association of hospitalization and/or surgery with incident dementia in three models: (1) unadjusted, (2) adjusted for age, and (3) adjusted for age, sex, race, education, and cardiovascular risk factors (fully adjusted).

Results: Of 482 participants with MCI, 187 (39%) were never hospitalized, 95 (20%) were hospitalized without surgery, and 200 (41%) were hospitalized with surgery. Data on the final visit were missing in 12 instances, so the analytic sample consisted of 470 participants. As shown in Table 1, age was similar by hospitalization status, but those hospitalized were more often male, Caucasian, and had more comorbidities. The incidence of dementia was 45.9% (83/181) among non-hospitalized patients, 43% (40/93) among patients hospitalized without surgery, and 38.8% (76/196) among patients hospitalized with surgery. Taking into account time of hospitalization, the incidence rate of dementia after first hospitalization was 0.164/year, compared to 0.064/year in the never hospitalized group. Using Cox proportional hazards models accounting for timing of hospitalization, the hazard of dementia was significantly higher after hospitalization compared with non-hospitalization (Hazard Ratio [HR]=1.81, 95% CI 1.35-2.41). Results were similar when adjusted for age (HR 1.76, 95% CI 1.32-2.34) and in fully adjusted models (HR 1.79, 95% CI 1.33-2.40). In Cox models examining the effect of surgery/anesthesia, the hazard ratio for dementia in those after surgery/anesthesia compared to participants who never had surgery/anesthesia was 1.54 (95% CI 1.15-2.074). Results were similar when adjusted for age (HR 1.47, 95% CI 1.09-1.98) and in fully-adjusted models (HR 1.48, 95% CI 1.1-2.0).

Conclusion: These secondary results suggest that hospitalization and surgery may be associated with an increased hazard of dementia in participants with MCI at baseline.

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Table 1: Comparison of Patient Characteristics

	No hospitalization (n=187)	Hospitalization without surgery (n=95)	Hospitalization with surgery (n=200)
Age (years)	79.5 (3.6)	79.1 (3.9)	79.8 (3.7)
Male, n (%)	84 (44.9%)	52 (54.7%)	107 (53.5)
Caucasian, n (%)	157 (84%)	89 (93.7%)	183 (91.5%)
Hypertension, n (%)	78 (42.4%)	42 (46.2%)	87 (44.4%)
Stroke, n (%)	4 (2.2%)	5 (5.4%)	14 (7.2%)
Diabetes, n (%)	13 (7.1%)	11 (12%)	27 (13.6%)
Composite cardiac risk score[1], n (%)	119 (63.6%)	73 (76.8%)	139 (69.5%)

[1] Cardiac risk is defined as medical history of any of the following factors: hypertension, heart attack, angina, CABG, balloon angioplasty, pacemaker, defibrillator, any other heart surgery, any heart/circulatory problem, heart failure, atrial fibrillation (history and current), stroke, TIA and diabetes mellitus

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NR 34 (1996)
Reconstructing Consciousness and Cognition: Human Neurobehavioral Recovery Following Exposure to Isoflurane

Max Kelz, MD, PhD[1], Michael S. Avidan, MBBCh[2]; George Mashour, MD, PhD[3]; Andrew McKinstry-Wu, MD[1]; Ben Palanca, MD, PhD[2]; Stefanie Blain-Moraes, PhD[4]; Mathias Basner, MD, PhD[1]

[1]University of Pennsylvania, Philadelphia, Pennsylvania, [2]Washington University School of Medicine, St. Louis, Missouri, [3]University of Michigan, Ann Arbor, Michigan, [4]McGill, Montreal, Quebec

Introduction: A major focus for research both in neuroscience and anesthesiology is understanding the mechanisms enabling human consciousness and cognition. One approach to understanding these complex neural processes is to characterize how they emerge or are reconstituted after states of unconsciousness. Recovery from sleep or coma offer potential experimental opportunities. However, reversal of coma is unpredictable and slow while reversal of sleep may be too rapid. By contrast, emergence from general anesthesia provides a reproducible model of state transitions from unconsciousness to consciousness and higher cognition. We tested the hypothesis that emergence from anesthesia is a process that evolves over time, beginning.

Methods: After IRB approval, sixty healthy ASA I or II adults were recruited across three institutions. Half were randomized to serve as awake controls, while the other half underwent induction of anesthesia with propofol followed by maintenance of anesthesia with 1.3 age-adjusted MAC of isoflurane for three hours. All participants were fit with 32- or 128-channel EEG head caps, and underwent serial neurobehavioral testing of attention, memory, sensory-motor function, abstract reasoning, and cognitive processing speed. Tests were administered at baseline, immediately before induction of anesthesia, and every 30 minutes for the three hours following emergence. Non-anesthetized, awake volunteers also had serial cognitive testing at similar time points to control for learning effects of repeated testing and for potential circadian confounders.

Results: The mean (SD) time required until subjects could follow the pre-specified command was 39.0 (14.5) minutes after discontinuing isoflurane. Recovery of each neurocognitive domain was well-fit by a single rate exponential with r^2 values ranging from 0.88 to 0.999. Abstract reasoning, a measure of higher executive function, was the fastest domain to recover, while sustained attention was the slowest.

Conclusion: We identified dissociable trajectories of neurocognitive recovery after a clinically-relevant anesthetic in healthy volunteers. Contrary to our hypothesis and expectations, abstract cognitive function recovered faster than attentional or mnemonic processes.

References:

N/A

SM 35 (1838)
A Novel Role for TIMELESS in Mammalian Circadian Clocks using a Murine Model of Human Familial Advanced Sleep Phase

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Introduction: The circadian protein TIMELESS (TIM) has an established role as a light-sensitive negative regulator of the core circadian clock in drosophila [1,2]. The regulatory role that TIM plays in mammal circadian clocks has not been established and is thought to be a vestigial clock protein [3]. Previous studies in mice show that TIM levels do not oscillate in the SCN, questioning its relevance in mammalian circadian rhythm maintenance [4]. Based on a mutation in kindred with Familial Advanced Phase (FASP), we demonstrate the role of mutant TIM in mammals as a destabilizer of CRY2, a key negative repressor of the mammalian core circadian clock.

Methods: Subjects in a family with FASP were rigorously phenotyped and DNA from peripheral blood leukocytes from affected and non-affected individuals was isolated for whole exome sequencing. Using standard sifting and prioritization strategies, a novel SNP in the timeless gene was identified that co-segregated with the phenotype. Mutant and WT proteins were over-expressed in U2OS cells with a BMAL:LUC fusion construct to assay period length and repressor activity using a lumicycler. Localization of mutant and WT TIM was assayed using nuclear-cytoplasmic fractionation, and confocal microscopy in HEK cells. Reciprocal co-immunoprecipitation was performed to identify binding partners and binding affinity of TIM in vitro. The stability of TIM WT and mutant proteins was assayed by cyclohexamide pulse whole cell lysate and by lumicycler experiments. CRISPR mutant and WT (mutant negative littermates) mice were assayed for endogenous period length, phase responsiveness, and advanced phase in singly housed wheel-running cages and data was analyzed using Clock-Lab software.

Results: Candidate genes from the FASP family were prioritized and sifted to identify a mutation in the in a nuclear localization sequence of the timeless gene. Examining the endogenous period length in transfected U2OS cells stably expressing BMAL:LUC revealed a 30 minute reduction in endogenous period length with mutant TIM compared to WT control. TIM mutant protein has a dose-dependent reduction of repressor activity of the core circadian clock as assayed in a lumicycler. Mutant TIM has impaired nuclear localization in nuclear-cytoplasmic lysates from transfected HEK-293 cells and by confocal microscopy using TIM-YFP tagged fusion proteins. Reciprocal co-immunoprecipitation of TIM-GFP and CRY2-FLAG or PER2-FLAG proteins indicate that TIM binds CRY2 but not PER2, and that the CRY2-TIM interaction is weakened by the FASP mutation. As a consequence of mutant TIM remaining outside the nucleus, CRY2 is destabilized as measured by luciferase degradation assays. We have previously shown that the degradation of CRY2 protein causes shortened period (5). TIM CRISPR mutant mice have 30 minutes of advanced phase in circadian wheel-running assays, but normal period length compared with WT littermate controls.

Conclusion: We show that mutant TIMELESS binds the circadian protein CRY2 causing destabilization of the PER-CRY heterodimer, leading to shortened period in vitro and advanced phase in CRISPR modified mutant TIMELESS mice. These are the first data to demonstrate a role for TIMELESS in mammalian circadian clock regulation. This work also provides information about the stability of critical negative regulators of the circadian clock and, more broadly, insight into mechanisms that play a role in circadian disruption, and recovery.

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Poster Presentations, *continued from page 264*

OB 36 (1422)
Comparative Potency of Calcium-Activated Chloride Channel Anoctamin 1 Antagonists on Human Uterine Smooth Muscle (USM) Contractility

Shunsuke Hyuga, MD[1], Joelle H. Shosfy, MA[2]; Wen Fu, PhD[1]; Joy Vink, MD[1]

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Introduction: Pre-term birth resulting from preterm labor is a major health care challenge facing the United States. We previously described that anoctamin 1 (ANO-1) channel blockade results in relaxation of pre-contracted human USM. Three drug classes possess ANO-1 anatagonism and have been safely used in humans (gallotannins, benzofurans and anthranilic acid derivatives). In this study, we compared the relative potency between these drug classes to promote human USM relaxation and inhibit contraction frequency.

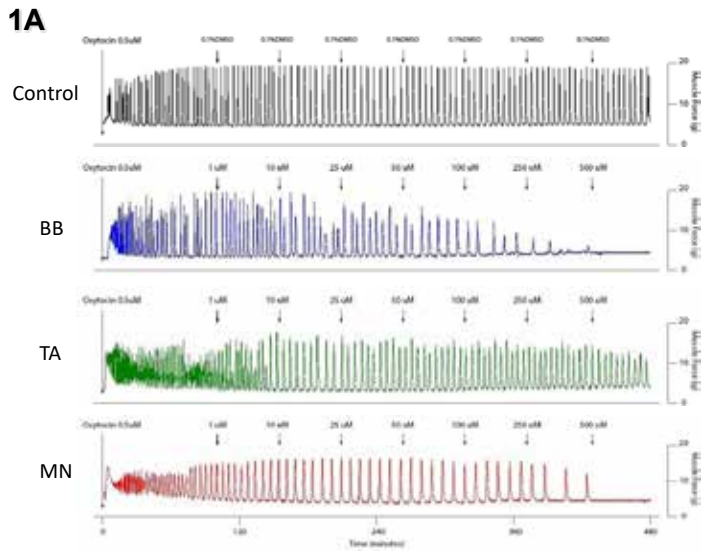

Figure: 1. **Comparative pharmicological antagonism of human uterine smooth muscle (USM) anoctamin-1 on oxytocin-induced enhanced force**
Organ bath experiments were performed with pregnant human USM(n=5 patients). Following contractile stimulation with oxytocin(0.5 µM) each bath was treated with increasing doses of benzbromarone, tannic acid, MONNA (1 µM-500 µM) or vehicle control (0.1%DMSO). Integral change in force was then measured over 60 minutes per dose and processed as a percentage of reduction in integral force (g*sec) from baseline oxytocin-induced contractility.
1A. Representative force tracing showing the differential potency (BB>MN>TA) of benzbromarone (blue tracing), tannic acid (green tracing) and MONNA (red tracing) on contractive frequency and force compared to vehicle control (black tracing) . * BB=benzbromarone, TA=tannic acid, MN=MONNA.

Methods: With IRB approval (#AAAL4005), ex vivo organ bath experiments were performed utilizing strips of late gestation human USM (n=5 patients). Samples were pre-contracted with oxytocin (0.5 Î¼M), equilibrated for 60 minutes, and treated with sequentially increasing doses of an ANO-1 antagonist (benzbromarone, Tannic acid and MONNA;1 Î¼M - 500 Î¼M) or vehicle control (0.1% DMSO final). Resulting changes in force/time were processed as an integral measured over 60 minutes, processed as a percentage of reduction in integral force (g*sec) from baseline contractility, and compiled then plotted (mean + SEM) using a variable slope sigmoidal dose-response curve to determine IC 50 and Imax values. Statistical analysis utilized ANOVA with Bonferroni's Multiple Comparison Test ($p<0.05$ was taken as significant). Percent reduction in contraction frequency (contractions/hr) was also plotted using a variable slope sigmoidal dose-response curve and ANOVA analysis.

Results: The IC 50 of benzbromarone, tannic acid and MONNA on oxytocin- induced contractility of human USM is 34 Î¼M, 45 Î¼M and 59 Î¼M respectively (Figure 1). The threshold concentration to achieve Imax for benzbromarone, tannic acid and MONNA on oxytocin-induced contractility is 50 Î¼M, 100 Î¼M or 100 Î¼M respectively. We also observed ANO-1 antagonism mediated by benzbromarone at 1 Î¼M (***$p<0.001$), tannic acid at 10 Î¼M (***$p<0.001$) or MONNA at 10 Î¼M (***$p<0.001$) allowed for statistically significant reductions in frequency.

Conclusion: Blockade of ANO-1 attenuates oxytocin-induced contractions in pregnant human uterine tissue. Of the compounds tested, benzbromarone is the most potent tocolytic drug ex vivo.

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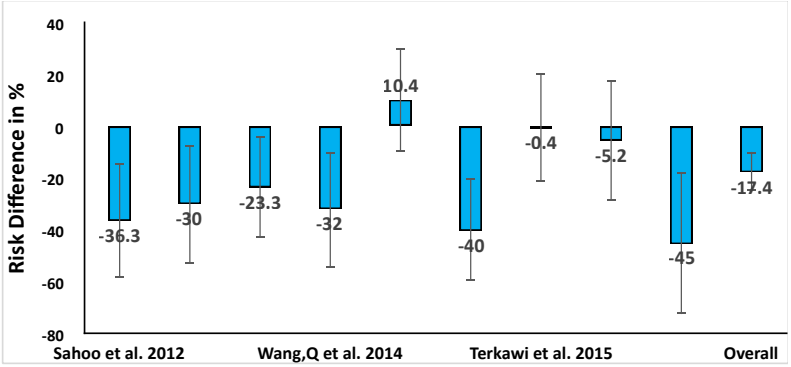
Poster Presentations, *continued from page 265*

OB 37 (2011)
Ondansetron and Spinal Anesthesia-Associated Hypotension During Cesarean section: Using Risk Difference to Assess Therapeutic Effectiveness

Courtney Masear, MD[1], Sharon C. Reale, MD[1]; Sarabdeep Singh, PhD[1]; Karen Lindeman, MD[1]

[1]*Johns Hopkins University, Baltimore, MD*

Introduction: Ondansetron, an agent frequently used for nausea and vomiting prophylaxis and treatment, is thought to reduce spinal anesthesia-related hypotension, bradycardia, nausea, and vomiting in obstetric and non-obstetric patients.[1,2] During cesarean delivery, ondansetron could be administered before initiation of spinal anesthesia or after delivery of the infant. Given the potential adverse effects of antepartum administration of ondansetron, we questioned the clinical relevance of these findings.



Methods: We included data from nine randomized controlled trials identified in a recent meta-analysis that evaluated risk ratios in treatment and control groups[2-11] Inclusion and exclusion criteria were as described We calculated risk differences with 95% confidence intervals (CIs).

Results: Six of the nine randomized trials revealed at least a 20% risk difference between ondansetron and control groups (figure), such that ondansetron prevented hypotension. The overall risk difference of ondansetron administration vs. placebo was -17.37 (95% CI -24.81 to -9.93). For prevention of bradycardia, the overall risk difference was -8.96 (95% CI -13.11 to -4.81).

Conclusion: Two recent meta-analyses 1-2 used risk ratios to determine whether prophylactic ondansetron attenuates spinal anesthesia-associated hypotension and bradycardia. In each meta-analysis, ondansetron was associated with decreased hypotension. Estimates of risk difference provide more clinically relevant information than risk ratio.[12,13] Risk difference provides useful information for decision analysis by elucidating the difference in the number of cases in treatment versus control group. Using risk difference to analyze data from nine randomized controlled trials, we found that patients in the ondansetron group had only 17 fewer cases of hypotension per 100 patients when compared with control group. Thus, the clinical significance of ondansetron's effect on spinal anesthesia-related hypotension is minimal. One meta-analysis cautions that the data in the trials could be misleading because of bias and sample size.2 Because of the questionable clinical significance and the risks of antenatal administration, including QT prolongation and potential effects on the fetus, we would urge caution in deciding whether to administer ondansetron before delivery of the infant for the purpose of attenuating spinal anesthesia-associated hypotension.

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TCSEM 39 (1417)
Initiation of an Emulsion Microinfusion: Flow Direction Influences Onset Rate

Robert A. Peterfreund, MD, PhD[1], Amy C. Tsao, BA[1]; Michael Parker, MD[2]; Mark A. Lovich, MD, PhD[3]; Hao Deng, MD[1]; Timothy Houle, PhD[1]

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Introduction: Laboratory studies show long onset lag times to steady state drug delivery rates when initiating microinfusions (carrier and concentrated drug at slow flows). [1, 2] Past experiments evaluated starting infusions of water soluble agents joining a carrier flow via a manifold. Hydrophobic drugs may be delivered as emulsions. The time to achieve steady state delivery after initiating an emulsion infusion has not been assessed. We tested the hypothesis that the mixing characteristics of an emulsion will influence the onset of drug delivery by infusion. We compared initiating emulsion infusions through a manifold oriented either horizontally or vertically, with vertical flow either up or down.

Methods: We adapted a previously studied laboratory model. [2, 3] The emulsion containing propofol was the marker. Standard syringe pumps delivered the emulsion (3 ml/hr) and saline carrier (10 ml/hr). The 2 flows joined at a standard linear 4 stopcock manifold and then flowed together through a standard central line catheter (total dead volume ~1.14 ml). The outflow was collected at one minute intervals. Emulsion delivery was measured by optical density compared to a standard curve and reported as delivery units. The delivery plateau was determined as the average values of the last 10 samples in the 40 minute infusion. The curves were inspected to determine the time points. Identical experiments were performed with methylene blue (MB) as a water soluble marker. Data were compared via ANOVA with the Bonferonni correction for multiple comparisons.

Results: Manifold orientation did not influence the time to intended steady state delivery after initiating an MB infusion (Fig 1). Manifold orientation influenced the time required for a newly initiated emulsion infusion to achieve steady state. The times to achieve 5%, 50% and 95% (t5, t50, t95 respectively) of steady state emulsion delivery were similar for manifold orientations horizontal and vertical (flow down) (Tables 1 & 2, Fig 2). t5 and t50 delivery times were significantly faster with vertical manifold orientation and flow up (Table 2). For the vertical (flow up) manifold orientation, t95 could not be determined because of the rapid rise with overshoot (Fig 2). The area under the curve for emulsion delivery initiated with vertically upwards flow was 0.471 (0.068 SD) delivery units. This differed significantly from horizontal (0.067 (0.044 SD)) and vertical down flow (0.028 (0.022 SD)) initiation (Table 2).

Conclusion: The data show the expected long lag times to achieve steady state when initiating an emulsion microinfusion with manifold orientation either horizontal or vertical (down) flow. The time constant for this assembly of infusion components and total system flow 13 ml/hr is 5.3 minutes. Delivery to t95 is ~3 time constants for horizontal flow and ~4 time constants with vertical (down) flow. These delivery characteristics are consistent with a 'well mixed' model of drug delivery.[4] Initiating microinfusion emulsion delivery with vertical (up) manifold orientation essentially results in a bolus. This suggests that emulsion infusions feature initial mixing characteristics not found in aqueous infusions. An emulsion might carry a high potency drug having significant physiologic effects, e.g. clevidipine. If unrecognized, the differences in initial emulsion delivery kinetics depending on manifold orientation may have clinical implications for both efficacy and safety.

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continued on page 268

TABLE 1

	HORIZONTAL AVG (SD)		***Vertical UP*** AVG (SD)		***Vertical DOWN*** AVG (SD)
t5	8.5 (1.0)		2.25 (0.50)		8 (1.4)
t50	10.0 (1.4)		3 (0)		13(1.6)
t95	16.75 (3.77)		NA		22 (2.2)

t5, t50 and t95 indicate time to achieve 5%, 50% and 95% of estimated plateau delivery values, respectively
Values are reported as minutes (Average, SD), N = 4
NA indicates that t95 cannot be determined for Vertical (Upward s) flow; *See graph*

TABLE 2

	Horizontal vs Vertical Down			***Horizontal vs Vertical Up***			***Vertical Up vs Vertical Down***	
	Mean Difference(95% CI)	P-Value		Mean Difference(95% CI)	P-Value		Mean Difference(95% CI)	P-Value
t5	0.5(-3.36,4.36)	1		6.25(3.43,9.07)	<0.001		5.75(1.44,10.06)	0.018
t50	-3(-7.6,1.6)	0.297		7(1.92,12.08)	0.018		10(4.13,15.87)	0.009
t95	-5.25(-15.67,5.17)	0.567		NA	NA		NA	NA
AUC	0.04(-0.09,0.16)	1		-0.4(-0.59,-0.22)	<0.001		-0.44(-0.65,-0.23)	<0.001

t5, t50 and t95 indicate 5%, 50% and 95% of estimated plateau delivery values, respectively
AUC indicates delivery in the interval between timepoints 6 and 15 minutes
Values are reported as Mean Difference (95% CI), N = 4
Analysis by T-test; P -Values are corrected for multiple (9) comparisons
NA indicates that t95 cannot be determined for Vertical (Upward s) flow; see graph

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Poster Presentations, *continued from page 268*

TCSEM 40 (1523)
Effective Evaluation of Arterial Pulse Waveform Analysis: the Online Two-Dimensional Log[10](SVV)-SVI Plots

Teiji Sawa, MD, PhD[1], Atsushi Kainuma, MD[2]; Koichi Akiyama, MD[2]; Saeko Hamaoka, MD[3]; Mao Kinoshita, MD, PhD[2]

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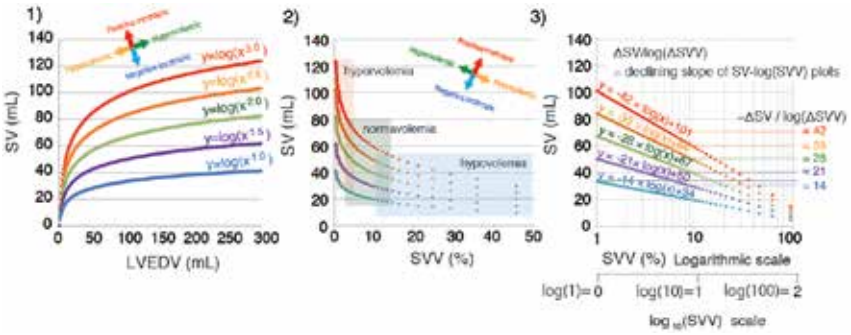
Introduction: The arterial pulse waveform analysis (APWA) with less-invasive cardiac output monitoring devices, such as FloTrac/Vigileo and ClearSight/EV1000 plus (Edwards Lifesciences Co., USA), has become popular in perioperative hemodynamic and fluid management by critical care clinicians and anesthesiologists. In goal-directed fluid therapy (GDFT), the target goal in hemodynamic parameters is set up by measuring cardiac output (CO), estimated preload, and afterload. We previously made application software GDT 2D-visualizer to visualize APWA data, and analyzed SVV-SVI plots [(1)]. The GDT 2D-visualizer analyzes stroke volume variation (SVV) and stroke volume (SV) derived from APWA to effectively perform GDFT. From the arithmetical analysis of Frank-Starling curves, we found that the relationship between SVV and SVI can be described as a primary linear regression in log10(SVV)-SVI plots. In addition, the slope of the linear regression line theoretically represents averaged cardiac contractility. In this study, we performed a clinical study to examine the log10(SVV)-SVI plot theory by using a non-invasive APWA monitor ClearSight/EV1000 plus.



Methods: Five anesthesia cases were applied to the on-line log10(SVV) €"SVI (stroke volume variation index) plotting system by using both the FloTrac/Vigileo system and the ClearSight/EV1000 plus. On-line arithmetical calculations were performed to evaluate the linear regression of 2D-plotted data.

Results: The plots obtained from the ClearSight/EV1000 plus well correlated with those from the FloTrac/Vigileo system. In the on-line arithmetical analysis of log10(SVV)-SVI plots, the relationship between log10(SVV) and SVI could be drawn as a linear correlation with good a correlation coefficient, and the plots approximately shifted on the regression lines depending on fluid therapy.

Conclusion: Arithmetic estimation is close to real measurement of the log10(SVV)-SVI interaction in linear regression. In APWA, using log10(SVV) as an index of preload and SVI derived from arterial pressure-based cardiac output as an index of cardiac function, is likely to be appropriate for categorizing hemodynamic stages as a substitute for Forrester subsets. We concluded that the log10(SVV)-SVI plotting system in APWA is useful to visualize the GDFT during anesthesia management.

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ww4.aievolution.com/ars1701/files/content/abstracts/abs_1523/logSVV-SVI2.jpg

Poster Presentations, *continued from page 269*

TCSEM 41 (1739)
Automated Feedback System Improves Perioperative Outcome Awareness

Jonathan Wanderer, MD[1], Leslie Fowler, Med[2]; Jesse Ehrenfeld, MD[1]; Teus Kappen, MD[3]; Warren Sandberg, MD, PhD[3]; Matthew D. McEvoy, MD[2]

[1]Vanderbilt University School of Medicine, Nashville, TN, [2]Vanderbilt University Medical Center, Nashville, TN

Introduction: Healthcare is increasingly moving towards value-based medicine, where the value of the services provided will be determined by the ratio of the cost of providing that service to the outcomes achieved.[1] Anesthesia providers have a critical role in the management of surgical patients. While intraoperative management may be linked to postoperative outcomes such as myocardial infarction,[2] acute lung injury[3] and acute kidney injury,[4] most anesthesia providers are unlikely to perform active surveillance on all patients that they have cared for beyond the immediate postoperative period. We hypothesize that current awareness of postoperative outcomes among anesthesiologists is low, and that it can be improved by providing anesthesia providers with these data.

Methods: We developed an automated system that retrieves data from our electronic medical record and identifies postoperative morbidity and mortality, including postoperative nausea and vomiting, reintubation, care escalation, myocardial infarction, acute renal failure, rapid response calls and in-hospital mortality. These events are linked back to each member of the anesthesia team caring for each patient. A personalized email is sent each week to each clinician with a summary of patient outcomes from the prior week, linked to a dashboard with full detail. Prior to launching this system and six months after completion of the phased the intervention, the department was surveyed regarding outcome awareness. Participants were asked to assess if they were consistently aware of outcome events for patients they had taken care of. Responses were recorded on a 5-point Likert scale, grouped (strongly disagree/disagree/neutral vs agree/strongly agree) for descriptive purposes and compared using the independent 2-group Mann-Whitney U test. Additionally, we determined the number of participants in, and communications from, the system.

Results: Over the 8 month study period, 6,883 personalized outcome emails were sent to 385 clinicians. There was an increase in awareness for all outcome events, including postoperative nausea and vomiting (44% strongly agree/agree with consistent awareness pre vs 60% post-intervention, $p<0.001$), reintubation (41% vs 58%, $p<0.001$), care escalation (25% vs 44%, $p<0.001$), myocardial infarction (31% vs 45%, $p<0.001$), acute renal failure (24% vs 41%, $p<0.001$), and in-hospital mortality (51% vs 60%, $p=0.02$). Satisfaction increased with both the amount of feedback provided (13% vs 40%, $p<0.001$) and timeliness (13% vs 44%, $p<0.001$). The majority of respondents in both groups preferred weekly feedback compare to other intervals (87% pre, 83% post) as well as email-based information delivery. The response rate for the pre-intervention survey was 54% (181/335), and 39% (156/374) for the post-intervention survey.

Conclusion: An intervention to automatically identify important postoperative patient outcomes and connect them to clinicians who cared for those patients is technically feasible and resulted in improved outcomes awareness across every assessed outcome type. Clinicians expressed a preference for receiving feedback in a weekly email containing summarized data. Automated systems such as this one may play a critical role in extending the reach of anesthesiologists outside of the immediate perioperative period and may be positively affect intraoperative care planning as it relates to postoperative outcomes.

continued on page 271

Poster Presentations, *continued from page 270*

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Figure 1a and 1b: Examples of summarized patient outcome emails.

Here are your patients' outcomes:

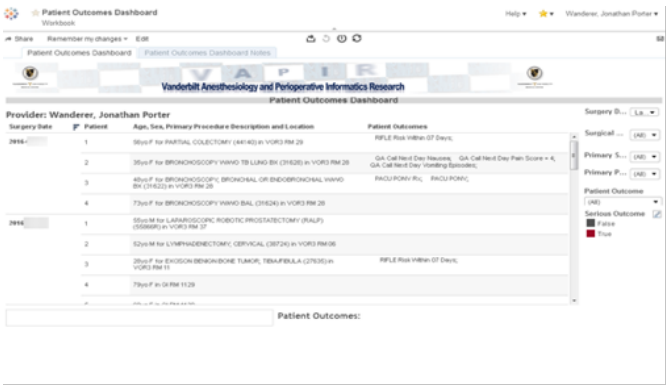
Surgery Date	Description	Length Of Stay	Patient Outcomes
	64yo F with Gamboa	No d/c found	RIFLE Risk Within 07 Days
	34yo F with Wiese	0.31	
	31yo F with Bream	No d/c found	Repeat Anesthetic Within 7 Days; RIFLE Risk Within 07 Days
	70yo F for THROMBOENDARTERECTOMY, W/PATCH GRAFT; CAROTID, VERTEBRAL, SUBCLAVIAN, BY NECK INCISION (35301)(35301) with Garrard	No d/c found	PACU PONV; PACU PONV Rx
	70yo F for ABDOMINAL TUMOR EXCISION & DEBULKING (49205) (49205) with Idrees	No d/c found	
	69yo F for EXPLORATORY LAPAROTOMY (49000)(49000) with Garrard	No d/c found	Death In Hospital;; RIFLE Injury Within 07 Days; RIFLE Risk Within 07 Days
	59yo M for LAPAROTOMY FOR OPEN ABD (49002)(49002) with Hopper	No d/c found	Repeat Anesthetic Within 7 Days
	56yo M for EXPLORATORY LAPAROSCOPY (49320)(49320) with Idrees	0.33	Elevated PostOperative Troponin within 7 days

For detailed information on your cases' outcomes, please visit the Patient Outcomes Dashboard

Here are your patients' outcomes:

Surgery Date	Description	Length Of Stay	Patient Outcomes
	87yo M with Scanga	No d/c found	Rapid Response Team Call Within 7 Days
	79yo M with Yachimski	0.46	
	74yo F with Scanga	3.64	Repeat Anesthetic Within 7 Days
	74yo F with Penn	0.42	
	73yo M for CYSTECTOMY W/ILEAL CONDUIT (51595)(51595) with Barocas	No d/c found	RIFLE Risk Within 07 Days
	60yo M with Scanga	0.42	
	60yo F with Penn	0.42	
	60yo F with Penn	0.42	
	57yo M with Penn	0.42	
	49yo F with Penn	0.42	
	37yo M with Penn	0.42	
	31yo F with Scanga	3.01	
	86yo F for CASE CANCELLED AFTER ADMISSION TO OR(CANCEL) with Chang	2.13	Repeat Anesthetic Within 7 Days
	74yo F for INSERTION INTERSTIM, STAGE 2 (64590)(64590) with Kaufman	0.33	QA Call Next Day Pain Score = 4

Figure 2: Example screenshot for outcome dashboard



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PME 43 (2123)
Brain Mechanisms of Mood Treatment in Chronic Low Back Pain: Preliminary Analysis

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Introduction: Chronic low back pain (cLBP) patients frequently suffer coexisting psychological disorders, such as major depression, generalized anxiety disorder, and/or high levels of pain catastrophizing [1]. These pathologies most often present as a symptom cluster, termed negative affect (NA). High NA predicts higher pain levels and poor pain treatment outcomes [2], but we know little of the brain mechanisms linking NA to chronic pain. We have shown that increases in mechanical cLBP are correlated with increased functional connectivity between the Default Mode Network (DMN) brain regions and the right insula[3]. We seek to replicate this finding in patients with cLBP and high NA, and investigate if worsening negative mood during a scan session in cLBP patients worsens pain. Finally, we are testing the relationship to the DMN-right insula metric in the scenario of worsening pain through worsening mood.

Methods: To date, 5 of 40 cLBP patients with high NA, characterized by high depression and anxiety symptoms, have been enrolled in this University of Pittsburgh IRB approved clinical study. For each session, patients complete four fMRI sessions in one scanning visit. The first is a baseline scan. The subject then performs clinical maneuvers designed to exacerbate clinical back pain, and complete the second session. The third and fourth scans are collected after two tasks that induce neutral and negative moods, after cLBP has returned to baseline. Both pseudo continuous Arterial Spin Labeling (pCASL) and Blood Oxygen Level Dependent (BOLD) fMRI data are collected for each session. Pain, anxiety, and mood are assessed immediately before and after each scan. Images are collected with a 3T Siemens Skyra System. Perfusion data is generated from the pCASL images using ASTtbx. Analysis of this data, and of the BOLD images, for functional connectivity (fcMRI) is connected using the Functional Connectivity Toolbox (Conn). After standard preprocessing [4], signal time courses are extracted from pre defined target ROIs of the Default Mode Network (DMN) and the insula using Conn's built in atlases. Functional connectivity is defined as the correlation coefficient between the signal time courses.

Results: Data from all subjects were used in the analysis, even if their pain did not increase, to provide a greater dynamic range of pain scores for connectivity relationship testing. For most subjects, pain increased as expected after the clinical maneuvers and the negative mood induction (Fig 1). Corresponding with the increase in pain scores, DMN Insula connectivity also increased for the BOLD data (Fig. 2, linear fit R2 = 0.6759 and 0.5643). The pCASL data suggested the same for the comparison between Baseline and Negative Mood (Fig. 3). The linear trend line for the pCASL Baseline and Maneuvers connectivity scatterplot does not follow the same relationship, however it seems to be heavily influenced by the potential outlying point (shown in red). Given the small number of subjects, further statistical analysis was not performed.

Conclusion: The data gathered to date suggests that 1) the negative mood induction itself worsens the ratings of cLBP pain exacerbationÍ¾ 2) both BOLD and pCASL modalities are able to monitor acute brain connectivity changesÍ¾ and 3) connectivity between the DMN and the insula is involved in processing clinical pain and may also reflect the effect of NA on pain levels.

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PME 44 (2043)
Enabling TRPV1-Based Pre-Emptive Analgesia for Post-Surgical Pain in the Rat: Behavioral and Transcriptomic Analysis

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Introduction: Post-operative pain is a major cause of suffering, increasing the risk for chronic post-surgical pain and opioid use [(1,2)]. Nociceptors that express the noxious heat channel TRPV1 (transient receptor potential cation channel subfamily V) have been implicated in pain after surgical incision [(3)]. Peripheral TRPV1+ nerve terminal ablation with RTX (resiniferatoxin) was examined for its ability to suppress the peripheral pain generator and provide pre-emptive analgesia. We considered favorable characteristics of a preemptive analgesic to be efficacy with one administration, rapid onset of action, long duration of action, and highly selective suppression of clinically-relevant subpopulations of nociceptive primary afferents with few or no side effects. The present study utilized multiple stimulus modalities to evaluate the behavioral action of pre-operative nerve terminal inactivation on post-operative incisional pain as well as molecular changes in the dorsal spinal cord. Our objective was (a) to evaluate RTX to determine if it met our criteria for a preemptive analgesic and (b) to probe the underlying molecular alterations that accompany post-operative central sensitization at the spinal level and (c) to determine whether this transcriptional plasticity was reduced by pre-emptive RTX.

Methods: Sprague-Dawley rats (n=24) were randomized to receive intraplantar injections of RTX and/or lidocaine prior to intraplantar incision and were assessed for evoked pain (mechanical and thermal) as well as spontaneous pain (paw guarding score and home cage monitoring) post-operatively for 10 days. Rats were also assessed for motoric function by duration of time on rotarod. Statistical analysis was by 2-way ANOVA. We conducted RNA-sequencing of the dorsal horn in control rats, rats with surgical incision, and rats with surgical incision plus pre-operative RTX and lidocaine.

Results: Plantar incision caused thermal hyperalgesia post-operatively to both A-delta and C-fiber stimuli for the first 4 days. Pre-emptive intraplantar RTX attenuated these responses (2-way ANOVA $p<0.05$). Rats developed mechanical allodynia over the first 2 post-operative days, and this was also attenuated by pre-emptive RTX. Guarding of the wound was most pronounced at 4 hours and 24 hours; pre-emptive RTX attenuated this measure of spontaneous pain (assessed by guarding score, $p<0.05$). Analgesia was modality selective and there was no effect of RTX on response to pinprick sensation; furthermore, motoric integrity of animals was preserved as assessed by rotarod assay. The combination of lidocaine and RTX was no more effective than RTX alone. RNA-Seq assessment of dorsal horn plasticity is pending.

Conclusion: Peri-operative administration of RTX, delivered in a clinically relevant manner, was efficacious in decreasing spontaneous and evoked measures of post-operative pain in rats. Furthermore, RTX fulfilled all of the criteria enumerated for a favorable pre-emptive analgesic and provided highly efficacious analgesia over multiple post-operative days.

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PM 45 (2027)
Development of ROS-Responsive Microspheres for Sustained Local Delivery of Therapeutics for the Treatment of Chronic Pain

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Introduction: It is estimated that over 100 million adults in the US suffer from chronic pain, placing an estimated $300 billion economic burden on the health care system[(1,2)]. Despite its profound impact on both individuals and the health care system, treatments remain fraught with suboptimal efficacy and, at times, significant adverse effects. An emerging body of evidence indicates that reactive oxygen species (ROS) play a role in several pain etiologies such as opiate induced hyperalgesia, neuropathic pain, and inflammatory pain [(3)]. We therefore hypothesize that delivery of therapeutic agents using a ROS-dependent drug delivery system may be beneficial in the treatment of chronic pain. By leveraging the ROS-responsiveness of poly(propylene sulfide) (PPS), we aim to create microspheres that can be tailored to deliver, on demand, a multitude of drugs to areas with elevated ROS production [(4)]. As a proof of concept, we created and optimized PPS microspheres loaded with the widely used amide local anesthetic, bupivacaine.

Methods: PPS-bupivacaine microspheres were created using a previously described oil-in-water emulsion solvent evaporation technique (5). Bupivacaine loading into the PPS microspheres was measured using spectrophotometry and HPLC. Loading of bupivacaine into the microspheres was optimized by changing emulsion conditions, using varying molecular weight PPS, and adding stabilizing polymers, poly(lactic-co-glycolic acid) (PLGA) or poly[N-(2-benzoyloxypropyl) methacrylamide] (PBPMA).

Results: Bupivacaine loading efficiency (LE) into PPS microspheres was found to be 8.4% (w/w) using the previously described technique. The addition of Tris buffer to the water phase of the emulsion and changing the surfactant from poly(vinyl alcohol) to Pluronic F-127 reduced LE to 5.8% and 4.5% (w/w), respectively. Increasing the molecular weight of PPS from 5 kDa to 20 kDa resulted in a LE of 14.7% (w/w), and the addition of PLGA resulted in a LE of 12.7%. The addition of PBPMA had the largest effect on outcome, resulting in a LE of 17.9% (w/w).

Conclusion: The development of PPS microspheres for targeted drug delivery may offer new alternatives for the treatment of chronic pain. While bupivacaine loading into PPS microspheres was found to correlate with increasing molecular weight of PPS and the addition of stabilizing polymers, it was marginally impacted by other formulation parameters studied. This data opens exciting avenues for exploring the use of PPS to deliver a host of drugs like ROS-scavengers, μ-opioid receptor agonists, and anti-inflammatory agents. Forthcoming studies will assess the pharmacokinetics and pharmacodynamics of the optimized formulation relative to free bupivacaine with in vitro assays and animal models of chronic pain.

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PM 46 (1028)
Effect of Ultra Short Wave Irradiation on Stellate Ganglion on Brachial Blood Flow

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Introduction: The purpose of this study is to clarify that the irradiation of USW around the stellate ganglion proves the increase of blood flow and the dilation of radial and brachial arteries. Consequently we very that the relief from stiff shoulder is not only due to softness and relaxation of muscles but is also due to increased blood flow and dilated vessels in the related muscles.

Methods: Prior to the study, informed consent was obtained from subjects. 15 healthy adult volunteers (mean age 42 ±11 years), (male n=10, female n=5), and (weight 65 ±10kg) were included in this study. The irradiation of USW was applied around the stellate ganglion of the studied side unilaterally for 10 minutes. Before and after the irradiation of USW, we measered by ultrasound echography the changes of diameter of the orifice and blood flow in the radial and brachial arteries.

Results: The diamater of the orifice of radial and brachial arteries were dilated from 0.29 ±0.04cm2 to 0.31 ±0.03cm2 ($p<0.12$), and from 0.36 ±0.05cm2 to 0.38 ±0.07cm2 ($p<0.10$) respectively. The blood flow of radial and brachial arteries increased from 39.4 ±15.0ml/min to 51.8 ±17.0ml/min ($p<0.05$), and from 77.9 ±32.8ml/min to 101.3 ±37.3ml/min ($p<0.12$) respectively. From the above results we confrimed that the irradiation of USW over the stellate ganglion brought forth the increase of blood flow and the dilation of blood vessel in the radial and brachial arteries of the irradiated side.

Conclusion: We confirmed that after the irradiation of USW around the stellate ganglion, there was the dilation of blood vessels and the significantly increased blood flow in the radial and brachial ateries of the studied side. From the result we speculated that the relief of stiff shoulder was not only due to the relaxation of muscle but also due to the increased blood flow in the affiliated muscles. We considered that the irradiation of USW around the stellate ganglion was a useful, reliable and non-invasive method to get achieve increased blood circulation in the upper extremity instead of the stellate ganglion block.

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N/A

PM 48 (1421)
First Literature Report of Ketamine Infusion for Treatment of Refractory Postherpetic Neuralgia

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Introduction: Herpes zoster is a form of reactivated latent varicella zoster infection with lesions spanning day to weeks. Postherpetic neuralgia (PHN) is a form of neuropathic pain that can persist for months to years after resolution of rash. Pain stems from an inflammatory response due to damage along a specific nerve root. The burden of PHN pain interferes with quality of live and performing daily necessities. The mainstay of treatment consists of tricyclic antidepressants (TCAs), gabapentin and pregabalin. Treatment can be supplemented with opioids, topical lidocaine patches, and topical capsaicin patch or cream. If pain remains refractory, oral and topical agents are used. Botulinum toxin is thought to be effective due to interfering with presynaptic nerve acetylcholine release. However, data indicates it is mostly beneficial as an adjunct therapy. Our challenging case is a patient with refractory PHN, having failed combination therapy, treated successfully with a ketamine infusion.

Methods: This is a 74 year old female with a two year history of PHN, in all three distributions of the trigeminal nerve, pain rated 7/10. Her recent pain regimen consisted of amitryptyline HCl 10mg qd, fentanyl 100 mcg/hr transdermal patch 72 hours, gabapentin 100 mg, hydrocodone-acetaminophen 2.5-325 mg, lidocaine 5% patch, oxymorphone HCl 5mg, prednisone 1 mg, pregabalin 25 mg and trazodone HCl 50 mg. Despite these agents, patient reported inability to function secondary to pain. Patient was offered a ketamine infusion at 5 mg/h ketamine infusion for a total of 20 mg along with pretreatment with midazolam.

Results: Immediately after the procedure, patient stated she felt 'relaxed.' On her first post procedure visit, ten days after, patient was on her pain regimen and noted improvement in sensitivity to tactile stimulation. Patient advised to discontinue oxymorphone and hydrocodone-acetaminophen as tolerated. Her next office visit, one month after receiving the ketamine infusion, patient reported significant improvement with a constant pain level of 5/10. Occasionally she experienced 7/10 pain, triggered by temperature change. Over two months have elapsed since this treatment and patient has not experienced any worsening of pain.

Conclusion: Ketamine has excellent analgesic properties however evidence for chronic pain management is limited. Given its widespread receptor effect, ketamine can have multiple mechanisms owing to its potential for pain control. The different routes of ketamine also make its use practical. For PHN, subcutaneous ketamine at low doses provides relief of continuous pain with increase improvement in increasing doses. Additional data exists for resolution of ophthalmic PHN via PO ketamine. However, our case is the first in literature to report ketamine infusion as a therapy for treating PHN. In episodes of central pain, intravenous and oral ketamine have shown reduced narcotic requirement. Ketamine can control acute episodes of refractory neuropathic pain, often hyperalgesic pain from opioid administration. Data shows benefit of epidural ketamine for complex regional pain syndromes. Other syndromes with potential benefit from ketamine are phantom limb and fibromyalgia. Our hope is management of this challenging case will serve as an innovative adjunct to relieve disability from PHN.

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PM 49 (2240)
Chiari Malformation Type 1 and Pain Management of Chronic Headache: A Literature Review

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Introduction: Chiari malformation type 1 (CM1) is characterized by the downward displacement of the cerebellar tonsils through the foramen magnum into the spinal canal. Headache is one of the most common presentations for these patients, specifically a unique 'cough' headache. Symptomatic 'cough' headaches are tend to be more severe, longer duration and constant in nature compared to benign. Cough headaches are distinguished from other forms of headache due to onset by any maneuver resulting in intracranial pressure gradient such as cough or valsalva maneuvers. A minority of these headaches are seen in the context of Ehlers-Danlos syndrome (EDS) with headaches due to joint hypermobility. There is limited research as to the standard of care for pain management of this unique headache. We present a review of the literature to best describe current management of headache pain in these patients.

Methods: A retrospective review of prior publications in the PubMed database was performed looking for reports of 'Chiari 1 malformation' and 'pain management'. Relevant papers were reviewed regarding current pain management for CM1. In total, 300 CM1 cases with contrasting severities of headaches were reviewed. A small subset of patients also had a diagnosis of EDS which was noted to impact management. The search was limited to medical management prior to requiring surgical intervention.

Results: The origin of CM1 headaches are thought to be attributed to 'crowding' of the posterior fossa. Specific characteristics include a bilateral occipital and suboccipital headache of sudden onset, lasting less than one minute, and precipitated by coughing in the absence of any intracranial disorder. Most 'benign' headaches are initially treated with medical management while more symptomatic headaches require invasive and/or surgical intervention. Given the limited data there is no standard care currently for managing pain in CM1 patients.

Conclusion: The literature suggests indomethacin is the mainstay as the initial approach to therapy. One problem has been however that up to 75% of patients will outgrow its benefits despite dosage increases. Next, a diagnostic and/or therapeutic lumbar puncture (LP) is performed. It is unclear however, whether an LP adequately provides pain relief as reports have shown they provide only brief lasting relief and are associated with risks of the procedure in addition to requiring a cooperative patient. Another modality, acetazolamide, has been used to reduce the intracranial pressure and thus alleviates strain leading to headaches. In the minimal data that exists, acetazolamide provides effective analgesia for cough headaches, however only those classified as 'benign.' In patients with an EDS etiology, a multimodal approach is utilized, consisting of physical therapy, abortive and prophylactic therapy. Therapy noted to be most effective consists of NSAIDs with the addition of triptans, codeine, and caffeine as prescribed for prophylaxis. After an individual has failed multiple rounds of medical therapy, surgical intervention is usually sought though remains controversial. There is substantial potential for research to help improve management of these patients. We hope this literature review will not only highlight current management but also highlight the need for more research on this topic.

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PM 51 (1722)
Longitudinal Pain Sensitivity Phenotyping Using Portable, Brief Bedside QST in Mastectomy Patients for Prediction of Persistent Postsurgical Pain

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Introduction: Quantitative sensory testing (QST) is increasingly applied in clinical pain phenotyping studies to characterize individual differences in sensory profiles (1-3). However, formal laboratory QST is often not feasible in clinical settings. We used a brief 'bedside' QST battery in women undergoing mastectomy to investigate: 1) postoperative changes in sensory processing, 2) the predictive relationship between QST and the subsequent trajectory of postsurgical pain, 3) QST's association with psychosocial variables throughout the perioperative and postoperative course.

Methods: Over 200 women scheduled to undergo partial or total mastectomy underwent brief QST, including pressure pain threshold (PPTh) and tolerance (PPT), a test of mechanical temporal summation of pain (TSP), and an evaluation of painful aftersensations (PAS). Severity and frequency of pain in the surgical areas was determined using a specialized breast cancer pain questionnaire, to give a pain burden index (PBI) at timepoints ranging from baseline to 1 year after surgery.

Results: QST measures were relatively consistent between baseline, 2 weeks and 1 year postop. PPTh and PPT were highly intercorrelated between truncal and extremity sites, and no significant surgical sidedness effects were observed for those who had unilateral surgery. Lower truncal PPTH was associated with higher movement-related pain on postoperative day 1. Both baseline TSP and PAS predicted clinical pain at 1 year. TSP was positively correlated with catastrophizing scores, while PAS correlated with somatization scores. In a subset of patient undergoing mastectomy, those who had paravertebral block (PVB) had increased post-operative PPTh and lower PAS scores, while those without PVB showed the opposite pattern of changes.

Conclusion: These studies suggest that brief bedside QST may be useful in discerning important interindividual differences in pain processing , and predict patients' risk for persistent postsurgical pain, as well as give insights into the impact of perioperative interventions on pain processing.

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Poster Presentations, *continued from page 278*

PM 52 (2013)
DREADDs Activation of Periaqueductal Gray Dopamine Neurons Produces Gender Specific Analgesic Responses

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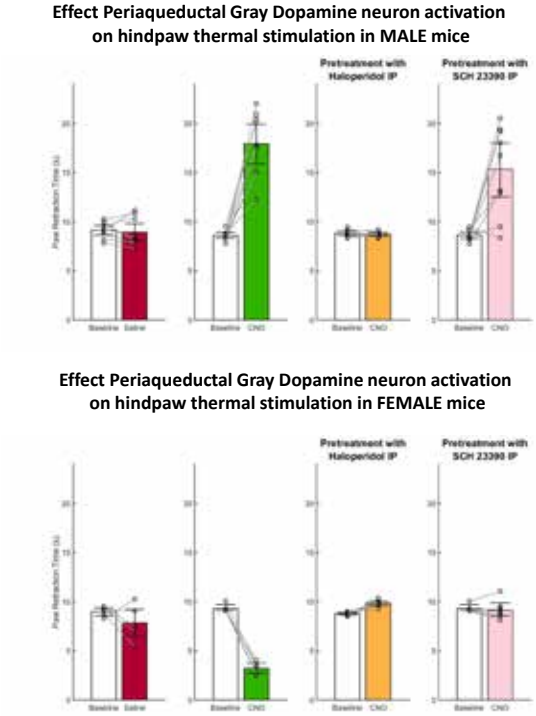
Introduction: Drugs which modulate neural dopamine (DA) represent an important novel analgesic, and yet their effects have never been studied in females. This is important as studies of experimentally induced pain consistently show that women exhibit greater pain sensitivity, enhanced pain facilitation and reduced pain inhibition compared with men [1]. We therefore hypothesized that stimulation of DA neurons in the ventral lateral periaqueductal grey (PAG) would be less effective in treating thermal hyperalgesia in female mice compared to males. 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 sex differences in analgesic response.



Methods: This study was approved by the authors' IRB for animal research. Adult male and female DAT-cre mice received bilateral injections of adeno-associated virus (AAV) carrying an excitatory DREADD (HM3Dq) in the ventral lateral PAG. DREADDs are G-protein coupled receptors engineered to be selectively activated by the ligand Clozapine N-Oxide (CNO). Mice receiving injections of AAV lacking DREADDs served as controls. After at least 4 weeks to allow for viral transfection, thermal hyperalgesia was tested. Immunohistochemistry was used to confirm viral expression and co-localization.

Results: DREADD activation of vlPAG DA neurons produced analgesia in male mice, with paw withdrawal latencies increased from a baseline of 9.2 Â±1.4s to 17.9 Â±3.0s (n=9) when exposed to a thermal stimulus to the hind paw. This contrasts with the response seen in the females, where vlPAG DA neurons activation produced hyperalgesia, with paw withdrawal latencies decreasing from a baseline of 8.9 Â±0.6s to 3.2 Â±1.1s (n=7) following the thermal stimulus. Both analgesic and hyperaglesic responses were prevented when the mice were treated with the nonspecific dopamine receptor antagonist haloperiodol. However, only the hyperalgesia exhibited by the females was significantly reduced by the specific D1 antagonist SCH-23390.

Conclusion: In summary, selective activation of DA neurons in the vlPAG induced sex specific effects to a thermal stimulus, producing analgesic effects in males and hyperalgesic effects in females. The hyperalgesia appears to be a D1 receptor mediated effect. Understanding the mechanism by which DA modulates analgesic response may provide insight into more effective treatments of pain in males and females.

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PS 54 (1970)
A Pilot Study on Critical Event Debriefing at an Academic Medical Center

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Introduction: The majority of practicing anesthesiologists experience at least one perioperative death or catastrophe over the course of their career[1]. While these crises are known to place significant emotional burden on the healthcare provider, they often remain unaddressed. Critical event debriefing is known to be a valuable tool in mitigating the negative impact of perioperative crises on healthcare providers[2]. Despite debriefing's documented utility, there persists a gap between evidence-based theory and practice[3]. This pilot study aimed to characterize the current status of critical event debriefing in an anesthesia department and to better elucidate the nature of events that warrant debriefing.

Initial Location (Frequency [%])	Predominant Event	Percent Debriefed
Operating Room* (14/37 [38%])	Significant or prolonged hypotension, desaturation, and/or cardiac arrest	36% (5/14)
Inpatient Floor/ICU (16/37 [43%])	Challenging/difficult airway or notable cardiac arrest	44% (7/16)
Other (PACU, preoperative receiving area, etc.) (7/37 [19%])	Communication breakdown with impact on patient care	29% (2/7)

Methods: At a large academic medical center, anesthesiology residents were randomly audited for the occurrence of specified events during their current or previous shift: (1) a surgical crisis, (2) a significant deviation in patient care (both as previously described in the literature) [4,5], (3) occurrence of disruptive behavior that undermined a culture of safety [6], or (4) other event for which the resident would have desired a debriefing. Residents were also asked whether at least some bare-minimum components of a proximal debriefing were associated with the events, such as a short, dedicated conversation about the event soon after the event or care associated with it.

Results: A total of 37 critical events were identified over a three-month period. All residents opted to participate when approached (100% response rate). The majority of events experienced by the anesthesia residents occurred outside the operating room, with a spectrum of events that ranged from significant hemodynamic instability/cardiac arrest to human factors between providers (see Table). The overall rate of debriefing was less than 40%, and over one-third of all events involved at least one communication breakdown.

Conclusion: Perioperative crises occur multiple times each week at a large medical center. The distribution of event locations may represent the broad scope of responsibility of the anesthesia resident in this setting. Although residents frequently expressed a desire for further discussion following critical events, debriefing only occurred for 14 of the 37 documented events (37.8%). Knowledge of the diversity of critical events can inform and empower a more effective implementation of a departmental debriefing program. This pilot study helps to describe and expand upon what residents perceive as being critical events, and in doing so further identifies strategic avenues for successful program implementation. Given current priorities in health services research towards provider wellness, physician burnout, and crisis management, further research on this topic is imperative.

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PS 56 (2000)
Predicting Need for Intubation in the Field: Comparison of Glasgow Coma Scale To Vital Signs

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Introduction: A significant cause of preventable pre-hospital deaths in trauma patients is the failure to adequately secure the airway. Endotracheal intubation is the primary technique to control an unsecured airway in the field. The ability to predict the intubation needs of trauma patients in the field will improve pre-hospital care by refining the decision-making of providers in the field. In the field, objective data includes vital signs, saturation, and the glascow coma scale (GCS). We hypothesized that GCS would be a better predictor of the need for intubation in the field compared to vital signs (VS).

Methods: The study was approved by the Institutional Review Boards(IRB) from the University of Maryland. From our trauma registry, we identified all patients > 17 years of age transferred directly to our level one trauma center and their associated field intubation status between Jan 1, 2006 and Nov 5, 2015. The following data were available: systolic blood pressure (SBP), respiratory rate (RR), heart rate (HR), peripheral oxygen saturation (SPO2), field Glasgow Coma Scale (GCS), and its components verbal (GCSv), eye movement (GCSe) and motor (GCSm). The Shock Index (SI=HR/SBP) is predictive of mortality and other critical events in emergency department [Ref 1], so it was included and compared with other VS. Using logistic regression analysis, we assessed the individual and combination of VS and GCS as predictors of field intubation. Receiver operating characteristic (ROC) curves were constructed and the area under the ROC (AUROC) was used to assess the prediction power. To compare the difference of AUROC results, the DeLong method [Ref 2] was used and a p-value <0.05 was considered as statistically significant.

Results: Over the study period, 2365 of 49611 (4.8%) adult trauma patients received field intubation prior to trauma center arrival. The total GCS and each element of the GCS (GCSe, GCSv, GCSm) predicts the need for intubation in the filed with AUROCs of 0.84, 0.83, 0.81, and 0.82 respectively. SBP, RR, HR, SPO2, SI and combination of all VS predicts the need for intubation in the field with AUROCs of 0.60, 0.58, 0.50, 0.58,0.62 and 0.62 respectively. The optimal field intubation thresholds for GCS's were GCS â‰¤ 11, GCSe â‰¤ 2, GCSv â‰¤ 3 and GCSm â‰¤ 5. All of the GCS's AUROCs were significantly better than VS ($p<0.0001$). Combining GCS and VS improves the AUROC up to 0.85. Adding age to GCS and VS does not improve the prediction results. All individual AUROC results were statistically significant.

Conclusion: Field vital signs do not show strong prediction power for field intubation. Pre-hospital GCS is a better predictor for field intubation than vital signs. Patients in less conscious states are more likely to require intubation.

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PS 57 (2036)
What are the Characteristics of Patients Who Want Perioperative Music Therapy?

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Introduction: Music decreases activity of the sympathetic nervous system,[1] and in the perioperative setting, has been shown to reduce anxiety, pain, the need for analgesia, and also to improve satisfaction.[2] Since this cost-effective intervention has a large body of supportive evidence, we sought to offer music - delivered via iPods and headphones - in the perioperative period to Veterans scheduled to undergo major surgery at the Durham Veterans Affairs Medical Center (VAMC).[2] We examined the characteristics of patients who 'wanted to listen to music during surgery'.

Table 1.

	Yes (n=2,179)	No (n=1,035)	Total Population* (n=3,235)
Average Age (years)	60	65	62
Gender			
Male	1,930 (66%)	974 (33%)	2,924 (90%)
Female	249 (80%)	61 (20%)	311 (10%)
Race **			
Caucasian	1,142 (63%)	654 (36%)	1,808 (56%)
African-American	957 (72%)	358 (27%)	1,322 (41%)
Other	113 (76%)	32 (22%)	148 (5%)
Co-morbidities			
% visited Mental Health Clinic	599 (69%)	260 (30%)	865 (27%)
% visited Pain Clinic	177 (70%)	73 (29%)	252 (8%)
% visited SUD Clinic	133 (68%)	63 (32%)	197 (6%)
% with Opioid Use ***			
Chronic Use > 90d supply	348 (67%)	169 (33%)	519 (16%)
Non-chronic Use ≤ 90d supply	1,800 (67%)	852 (32%)	2,671 (83%)
Mean Pain Score > 4	917 (71%)	371 (29%)	1,294 (40%)

* 21 Veterans (<0.1%) in Total Population answered Unsure/Doesn't Matter and were not included in Yes/No analyses.

** = Subjects could report more than one race.

*** = We do not have opioid data on a few subjects.

Methods: An assessment of readiness for the receipt of music among patients and readiness for the delivery of music among providers is warranted per the Consolidated Framework for Implementation Research (CFIR).3 To assess whether Veterans 'wanted' perioperative music therapy, we modified our standard pre-anesthesia evaluation note (in the VA's Computerized Patient Record System) to include a single question ('If available, do you want to listen to music during surgery?') with two possible responses (Yes/No). We identified patients who were asked this question in our outpatient pre-anesthesia clinic and extracted their responses by 'text-mining' the electronic note. We then extracted data on certain characteristics of these patients (attributes that might be relevant to the beneficial effects of perioperative music). Table 1 shows overall demographic characteristics and distribution of visits to Mental Health, Pain, and Substance Use Disorder (SUD) Clinics in the 2-year period prior to surgery, opioid use in the 180 days prior to surgery (chronic use defined as opioid prescriptions filled for >90 days), and mean pain scores in the 90 days prior to surgery. Differences between Veterans who answered Yes vs. No were examined to evaluate the characteristics of patients who 'wanted' to listen to music during surgery.

Results: Overall, of 3,235 Veterans with valid responses, the mean age was 62 years, 90% were male, 56% Caucasian, and 27%, 8%, and 6% had visited a Mental Health, Pain, and SUD Clinic, respectively. We found that 16% met the definition of chronic opioid use and 40% had a mean pain score >4 (on 0-10 numeric scale). About 2/3rd answered Yes, and these Veterans were, on average, slightly younger (60 vs. 65 years old) than those who said No. Women were more likely to answer Yes; African-Americans were more likely to answer Yes (vs. Caucasians); and, Veterans who had visited Mental Health, Pain, and SUD Clinics were all more likely to answer Yes (vs. No). Veterans who had mean pain scores >4 were more likely to answer Yes. Chronic opioid use was not associated with preference for music compared to non-chronic opioid use.

Conclusion: Of over 3,000 patients evaluated in an outpatient pre-anesthesia clinic at the Durham VAMC, 2/3 wanted to listen to music during surgery. Veterans with mental health diagnoses, chronic pain, and SUD were more likely to opt for music.

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PS 58 (1228)
A Qualitative Study of the Teaching and Learning of Internal Jugular Vein Cannulation

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Introduction: Cannulation of the Internal jugular vein, though usually uneventful, can be associated with life-threatening complications [1]. Ultrasound guidance is therefore advocated in national and international guidelines on the grounds of patient safety [1, 2], however audit indicates that its potential benefits have not translated universally into practice [3]. It has been suggested that inconsistent education and training may in-part be responsible for this; and case reports have demonstrated that serious complications can occur even during supervised procedures [4]. Clinical educators are therefore faced with a dilemma regarding the stage of competency at which 'hands-on' experience is appropriate. This study examined how ultrasound-guided internal jugular vein cannulation is taught and learned in the hospital environment.

Methods: An ethnographic approach, focussing on the observation of practice in its usual setting, was employed in general theatres, intensive care, and cardiothoracic theatres in two acute hospitals in the North of England. A 'maximum variation' sampling strategy was used, aiming to observe the widest possible variety of practice. Methods comprised interviews, observations of practice and focus group discussions. Field notes and interview transcripts were analysed using an inductive thematic method to identify themes relevant to education [5]. Thirty-nine attempted internal jugular cannulations were observed, of which 36 were successful. In addition, ten interviews and thee focus groups were conducted with anesthesiologists and critical care physicians. Quality measures included triangulation and participant validation [6].

Results: Thirty-three consultant and sixteen trainee anesthesiologists participated in the study. There were no exclusions. Three educational themes were identified from the data: 'resurgence', 'trust', and 'reciprocity'. In 'resurgence', it was identified that although apprenticeship gave way to didactic course-based learning during the introduction of ultrasound technology, learning has since reverted to apprenticeship in the clinical setting [7]. However the 'resurgent' apprenticeship takes a modified form characterised by the presence of multiple 'masters', necessitated by the structure of medical training in the United Kingdom. In 'trust' the need for trainers to trust their trainees in order to permit them to gain 'hands-on' experience of procedures, and the strategies by which trustworthiness is assessed are explored. In 'reciprocity' the beneficial influence of trainees and institutions on one another is described.

Conclusion: This study adds to our understanding of how procedural skills are taught and learned, and emphasises the importance of clinical teachers' understanding of the apprenticeship process. It provides insights into under-investigated topics such as the use of 'permitted mistakes' on real patients to stimulate reflection, the challenge of assessing competency, and the roles played by trainees in distributing innovations and promoting good practice.

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PS 59 (1547)

Trends of Intraoperative Opioid and Non-Opioid Analgesic Use and Associated Postoperative Pain Scores at an Academic Tertiary Care Hospital over a Four-Year Period

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Introduction: It is not known if reports by the Center for Disease Control and Prevention[1] and the Anesthesia Patient Safety Foundation[1-2] that highlight the significant morbidity and mortality associated with opioids have resulted in changes in perioperative opioid administration practices. This study investigates current trends of intraoperative opioid and non-opioid analgesic utilization at a large academic tertiary care hospital over a four-year period.

Methods: Intraoperative data of all surgical patients requiring anesthesia at the University of Virginia Health System were gathered retrospectively from an electronic medical record from March 2011 to November 2014. Intraoperative opioids doses were converted to units of morphine equivalents (ME) and monthly averages were compared to evaluate the trend of use over this time frame. Additionally, the number of non-opioid adjuncts used per case, which included acetaminophen, dexmedetomidine, ketamine, ketorolac, lidocaine infusion, and magnesium, were calculated into monthly averages to compare the trend of use during the same time frame. Pain scores on arrival at the post-anesthesia care unit (PACU) were evaluated on a 0-10 numeric pain rating scale. Median ME were also compared to grouped pain scores visually with box-and-whisker plots. As a sub-analysis, patients who received only opioids and were not treated with non-opioid adjuncts were also analyzed, comparing monthly ME and initial PACU pain scores over time. As a surrogate for case complexity, case duration was demonstrated with color variations in the graphs of this sub-group. Linear regression analyses were completed using Tableau analytics software with null hypotheses that the slopes were equal to zero.

Results: We identified 101,484 unique procedural cases requiring anesthesia during the study period. Mean intraoperative opioid use decreased over time from 14.2 mg ME in 2011 [95% Confidence Interval (CI) 13.5-15.0 ME] to 9 mg ME in 2014 (CI 8.3-9.8), a 37% reduction in opioid use ($p<0.001$) (Fig 1). Mean number of non-opioid analgesics per case increased over time from 0.66 in 2011 [95% CI, 0.64-0.71] to 1.45 in 2014 (CI, 1.42-1.51), a 120% increase in use of non-opioid analgesic adjuncts ($p<0.0001$) (Fig 2). Mean PACU pain scores over the same time period also decreased: from 5.5 (CI 5.2-5.6) to 3.8 (CI, 3.6-4.0), a 31% reduction ($p < 0.001$) (Fig 1). Grouped pain scores had a direct correlation with median ME (Fig 3). In our sub-analysis, we identified 3,076 cases treated only with opioids. In this sub-group mean intraoperative opioid use decreased over time from 15.0 mg ME in 2011 (CI 13.5-16.5) to 7.5 mg ME in 2014 (CI 6.0-9.0), a 50% reduction ($p < 0.0001$) (Fig 4). Mean PACU pain scores in this sub-group over the same time period also decreased from 3.6 (CI 3.2-4.0) to 1.3 (CI 0.9-1.7), a 64% reduction (Fig 5).

Conclusion: Our data demonstrate a decrease in intraoperative opioid use coinciding with an increased use of non-opioid adjunct analgesics, as well as improved pain scores over a four-year time period at our institution. The opioid-only sub-group analysis also demonstrated reduced intraoperative opioid use with improved pain scores over time. Reduced opioid-induced hyperalgesia and tolerance may play a part in the improved pain control. These findings support the use of non-opioid adjuncts in the perioperative setting and suggest that anesthesiologists have changed their practice based on concerns for opioid-induced complications.

continued on page 285

Poster Presentations, *continued from page 284*

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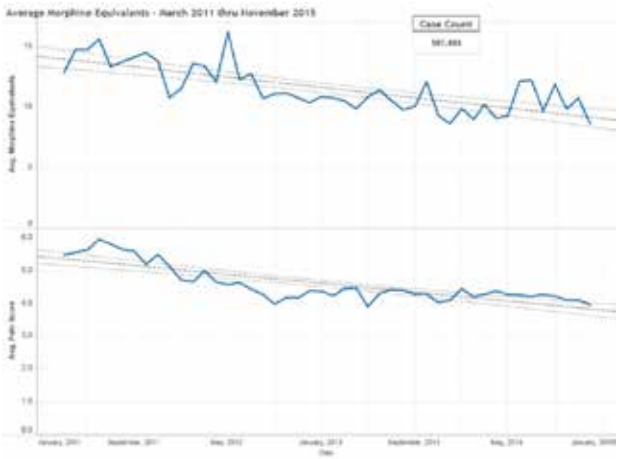
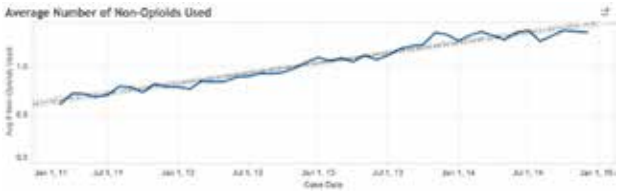
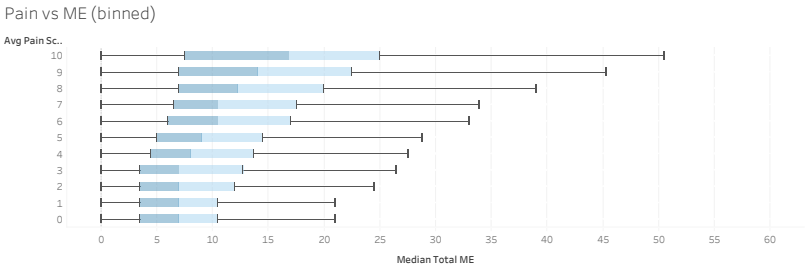
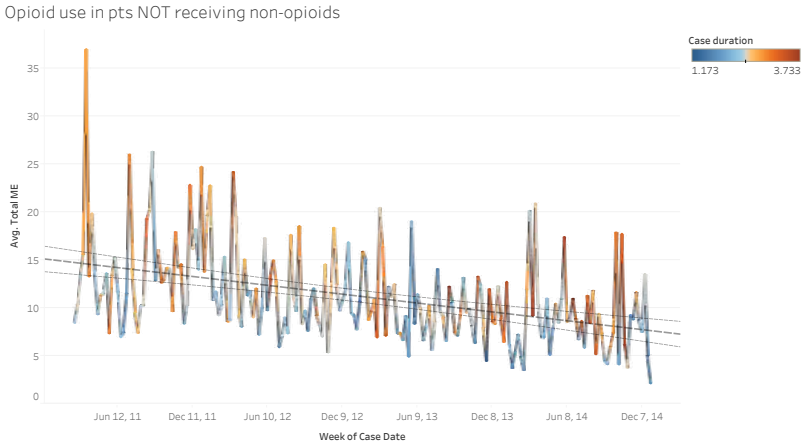






Median Total ME for each Avg Pain Score (bin). Details are shown for Avg Pain Score (bin). The data is filtered on Total ME and Avg Pain Score. The Total ME filter ranges from 0 to 60. The Avg Pain Score filter keeps non-Null values only.



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Poster Presentations, *continued from page 285*

PED 60 (1556)
Transfusion Thresholds and Adverse Outcomes in Pediatric Cardiac Surgery Patients with and without Cyanotic Disease

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Introduction: In adult and pediatric cardiac surgery patients the safety of a restrictive transfusion trigger has been suggested [(1-4)], but the ideal transfusion threshold in cyanotic children is unclear and the effects of higher hemoglobin (Hb) targets have not been studied. The primary hypothesis tested in this study was that higher hemoglobin (Hb) targets are associated with adverse outcomes in pediatric cardiac surgery patients, and the Hb threshold for this effect is higher in patients with cyanotic disease.

Methods: After IRB approval, we reviewed 314 pediatric cardiac surgery cases at Johns Hopkins Hospital from March 2013-June 2015. We merged three databases from our institution including: our Pediatric Cardiac Surgery STS Database, Blood Management Database, and Impact Online Database. The primary outcome (hospital-acquired infection) was determined using ICD-9 and ICD-10 codes. Secondary outcomes included mortality and length of stay (LOS). By chart review each patient was classified as cyanotic vs. acyanotic and we obtained the initial post-operative Hb upon admission to the PICU which was used to assess liberal vs. restrictive transfusion strategy. We used Wilcoxon Rank to compare medians for LOS, and Chi-square to compare percentages for infection rates.

Results: We included all pediatric cardiac surgery patients from from March 2013 until June 2015 and excluded patients where the first postoperative hemoglobin could not be identified by retrospective chart review. The infection rate was increased with a target Hb level above 13 g/dL in the acyanotic group (P<0.05), with a trend for an increase above 15 g/dL in the cyanotic group (P=0.10) (Figure 1A). Patients were more than 4-times more likely to have an infection in the highest Hb groups. LOS was increased in the highest Hb target groups in both the acyanotic and cyanotic subgroups (P<0.05) (Figure 1B). There was no significant difference in mortality among the groups. There was no evidence of confouding bias as the STAT scores 1-2 and 3-5 and re-do sternotomies were similar in the Hb target groups. There was a trend towards increased blood utilization in the higher Hb target groups but this was not statistically significant.

Fig. 1A

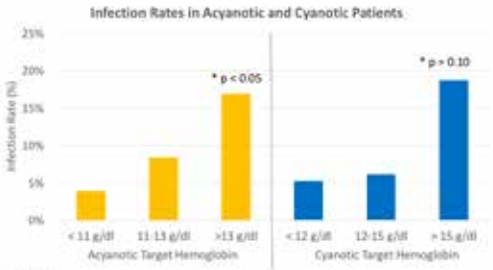
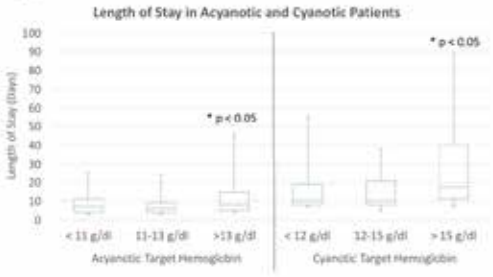


Fig. 1B



Conclusion: The results support our hypothesis that transfusing to a higher Hb target is associated with adverse outcomes, and the Hb threshold for this effect is higher with cyanotic disease. Previous studies have analyzed the effect of a restrictive transfusion strategy and shown no differences in clinical outcomes however our study is the first to show that transfusing to a higher Hb is associated with increased morbidity. Potential mechanisms for increased infections include non-transferrin bound iron in transfused blood which can promote infections (5).

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Poster Presentations, *continued from page 286*

PED 62 (1535)
The Under Accounted for Role of Hypercarbia & Hypoxia in the Neonatal Rodent Models of Anesthesia-Related Developmental Delay

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Introduction: The potential for anesthetics to cause developmental delay has resulted in two major prospective human studies, the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) (1) and General Anesthesia versus Spinal Anesthesia (GAS) (2) studies. Neither study found that a single exposure to inhalational anesthetics resulted in developmental delay. These results conflict with over a decade of research in neonatal rodent models. Animal modeling of anesthetic effects on human neonates is a challenge, as preterm infants, regardless of anesthetic exposure, are at risk of hypercarbia and hypoxia. Herein, through a detailed review, we test the hypothesis that hypercarbia and hypoxia occurs in rodent models of neurodevelopmental delay, potentially impacting its relevance to the human experience.

Methods: A literature search of PubMed and Medline from 2001-2016 was conducted using the search terms isoflurane, sevoflurane, nitrous oxide, propofol, ketamine, and midazolam in rat and mouse studies of PostNatal Day (PND)-15 or younger. Studies were categorized by animal age, anesthetic type, route, frequency, duration & outcomes (apoptosis, behavior, etc.). Studies were further characterized by FIO2 during exposure and recovery, spontaneous (SV) vs. controlled ventilation (CV), monitoring of oximetry and/or Arterial Blood Gas (ABG) and mortality. All articles were evaluated by three authors (RL, KK, and TF) for accuracy.

Results: One hundred & four studies, covering PND 3-15 were included. Outcomes included behavior (51), apoptosis (66), and other (50). Anesthetics included N20, midazolam, isoflurane, xenon, sevoflurane, ketamine, and propofol. SV occurred in 102/104 (98%), and CV in 2/104 (2%) studies. Animals underwent anesthetic exposure under 21-30% O2 (78%), with fewer (22%) under 60-100% O2. Recovery occurred in air in 100/104 (96%). ABG analysis was conducted in 40/104 (38%) studies, primarily via LV puncture. Most studies reported normoxia and normocarbia (77%), while others reported severe hypercarbia (23%). Surface oximetry was employed in 6/104 (6%) studies, reporting both normal oxygenation (67%) and hypoxia (33%). Mortality was only reported in 37/104 (36%) studies, and ranged from 0% - 60%.

Conclusion: We identified several concerns that may, in part, explain the divergence from rodent and human data. Most studies were conducted during SV, not the standard for humans. Monitoring of ventilation was inconsistent and the results widely divergent, with several studies reporting severe hypercarbia, others reporting hypoxia, while many others report both normoxia and normocarbia. Reporting of mortality was also inconsistent, but it is clear that both hypercarbia and hypoxia contributed to mortality and may have impacted outcomes in survivors. The inadequate quality of the ABG data is highlighted by studies reporting 'normal' ABG data while also reporting mortality. It is unlikely that LV sampling after sternotomy yields data representative of the undisturbed rodent under anesthesia. Consideration should also be given to conducting these studies with greater levels of supplemental oxygen both during anesthetic exposure, and in recovery. Both chemical and molecular approaches exist to detect the occurrence of hypoxia and should be employed. Reporting of mortality should be required for publication as it impacts interpretation of reported results.

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PED 63 (1120)
Mitochondrial cAMP-dependent Phosphorylation in the Developing Murine Brain

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Introduction: Oxidative stress has been implicated in anesthesia-induced neurotoxicity and ROS arise from mitochondria in this setting. We have demonstrated that isoflurane activates cytochrome oxidase (CcOX), the terminal oxidase of the respiratory chain, resulting in mitochondrial lipid peroxidation in the newborn mouse forebrain. However, combined exposure to isoflurane with carbon monoxide (CO), a known CcOX modulator, hyperphosphorylated CcOX tyrosine residues, prevented CcOX stimulation, limited oxidative stress in a dose-dependent manner for CO, and abrogated isoflurane-induced defects in memory acquisition. Phosphorylation of tyrosine 304 of CcOX subunit I, the active site, is thought to occur via a cAMP-dependent pathway, however, the mechanism of CcOX tyrosine hyperphosphorylation during combined exposure to isoflurane with CO is unknown. Thus, we hypothesized that CO would activate the cAMP-PKA pathway within forebrain mitochondria of newborn mice during isoflurane exposure. We aimed to identify components of the adenylyl cyclase-cAMP-PKA pathway within mitochondria, to quantify mitochondrial cAMP levels, and to measure PKA activity.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. 7-day old male and female C57Bl/6 mice underwent 1-hour exposure to 0 ppm (air), 5ppm, or 100 ppm CO in air with or without isoflurane (2%). Thus, six different cohorts were evaluated. Forebrain was harvested immediately after exposure and mitochondria isolated by differential centrifugation. Steady-state levels of sAC, AKAP121, and PKA were determined with immunoblot analysis and densities normalized to the VDAC loading control. Mitochondrial cAMP levels were determined with a direct fluorometric immunoassay and PKA activity measured via ELISA. We evaluated 4-6 animals per exposure group. Significance was assessed with non-parametric Kruskal-Wallis test and post hoc Bonferroni correction and set at $P < 0.05$.

Results: Each component of the adenylyl cyclase-cAMP-PKA pathway localized within forebrain mitochondria without differences in steady-state levels of sAC, AKAP121, or PKA between cohorts. Mitochondrial levels of cAMP were significantly increased in both cohorts exposed to CO with isoflurane. Specifically, cAMP increased in mice exposed to 5 ppm CO with isoflurane versus cohorts exposed to isoflurane or 5 ppm CO alone. In addition, cAMP increased in animals exposed to 100 ppm CO with isoflurane versus isoflurane-exposed mice. Surprisingly, forebrain mitochondrial PKA activity was increased only in animals exposed to 100 ppm CO with isoflurane.

Conclusion: The findings support the notion that CcOX tyrosine hyperphosphorylation occurs via a cAMP-dependent pathway following combined exposure to CO with isoflurane. However, activation of PKA within mitochondria occurred only following exposure to highest CO concentration. Thus, our data challenges the paradigm that phosphorylation of tyrosine 304 of CcOX subunit I is mediated by a tyrosine kinase downstream of PKA. Our results suggest that cAMP-mediated tyrosine kinase activation within mitochondria can occur via a PKA-dependent and PKA-independent manner. These provocative findings carry significance for our understanding of post-translational modification of CcOX, a key regulatory mechanism. Furthermore, the work provides insight into how combined exposure to CO with isoflurane confers anti-oxidant protection in the developing brain.

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PED 64 (1092)
Reduced Hemorrhage with Îµ-Aminocaproic Acid in Pediatric Craniofacial Reconstruction

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Introduction: Surgical correction of craniosynostosis is a complex procedure that often results in massive blood loss in pediatric patients. Antifibrinolytics have been shown to reduce hemorrhage in children undergoing other types of surgery and recent work suggests that Îµ-aminocaproic acid (EACA) may limit blood loss during pediatric craniofacial surgery. However, the efficacy of EACA using a targeted dosing strategy based on pharmacokinetics in this clinical context has never been evaluated. Thus, the aim of this study was to determine if pharmacokinetic-based dosing of EACA was associated with decreased hemorrhage in children undergoing craniofacial surgery. We hypothesized that patients who received EACA would have less intraoperative blood loss and fewer blood donor exposures compared with those not treated with antifibrinolytics.

Methods: 44 children with craniosynostosis (4 mo-8 yrs) who underwent reconstructive surgery at Children's National Medical Center (2013-2015) were retrospectively evaluated. 18 patients received EACA intraoperatively (100 mg/kg load prior to incision followed by 40 mg/kg/hr continuous infusion for the duration of surgery) while 26 patients did not receive any antifibrinolytic. Demographic data was analyzed and a multitude of continuous and categorical perioperative variables were assessed. Primary outcome measures were intraoperative calculated blood loss, red blood cell (RBC) transfusion volume, number of blood donor exposures, and postoperative surgical drain output. Secondary outcome measures included operative time, number of sutures repaired, ICU and hospital LOS, crystalloid and colloid administration, hematocrit, and coagulation times. Normality of continuous outcomes was determined and means compared using a student's t-test. Categorical outcomes were compared using Fisher's exact test. P-value of <0.05 was considered statistically significant.

Results: There were no significant demographic differences between the two groups. Children receiving EACA had significantly lower calculated blood loss, reduced RBC transfusion volume, and fewer intraoperative blood donor exposures than patients who were not administered EACA. However, there was no significant difference in surgical drain output during the first postoperative 24-hours. No other differences between groups were noted.

Conclusion: EACA, administered based on pharmacokinetic dosing, was associated with reduced intraoperative hemorrhage in children undergoing craniofacial reconstructive surgery. These finding suggest that EACA should be considered as part of the strategy for blood conservation in this clinical context. Furthermore, it is possible that EACA could reduce the risks and costs associated with blood transfusion in this vulnerable population. A prospective, randomized controlled trial is needed to confirm that EACA causes a decrease in blood loss, limits transfusion requirements, and minimizes blood donor exposures in children undergoing such surgery.

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PED 65 (1508)
Rhesus Macaques Exposed to Isoflurane Anesthesia as Infants Display Disrupted Functional Connectivity as Juveniles

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Introduction: Animal data provides strong evidence that early anesthesia exposure during brain development results in neuronal and glial death, as well as injury to the surviving neuropil including damage to axons, dendrites, and synapses. We and others have recently shown that anesthesia exposure in infant non-human primates (NHPs) is associated with durable behavioral deficits[1-3] While several retrospective clinical studies have suggested that early-life exposure of children to anesthesia results in long-term cognitive deficits (particularly prolonged or repeated exposures), other studies have found no such effects. Results from the only two prospective clinical trials suggest that a short anesthesia exposure at a young age might be safe in children.[4,5] A critical gap in this field is the absence of a reliable, non-invasive biomarker of injury. To this end, we used our established translational model of infant neurotoxicity to test the hypothesis that 5h exposure to isoflurane (ISO) in the first week of life causes changes in brain connectivity that persist into adolescence in NHPs.

Methods: Differences in resting state-functional connectivity MRI (rs-fcMRI) were examined in 2 year old rhesus macaques (Macaca mulatta) that underwent single or multiple ISO exposures in infancy when compared to control, unexposed animals. All experimental procedures and animal study protocols were approved by the IACUC of the ONPRC. Infants were randomized to 3 groups in which they were exposed to 5h of ISO anesthesia once (ISO-Lo, n=8), 3 times (ISO-Hi, n=7) or not at all (control, n=8). Males and females were distributed equally among groups. Each animal underwent brain rs-fcMRI at 2 years of age, and rs-fcMRI measurements were examined for differences in connectivity. To identify neural networks most strongly impacted by ISO exposure in macaques, functional connectivity was computed between 82 previously identified ROIs (Ro1 ref 4) which formed the 7 networks seen in Figure 1. An ANOVA was performed using the three cohorts and the 7 networks as factors. Finally, a post hoc analysis was conducted to identify the network interactions driving the relationships.

Results: rs-fcMRI in 2 yr-old NHP's unveiled significant exposure group:neuronal network interactions ($F(54,72596) = 4.62$, $p < 0.0001$). Post-hoc analyses revealed specific neuronal networks driving the interactions. As seen in Figure 2, there were significant differences between the following system pairs: Default mode network (Def):motor system (p=0.005), Def:limbic system (p=0.04), insular-opercular system: auditory network (p=0.02), limbic:visual system (p=0.02), and visual:visual system (p=0.03). In 3 of these pairs, the effects appear to be dose-dependent, revealing more drastic disruptions in ISO-Hi than ISO-Lo when compared to controls. (Figure 2)

Conclusion: Infant NHPs exposed to ISO display disrupted functional connectivity years after the exposure. The affected cortical areas are involved in higher order cognitive processes (i.e. episodic memory, visuospatial processing) and motor function. Though it requires further testing before clinical application, these data suggest that rs-fcMRI could be a sensitive, non-invasive biomarker of changes in functional brain architecture following anesthesia exposure. This technique holds promise for comparing anesthetic effects in different patient populations, comparing differing effects of multiple anesthetic agents, or measuring the efficacy of neuroprotective interventions.

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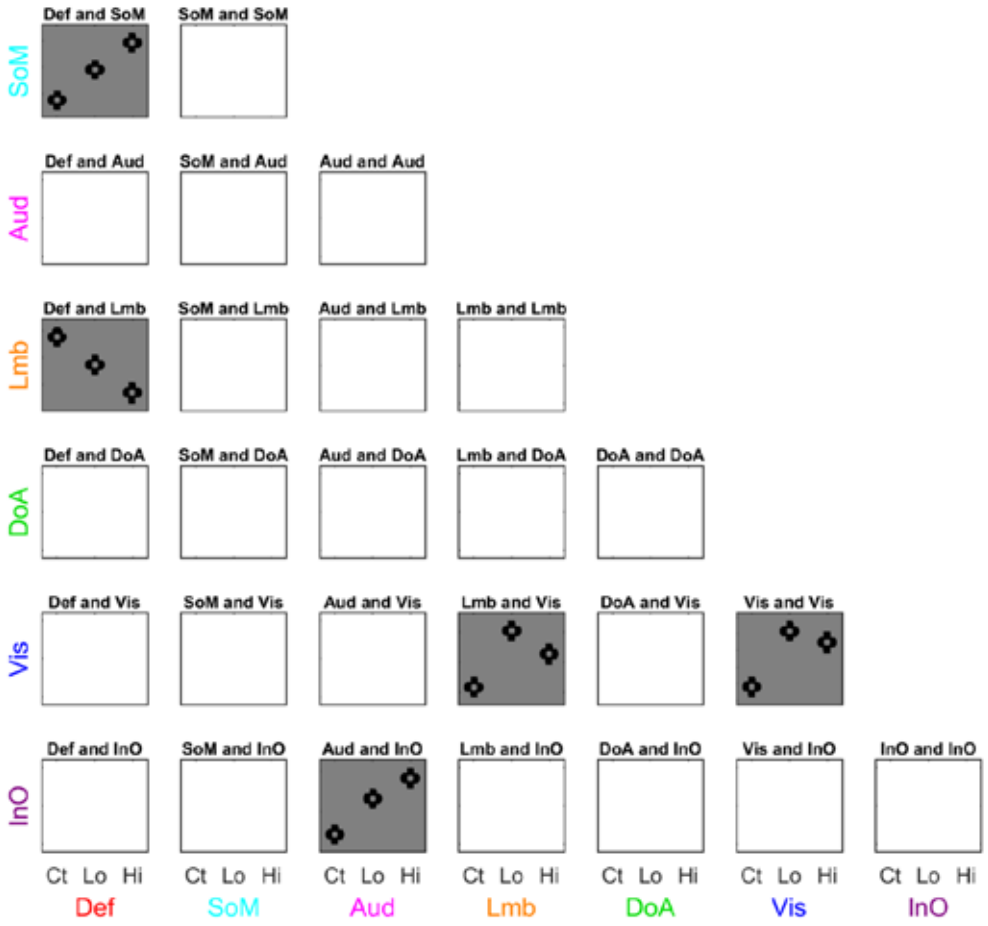

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PA 66 (1194)

Postoperative Pulmonary Complications Not Increased With Combined Regional + General Anesthesia Compared to General Anesthesia Alone: A Sub-Analysis Of The Perioperative Research Network Study

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Introduction: Postoperative pulmonary complications (PPCs) are a leading cause of poor surgical outcomes. The Perioperative Research Network (PRN) investigators recently investigated the incidence and impact on mortality and hospital use of PPCs in 1,202 ASA 3 physical status patients presenting for non-cardiothoracic surgery and requiring â‰¥2 hours general anesthesia and mechanical ventilation (the PRN PPC study) [(1)]. In this multicenter prospective observational study, patients who had combined regional + general anesthesia (RA+GA), compared to general anesthesia (GA) alone, were significantly more likely to have â‰¥1 PPC [(1,2)]. This was surprising considering the benefits in respiratory function presumed with regional anesthesia [(3,4,5)]. A meta-analysis of 141 trials and 9,559 patients found that neuraxial blockade reduced respiratory depression by 59% and pneumonia by 39% (both P<0.001) [(3)]. Receiving RA+GA is often considered a marker of surgery and/or patient complexity. For this sub-analysis of the PRN PPC study patients (1), we hypothesized that the presence of â‰¥1 PPC was not increased in patients receiving RA+GA than in GA patients after adjusting for confounders.

Methods: We performed a secondary analysis of the PRN PPC study patient cohort described above. The 1,202 patients participating in the original study (May to November 2014) were included. IRB approval was obtained at each participating institution. Predefined PPCs (pneumonia, bronchospasm, ARDS, atelectasis, pneumothorax, pleural effusion, prolonged [>1 day after end of surgery] supplemental oxygen by nasal cannula and/or facemask, postoperative noninvasive ventilation, and re-intubation with postoperative mechanical ventilation) occurring within the first 7 postoperative days were prospectively identified. For this sub-analysis patients were classified as receiving RA+GA or GA alone. Bivariable and multivariable hierarchical logistic regression analyses were used to investigate the association of RA+GA with â‰¥1 PPC. Relevant covariates adjusted for in the model were identified as those considered clinically relevant, those with p<0.05 in bivariable analysis, and those with no significant statistical association with other relevant variables.

Results: RA+GA was performed in 266 (22.1%) and GA in 936 (77.9%) patients. RA+GA patients were more likely to have cancer, abdominal/pelvic non-emergent surgery, greater estimated blood loss and intravenous fluid administration than GA patients (Table 1). RA+GA patients had a higher incidence of â‰¥1 PPC (42.1%) than GA patients (30.9%) (site adjusted p=0.007, Table 1). After adjusting for other significant covariates from the bivariable analysis, RA+GA was not independently associated with â‰¥1 PPC (adjusted OR 1.37; 95% CI, 0.83-2.25; p=0.165) (Table 2).

Conclusion: At least 1 PPC was more common in patients receiving RA+GA than GA alone. However, RA+GA was not associated with â‰¥1 PPC after adjusting for confounders in the logistic regression analysis. These results support that the more often presence of PPCs in patients receiving RA+GA in the PRN PPC study is likely related to surgical and/or patient complexity. Interpretation of associated variables from observational studies should be cautious and requires adjusting to confounders.

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PA 67 (1708)
Postoperative Complications Affecting Survival After Cardiac Arrest in General Surgery Patients

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Introduction: Postoperative cardiac arrest is a serious complication associated with an extremely high mortality rate. Prior studies have focused on identifying risk factors for postoperative cardiac arrest [1, 2], but the relationships between other postoperative complications and mortality in those with cardiac arrest have not been clearly defined. We examined the associations between complications occurring prior to cardiac arrest and 30-day mortality in general surgery patients experiencing a cardiac arrest event after surgery.

Methods: With IRB exemption, the 2012-2013 ACS-NSQIP was used to obtain a cohort of patients undergoing inpatient general surgery with cardiac arrest within 30 days of the procedure. Prior complication was defined as at least one of the following occurring prior to the postoperative day of cardiac arrest: 1) acute kidney injury, 2) acute respiratory failure, 3) deep vein thrombosis/pulmonary embolus, 4) myocardial infarction, 5) sepsis/septic shock, 6) stroke, and/or 7) transfusion. Complications were assessed as a single composite variable of one or more complications and as individual complications. Survival after cardiac arrest was assessed using Kaplan-Meier estimates and Cox proportional hazards modeling. For the analysis of individual complications, Bonferroni-adjusted criteria were used for multiple comparisons (P=0.05/7=0.007).

Results: A total of 1,730 patients with postoperative cardiac arrest were identified, representing an incidence rate of 0.5%. Among these patients, the day of surgery (Day #0) was the postoperative day with the greatest number of events (Figure 1), with 378 (22%) occurring on the operative day. Prior complications were significantly associated with patient characteristics such as ASA Physical Status, emergency procedure, chronic obstructive pulmonary disease, preoperative sepsis, and preoperative transfusions (Table 1). A total of 749 patients (43%) developed at least one complication prior to cardiac arrest and Kaplan-Meier plots demonstrated better survival in patients without complications compared to those with complications (Figure 2A), with Cox modeling also demonstrating an increased risk of mortality with prior complications in adjusted analyses (adjusted hazard ratio [aHR] 1.22, 95% confidence interval [CI] 1.08-1.37). Among individual complications, Kaplan-Meier plots demonstrated significant differences in post-cardiac arrest survival patterns comparing those with and without prior transfusion (Figure 2B) and myocardial infarction (Figure 2C), with acute kidney injury near the Bonferroni threshold (Figure 2D), but only myocardial infarction remained significantly associated with mortality in adjusted analyses (aHR 1.60, 95% CI [1.18, 2.18]).

Conclusion: Among general surgery patients with cardiac arrest, mortality is extremely high and many experience major postoperative complications prior to cardiac arrest, but only prior myocardial infarction is associated with excess mortality risk. Future studies should confirm these findings and identify factors affecting the risk of mortality in those with cardiac arrest after surgery to better manage the care of those who develop this devastating complication.

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Table 1. Characteristics of general surgery patients by complications prior to the day of cardiac arrest, American College of Surgeons National Surgical Quality Improvement Program, 2012-13.

Characteristic	No Complication N=984		Complication N=746		P-value
Age (years)	66.5	(14.9)	67.1	(14.2)	0.4
Female	432	(43.9)	323	(43.3)	0.8
White	641	(65.1)	472	(63.3)	0.4
ASA Physical Status					<0.001
1	5	(0.5)	3	(0.4)	
2	105	(10.7)	52	(7.0)	
3	462	(47.0)	303	(40.7)	
4	333	(33.8)	326	(43.8)	
5	79	(8.0)	61	(8.2)	
Emergency	405	(41.2)	351	(47.1)	0.014
Diabetic	282	(28.7)	242	(32.4)	0.09
Mechanical Ventilation	114	(11.6)	107	(14.3)	0.09
Dyspnea	180	(18.3)	115	(15.4)	0.12
Chronic Obstructive Pulmonary Disease	135	(13.7)	134	(18.0)	0.016
Current Smoker	186	(18.9)	159	(21.3)	0.2
Congestive Heart Failure	71	(7.2)	54	(7.2)	1.0
Hypertension	671	(68.2)	519	(69.6)	0.5
Acute Renal Failure/Dialysis	118	(12.0)	113	(15.2)	0.056
Sepsis/Septic Shock	363	(36.9)	354	(47.5)	<0.0001
Wound Infection	111	(11.3)	84	(11.3)	1.0
Functionally Dependent	141	(14.7)	133	(18.1)	0.063
Ascites	39	(4.0)	51	(6.8)	0.008
Steroid Use	91	(9.3)	96	(12.9)	0.016
Cancer	284	(28.9)	224	(30.0)	0.6
Bleeding Disorder	168	(17.1)	140	(18.8)	0.4
Preoperative Transfusion	92	(9.4)	107	(14.3)	0.001
Body Mass Index (kg/m^2)					0.4
<25	308	(31.3)	258	(34.6)	
25-30	243	(24.7)	205	(27.5)	
>30	384	(39.0)	257	(34.5)	
Missing	49	(5.0)	26	(3.5)	
Hematocrit (%)					<0.001
<29	165	(16.8)	170	(22.8)	
29-35	272	(27.6)	231	(31.0)	
35-41	287	(29.2)	210	(28.2)	
>41	241	(24.5)	126	(16.9)	
Missing	19	(1.9)	9	(1.2)	
Estimated glomerular filtration rate (mL/min/1.73 m^2)					0.2
<30	214	(21.8)	174	(23.3)	
30-60	248	(25.2)	198	(26.5)	
60-90	264	(26.8)	218	(29.2)	
>90	241	(24.5)	146	(19.6)	
Missing	17	(1.7)	10	(1.3)	

Continuous variables expressed as mean (SD). Categorical variables expressed as counts (%).
ASA, American Society of Anesthesiologists.

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PA 68 (1631)
Postoperative Acute Kidney Injury and Renal Recovery: A Report from the Multicenter Perioperative Outcomes Group

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Introduction: Acute kidney injury (AKI) is a serious complication following non-cardiac surgery, occurring in approximately 13% of patients and associated with a six-fold increased risk of mortality.[1,2] Postoperative AKI significantly increases patient care demands, as it is managed in 22% of intensive care unit admissions and leads to increased hospital cost and length of stay[2,3] Beyond the postoperative period, however, the impact of AKI on the recovery of a patient's renal function is less well described, with analyses limited to nonsurgical and frail elderly patient populations[4,5] To characterize the impact of AKI on renal recovery in a more generalizable surgical population, we performed this multicenter retrospective study.

Methods: We studied adult non-cardiac surgical cases from 2008 to 2015 across eight medical centers. Exclusions were outpatient procedures, patients with chronic renal failure, and specified surgical procedures (Figure 1). The primary outcome was AKI, defined as a serum creatinine increase of â‰¥0.3 mg/dL within 48 hours, or an increase of â‰¥50% above baseline within seven postoperative days. Secondary outcomes included â‰¥Stage 2 and Stage 3 AKI, defined as â‰¥100% and â‰¥200% increases from baseline, respectively; as well as renal recovery. Renal recovery was assessed by median creatinine value after postoperative day 30 and within 365 days. Complete recovery was defined by a creatinine returned to <0.3 mg/dL and <50% above baseline; partial recovery was defined by a persistently elevated creatinine improved by one AKI stage or greater; and no renal recovery was defined by maintained or worsened AKI stage. Preoperative patient characteristics studied included demographic, anthropometric, and medical history data classified by Elixhauser comorbidities. Procedural characteristics included procedure type, emergent status, case duration, and institution. Across perioperative characteristics studied, we developed a multivariable logistic regression model using AKI as the dependent variable; the regression model was developed with derivation (two-thirds) and validation (one-third) cohorts. Using a propensity score, patients were stratified by risk quartile (low, medium, high, and highest risk) for developing AKI. Renal recovery was assessed within each risk quartile.

Results: Of 141,809 cases studied, postoperative AKI occurred in 13,035 (9.2%) cases, with perioperative univariate risk factors similar to those identified via previous studies. Among patients with complete data for multivariable analysis in the derivation cohort, AKI incidence increased from 1.4% (low risk) to 4.0% (medium) to 7.8% (high) to 22% (highest risk) (Table 1). No renal recovery occurred for at least 13% of patients studied, whereas partial recovery occurred for at least 3.0% of patients studied. Among AKI risk quartiles, significantly lower rates of renal recovery were observed for higher risk quartiles ($p < 0.001$). Across AKI stages, complete renal recovery was greatest for among cases with Stage I (39%) compared to Stage II (31%) and Stage III (30%, $p < 0.001$).

Conclusion: Among a generalizable noncardiac surgical patient population, 9.2% of patients developed postoperative AKI. Among patients developing AKI, 16% demonstrated persistent renal injury up to one year after surgery. Our results confirm that long-term renal outcomes following postoperative AKI are significant, and that continued efforts to reduce risk of postoperative AKI must be sought.

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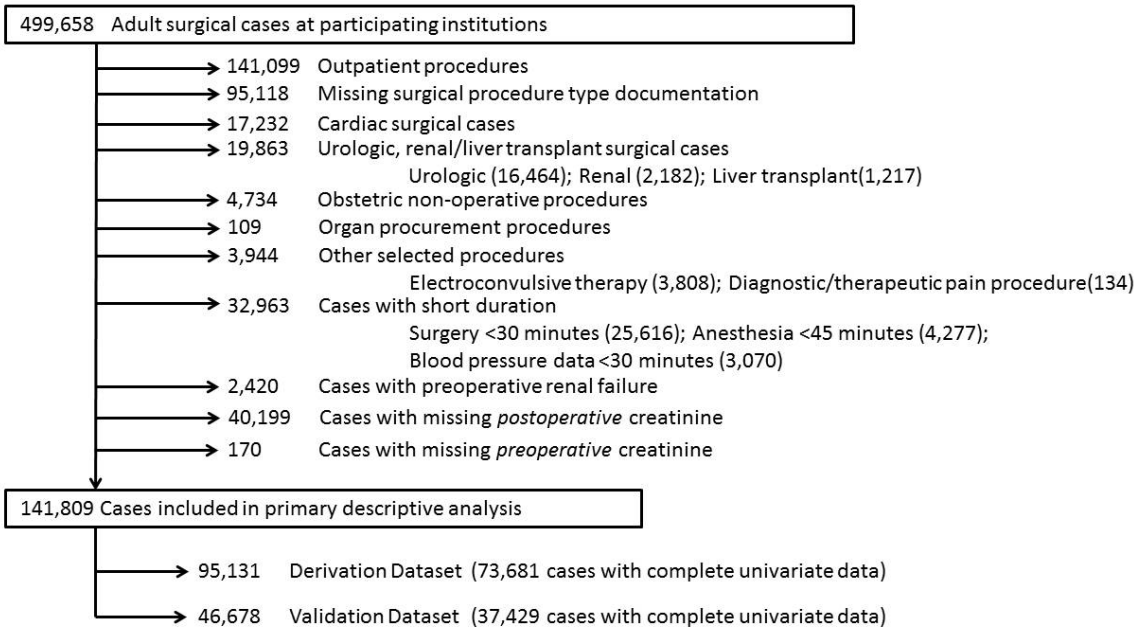

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PA 69 (1647)
An Evidence-Based Opioid Sparing Anesthetic Technique: Preliminary Data

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Introduction: Perioperative pain control remains problematic. Controlling acute pain, and acute on chronic pain, is an ongoing goal of research in anesthesiology. Opioid sparing techniques, due to side effects of the drugs (possible prolonged hospital length of stay) and increasing numbers of patients with physical dependence and/or tolerance to narcotics are also of particular concern. We developed an evidence-based and multimodal anesthetic technique using a lidocaine and dexmedetomidine infusion at its base. Since previous literature identifies benefit from opioid-sparing techniques in terms of return of bowel function, reduced pain scores, and shorter length of hospital stay in the perioperative period for abdominal procedures, we concentrated our investigation on urologic, gynecologic, and colorectal surgical patients [(1)]; there is no observed benefit with cranial or orthopedic procedures [(2)].

Methods: Over a two-month period we selected consecutive scheduled cases in which the procedure would last >2 hours. Study group 1 (25 patients): Prior to anesthetic induction, infusions of 1.) lidocaine, 0.03mg/kg/min, and 2.) dexmedetomidine, 0.05 mcg/kg/min were initiated without bolus. Anesthetic induction was achieved with propofol and volatile agent as necessary, then neuromuscular blocker and tracheal intubation. Ketamine, 10 mg IV was given prior to intubation and a second dose, 0.3 mg/kg IV bolus just prior to incision. Anesthetic maintenance was achieved with lidocaine and dexmedetomidine by continuous infusion and volatile anesthetic agent at 0.5 - 0.8 MAC. Hypotension was treated with a vasopressor in order to maintain a mean arterial blood pressure >65 mm Hg. Decadron, ondansetron, acetaminophen, ibuprofen, midazolam, and ketorolac were given if not contraindicated in both groups of patients. The target visual analog scale (VAS) during recovery was < 4. We compared the two groups using a two-sample t-test.

Results: With IRB approval, we compared 25 consecutive patients who had an opioid sparing anesthetic to 25 patients undergoing similar procedures, but with opioid supplementation to a general anesthetic. Our particular focus was on 1.) length of hospital stay, and 2.) post-operative analgesia requirements. We excluded patients with severe liver disease, end-stage renal disease, heart block or congestive heart failure.

Conclusion: Length of stay for the two study groups is not statistically significant. This is in agreement with another study which examined 'short stay' or same day discharge. Our study was also influenced by a preponderance of procedures accomplished with laparoscopy and robotic guidance. For example, there were no open nephrectomies performed during the study period, and some colorectal surgeries were also robotic procedures. In contrast to LOS data, no patient who underwent an opioid-sparing anesthetic was given an opioid during PACU stay or after discharge from PACU the next 24 hours. Either intravenous acetaminophen, ibuprofen, or ketorolac provided adequate analgesia. In this sense, the technique has been validated; when to use the technique, which patients would benefit, and cost comparison will require further study. Finally, in the PACU our study patients did not require use of opioids immediately and maintained visual analog scale (VAS) < 3. This confirms previously published data demonstrating an opioid-sparing effect [(3)].

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PA 70 (1781)
Identification of Barriers to Implementation of Lung Protective Ventilation in the Operating Room

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Introduction: Lung protective ventilation (LPV) with low tidal volumes (6 ml/kg), compared to high tidal volumes (>12 ml/kg) in the operative setting decreases post-operative pulmonary complications and the need for both invasive and non-invasive ventilatory support [1,2]. Despite the evidence, adoption of LPV in the operating room is not uniform across practices. An audit of 9,416 cases over a 6-month period at 5 sites in our institution demonstrated wide variation in delivered tidal volumes during general anesthesia. Determinants of healthcare professional practice are factors that might prevent or enable improvements in that practice. Understanding determinants of practice is a key step towards designing tailored interventions [3]. The objective of this study was to identify barriers and facilitators to implementation of lung protective ventilation in the operative setting at our academic medical center. This was part of a multidisciplinary quality improvement effort to increase adoption of LPV at our institution.

Table 1: Integrated Checklist for Determinants of Practice and Associated Survey Questions

Domain	Action or Survey Question
Guideline factors	Literature review
Health professional factors: Knowledge	Calculate TV for male and female patient examples What prevents you from using lung protective ventilation in the OR? What is lung protective ventilation? What would convince (or further convince) you to use lung protective ventilation? Education
Health professional factors: Attitudes	Do you believe that lung protective ventilation in the OR makes a difference on patient outcomes? The scientific evidence for lung protective ventilation in the OR is… What would convince you to use lung protective ventilation? Nothing - I do things my own way
Patient factors	Not included
Professional interactions	Not included
Incentives and resources	What is preventing you from practicing LPV? Information on my own practice patterns (feedback) What would convince you to use lung protective ventilation? A force function on the anesthesia machine
Capacity for organizational change	What is preventing you from practicing LPV? Time pressure
Social, political and legal factors	Not included

Methods: With IRB approval, a voluntary, anonymous 8-question survey was administered electronically to all anesthesia providers in our department through the Qualtrics survey platform. We used the Integrated Checklist for Determinants of Practice (4) as the framework for our questionnaire when applicable. This checklist divides determinants of practice into 7 broad domains (Table 1).

Results: A response rate of 38% was achieved. Across all providers, correct lung protective ventilator parameters (6-8 ml/kg) were chosen only 49% of the time, despite 73% of respondents indicating that they use lung protective ventilation all of the time or most of the time. The most common barrier to practice implementation was time pressure (56% of respondents). To better facilitate implementation of lung protective ventilation, survey responses indicate that further education on scientific evidence of the benefits of lung protective ventilation and education on how to implement lung protective ventilation in the operating room would be most beneficial. The perceived facilitators to implementation varied depending on title of respondent.

Conclusion: Though providers have background knowledge about lung protective ventilation, half are unable to correctly identify lung protective tidal volumes. Time pressure and knowledge appear to be the main barriers to practice implementation. These results will inform our implementation strategies, which will focus on audit & feedback, together with correct solution information (educational interventions regarding the evidence and the practical use of LPV).

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TRSL/BS 72 (1522)
Cerebral Vascular Thrombospondin-1 Associates with the Epsilon 4 Allele of Apolipoprotein E in Alzheimer's Disease

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Introduction: Alzheimer Disease (AD) is a global epidemic expected to affect over eight million people in the United States by 2030[(1)]. Inhaled anesthetics have been shown to increase beta (Î²)-amyloid in pre-clinical models, and inhalational anesthetics have also been associated specifically with post-operative cognitive dysfunction for elderly patients with the apolipoprotein E4 allele [(2,3)]. Î²-amyloid deposition within cerebral blood vessels, termed cerebral amyloid angiopathy (CAA), is found in up to 80% of patients with AD, and alters vascular integrity promoting micro- and intralobar-hemorrhage and stroke [(4)]. The matricellular protein thrombospondin-1 (TSP1) is a dominant inhibitor of the pleiotropic effects of vascular nitric oxide (NO) and has been linked to aging vasculopathy in animals and people [(5)]. We herein tested the hypothesis that TSP1 is induced in AD-associated CCA.

Methods: Quantification within cerebral vessels of immunofluorescent TSP1, as well as CCA and markers of reactive nitrogen and oxygen species (RNS and ROS), was performed in post-mortem brain tissue sections from a cohort of 24 individuals with AD and mild or severe CAA and further assessed in relation to expression of epsilon alleles 3 and 4 of apolipoprotein E (ApoE3 and 4) (institution approved protocol CORID #495). Samples were histologically graded for the severity of CAA.

Results: Immuno-reactive Î²-amyloid and TSP1 were significantly elevated in sections from individuals with the ApoE4 allele (ApoE3/4) when compared to individuals with only ApoE3 alleles (ApoE3/3). Additionally, vascular TSP1 expression was significantly decreased in women greater than 80 years old compared to women younger than 80. Conversely, vascular TSP1 expression was stable in cerebral vessels from elderly men suggesting an age-dependent sex association. Markers of ROS and RNS were significantly elevated in cerebral vessels with severe CAA compared to mild CAA burden, but were not altered as a function of ApoE allele expression.

Conclusion: These results for the first time demonstrate 1) a strong association in cerebral vessels of AD patients between anti-angiogenic TSP1 and the clinically more severe ApoE4 allele and 2) an association between vascular ROS and RNS with severe CAA burden. Future directions include examining the possible relationship between inhaled anesthetics with post-operative cognitive decline, CAA and micro-hemorrhage.

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TRSL/BS 73 (1709)

An Antagonist of the Anoctamin-1 Calcium-Activated Chloride Channel Relaxes Mouse Airway Smooth Muscle Despite ÃŸ-Adrenoceptor Desensitization and Attenuates MUC5AC Production

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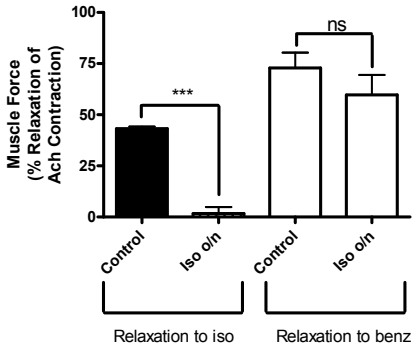
Introduction: As poorly controlled asthma is a major risk factor for acute bronchospasm, novel treatments for asthma are greatly needed. Anoctamin-1 (ANO1) is an important calcium-activated chloride channel expressed in both airway smooth muscle and airway epithelium. We have previously shown that antagonism of ANO1 acutely relaxes airway smooth muscle and have proposed ANO1 antagonists as novel therapies for asthma treatment. To further assess the clinical application of ANO1 antagonists, we investigated their effectiveness against two key components of asthma; epithelial cell mucus production and airway smooth muscle relaxation after ÃŸ-adrenoceptor desensitization since asthmatic patients often present with ÃŸ-agonist resistance. We hypothesized that ANO1 antagonists would retain the ability to relax airway smooth muscle despite ÃŸ-adrenoceptor desensitization. Furthermore, the potential therapeutic use of ANO1 antagonists for asthma raises some concern that antagonism could enhance mucus production as seen in cystic fibrosis. Thus, we measured the effect of ANO1 antagonists on the mRNA expression of MUC5AC, a primary component of airway mucus.



Muscle force in mouse tracheal rings. Tracheal rings were pre-incubated overnight +/- 100µM isoproterenol to induce β-adrenoceptor desensitization. Rings were mounted in a wire myograph and contracted with acetylcholine (Ach) and relaxed with a cumulative dose-response to isoproterenol (Iso). After washing, rings were re-contracted with Ach and then relaxed with 10µM benzbromarone (benz). Despite β-adrenoceptor desensitization (n=5; *** p< 0.001), benz was equally effective at relaxing Ach-contracted tracheal rings (n=5).

Methods: Tracheas of C57/BL6 mice were harvested and placed in Krebs buffer with or without 100ÂµM isoproterenol overnight. Tracheal rings were then mounted in a wire myograph in oxygenated Krebs buffer, contracted with acetylcholine (Ach) EC50 and then relaxed with isoproterenol (0.1nM to 10ÂµM) to demonstrate ÃŸ-adrenoceptor desensitization. Tracheas were then contracted again with an Ach EC50 and relaxed with 10ÂµM benzbromarone (ANO1 antagonist). NCI-H292 human mucoepidermoid cells were incubated with 5% cigarette smoke extract (CSE) for 24 hours in the presence of vehicle, 50ÂµM benzbromarone or 50ÂµM Eact (ANO1 agonist). Cells were harvested for RNA, and mRNA encoding MUC5AC and GAPDH was quantified using real time quantitative PCR.

Results: Mouse tracheal rings demonstrated ÃŸ-adrenoceptor desensitization after overnight incubation with isoproterenol (control 43.2 Â± 1.0%, vs iso overnight (o/n) 1.7 Â± 3.1% relaxation with isoproterenol, n=5, p<0.001). Benzbromarone (10ÂµM) relaxed control and ÃŸ-adrenoceptor-desensitized tracheal rings with equal efficacy (control 72.9 Â± 7.5%, vs 59.7 Â± 9.8 iso o/n, n=5, ns). CSE increased MUC5AC mRNA production 3.9 Â± 0.2 fold over control (p<0.05, n=6-7). When cells were treated with a combination of CSE and 50ÂµM benzbromarone, MUC5AC mRNA production was decreased to 0.7 Â± 0.1 fold of control. Treatment with Eact in combination with CSE increased MUC5AC to 64.8 Â± 35.1 fold (p<0.001, n=6-7).

Conclusion: The ANO1 antagonist benzbromarone relaxes airway smooth muscle after ÃŸ-adrenoceptor desensitization and also decreases MUC5AC production in airway epithelial cells. This data suggests a dual beneficial effect of ANO1 antagonism in airways; direct bronchorelaxation despite ÃŸ-adrenoceptor desensitization and attenuation of mucus production.

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None

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TRSL/BS 74 (1771)

Murine Cardiac Arrest and Cardiopulmonary Resuscitation Exposes the Glomerular Filtrate to Cardiac Protein and Leads to Chronic Kidney Disease

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Introduction: Perioperative acute cardiorenal syndrome leads to rapid development of chronic kidney disease (CKD)[1] However, current mechanistic studies in AKI to CKD transition have been carried out in animal models which do not mimic perioperative disease. We recently found that murine cardiac arrest and cardiopulmonary resuscitation (CA/CPR) is a model of acute cardiorenal syndrome.[2] A critical difference between CA/CPR and renal-only animal models of AKI is exposure to injury signals from the heart and other organs. We therefore hypothesized that CA/CPR would lead to CKD, and that cardiac-specific proteins would be upregulated in the glomerular filtrate after CA/CPR.

Methods: Murine CA/CPR was induced with potassium chloride and resuscitated 8m later with chest compressions and epinephrine. 2h after CA/CPR or sham (n=4/gr), 300 nL samples of glomerular filtrate were aspirated using a fluorophore-coated micropipette under in-vivo microscopic guidance and subjected to discovery nanoproteomics.[3] To determine organ specificity we developed an organ specificity (z) score for each protein identified in proteomic data from 28 mouse tissues.[4] 1 month after CA/CPR or sham, GFR and Î±SMA positive point fraction were measured to assess function and fibrosis. Statistical analysis was by t-test for 2 group comparisons and ANOVA with correction for multiple comparisons for proteomic organ specificity.

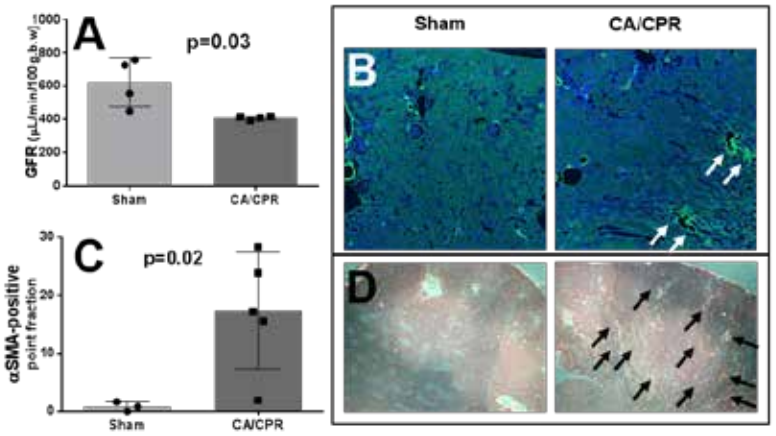

Figure 2: Renal failure and fibrosis 1 month after CA/CPR. A. GFR is reduced by 30% compared with sham. B. Renal αSMA (green) IHC in sham and CA/CPR. Arrows mark tubulointerstitial αSMA markedly enhanced in 1 month CA/CPR mice. C. Quantification of αSMA signal, n=8 total. D. Collagen stained with picrosirius red demonstrated with polarized light. Arrows mark extensive refraction only found in 1 month CA/CPR mice.

Results: 614 proteins were identified from in-vivo aspirated glomerular filtrate and MW distribution was consistent with filtered plasma. 355 matched proteins with organ specificity z score >3 SD. Kidney proteins were not upregulated 2h after CA/CPR. Cardiac-specific proteins were significantly more filtered 2h after CA/CPR (fold change 2.2Â±0.4, ANOVA p=0.002, figure 1). The mean molecular weight of cardiac-specific protein was 27346Â±18599 with max MW<60000. 1 mo after CA/CPR CA/CPR mice demonstrate 30% reduction in GFR (p=0.03, n=9) concomitant with tubulointerstitial fibrosis (17.3Â±4.9 v 0.8Â±0.5 %Î±SMA positive points, p=0.02, figure 2), hallmarks of CKD.

Conclusion: CA/CPR leads to renal filtration of cardiac-specific protein, exposing the protein-avid apical tubular epithelium to cardiac injury signals. 1 month after CA/CPR, mice demonstrate renal fibrosis and reduced GFR. We speculate that rapid development of CKD after acute cardiorenal syndrome may involve a novel cardiorenal signaling mechanism.

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TRSL/BS 75 (1692)

The Immortalisation of Primary Human Myoblasts Derived from Patients Susceptible to Malignant Hyperthermia and their Non-Susceptible Relatives

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Introduction: Malignant hyperthermia (MH) is a pharmacogenetic condition resulting in a potentially lethal reaction triggered during general anaesthesia. In susceptible individuals, a rapid hypermetabolic response results from skeletal muscle calcium dysregulation [1]. Current studies into MH are limited by the utility of non-human skeletal muscle models or human non-skeletal muscle cell lines such as HEK-293 cells [2,3]. Furthermore, experiments that use primary human tissue are inherently limited because of the rapid onset of replicative senescence that has been observed[4]. Thus, there is a crucial need to develop methods that will extend the life of cells derived from patients who are susceptible to MH (MHS) and their non-susceptible relatives (MHN) in order to allow an improved understanding of the mechanisms that underlie the pathophysiology of the human MH reaction. This study aims to develop such human skeletal muscle cell lines derived from patients with unique mutations associated with MH as well as those from their MHN relatives.

Methods: Following ethical approval, tissue from human biopsy samples taken for the diagnostic in vitro contracture tests were processed as previously described to isolate human myoblasts [5]. Myoblasts from three MHS patients, three MHN family members and a non-related MHN individual, were infected using the Î³-retroviral system to deliver genes encoding CDK-4 (cyclin dependent kinase) and hTERT (human telomerase reverse transcriptase). Successfully infected cells were selected using both puromycin (0.3 Î¼g/ml) and hygromycin (50 Î¼g/ml) for at least two weeks. Cells were then allowed to proliferate to over 10 doublings before undergoing fluorescent activated cell sorting (FACS) for CD56 and CD82 antigens in order to produce monoclonal and polyclonal pure myoblast cell lines.

Results: Myoblasts from two MHS patients and four MHN patients survived dual antibiotic selection for at least two weeks. These cells proliferated from approximately 10 000 cells to over one million cells prior to undergoing FACS, following which they were clonally expanded. All immortalized samples were found to contain cells positive for both CD56 and CD82, a combination which has recently been reported to be a marker of myoblasts that are able to differentiate into myotubes [6].

Conclusion: The immortalisation of these six primary human samples from MHS and MHN patients is novel, as to the best of our knowledge there have been no previous reports for the successful immortalisation of myoblasts from such patients. The cells are currently undergoing monoclonal expansion and further characterisation in order to produce a regenerative pool of cells that will have the ability to replicate by more than 100 doublings and potentially providing over 1 x 1030 cells per sample [4]. This will yield sufficient human cells derived from MHS and MHN patients that can then be used for numerous detailed studies investigating the fundamental mechanisms involved in MH. The successful immortalisation of primary human myoblasts also provides samples for the study of the functional mechanisms underlying other related skeletal muscle pathologies, such as central core disease.

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TRSL/BS 76 (1629)
IL-β-Mediated Disruption of the Tight Junction Permeability Barrier of Human Dermal Microvascular Endothelial Cells

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Introduction: Disruption of vascular endothelial cell barriers by cytokines such as interleukin-β (IL-β²) occurs first in adherens junction-dependent postcapillary venules of the microvasculature. However, during more severe inflammation (e.g. sepsis, ARDS), they may progress to involve capillaries, where barriers depend on tight junctions. Postconfluent human dermal microvascular endothelial cell (HDMEC) cultures form claudin 5-dependent tight junctions and can serve as a model for the study of capillary leak. NF-ÎºB-dependent de novo protein synthesis was found to be essential for TNF to trigger HDMEC leakiness, with more recent studies demonstrating a biphasic response. A recent report suggested that IL-β in cultured HDMEC mediates vascular leak early via activation of G-protein Arf6 independent of NF-ÎºB. Using our cultured HDMEC model, does IL-β disrupt HDMEC barriers in a sequential multiphasic manner? Does it involve activation of Arf6 and/or of NF-ÎºB?

Methods: HDMEC isolated from discarded tissue (approved by Yale University HIC) were cultured using EGM2MV medium (Lonza) onto fibronectin-coated 90W20idf + gold electrode 96-well plates and subject to IL-1Î² (Life Technologies) treatment. SecinH3 (Calbiochem) was used to inhibit ARNO, a known GEF of Arf6. Goat IÎºB-Î± antibody was from Santa Cruz Biotechnologies. LZRS control and 'super-repressor' IÎºB supernatant were obtained as described (JID 2007). For all experiments, barrier functions of HDMEC were assessed by electrical cell-substrate impendance sensing (Applied BioPhysics). Fluorescence-activated cell sorting analyses were done to observe degrees of apoptosis and necrosis using propidium iodide and FITC-conjugated annexin. Levels of Arf6 activation were measured in GTPase-linked immunosorbent assay kits prepared by Cytoskeleton. Data were analyzed with Prism 6.0e. Significance of differences was tested by one-way analysis of variance followed by two-tailed t-tests that were paired or unpaired as fitting the experiment. EC50 values were analyzed by nonlinear regression (curve fit) using a least squares method. Data are expressed as mean value Â± SEM. P <0.05 was considered significant.

Results: 1. HDMEC barrier disruption due to IL-β is biphasic. 2. IL-β-induced HDMEC barrier disruption is due to cell death, based on FACS analysis of necrosis/apoptosis in IL-β treated HDMEC at the time points of the early and late TEER nadirs. 3. Arf6 activation in HDMEC does not always correlate with increasing [IL-β] or with IL-β-induced decreases in transendothelial electrical resistance (TEER). 4. SecinH3 effectively inhibits Arf6 activation in HDMEC. However, it does not abrogate barrier disruption. 5. Sr-IÎºB-transduced HDMEC blocks early and late leak due to IL-β, suggesting a mechanism of microvascular permeability that is NF-ÎºB dependent.

Conclusion: These preliminary data suggests IL-1Î² induces biphasic leak in HDMEC. Absence of apoptosis suggests that IL-β triggers a pathway that modulates paracellular junction integrity in living cells, most likely tight junction-associated claudin-5. The early and late phases of IL-β-induced leak in HDMEC do not require activation of Arf6. Blocking NF-ÎºB activation significantly abrogates early and late HDMEC barrier disruption due to IL-β, likely via synthesis of new proteins that may serve as novel therapeutic targets for leak inhibition and barrier stability.

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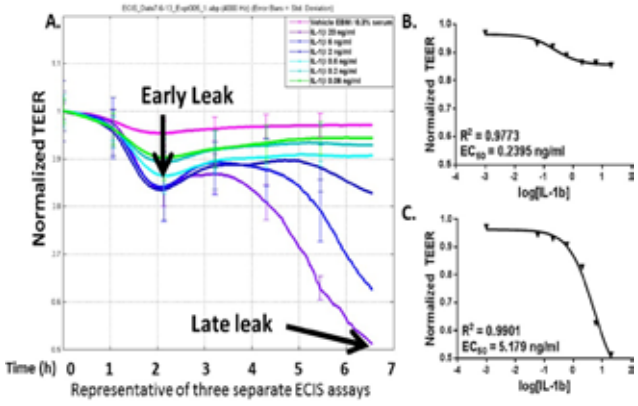
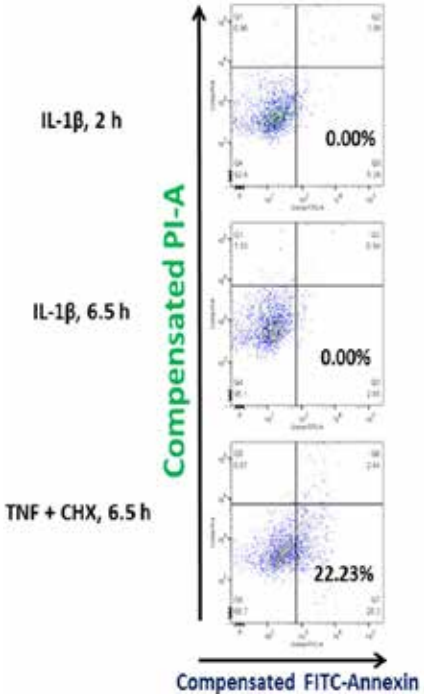
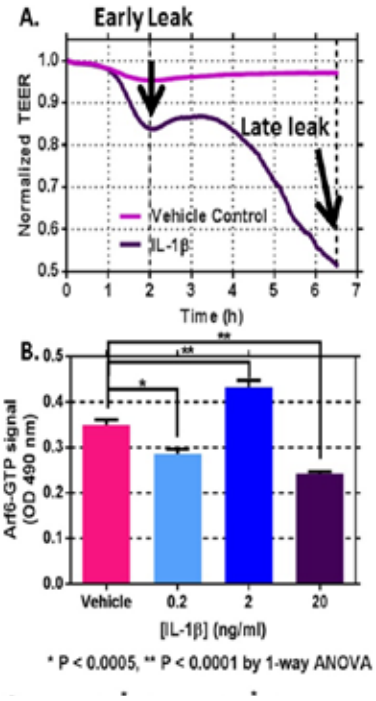
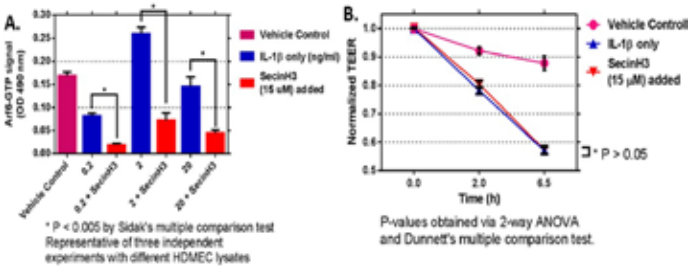
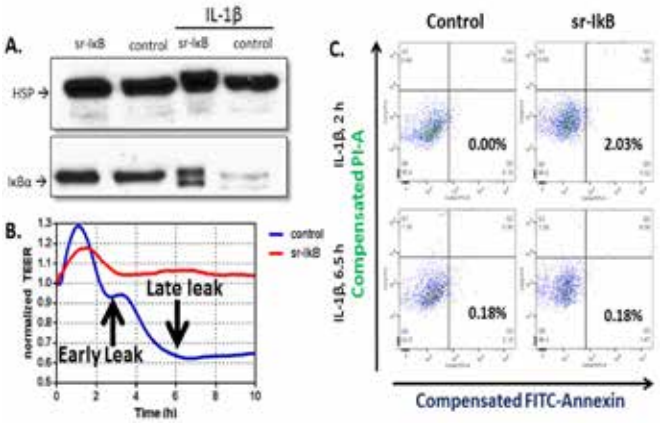
Poster Presentations, *continued from page 303*











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TRSL/BS 77 (1650)
NOX2 Deficiency Alters Macrophage Phenotype through an IL-10/STAT3 Dependent Mechanism: Implications for Traumatic Brain Injury

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Introduction: NADPH oxidase (NOX2) is an enzyme system that generates reactive oxygen species (ROS) in microglia and macrophages. Excessive ROS production is linked with neuroinflammation and chronic neurodegeneration following traumatic brain injury (TBI). Redox signaling regulates macrophage/microglial phenotypic responses (pro-inflammatory M1-like versus anti-inflammatory M2-like), and NOX2 inhibition following moderate-to-severe TBI markedly reduces markers of M1-like activation resulting in concomitant increases in M2-like activation [(1)]. Here we report the signaling pathways that regulate the NOX2-dependent macrophage/microglial phenotype switch in the TBI brain.

Methods: Bone marrow-derived macrophages (BMDMs) prepared from wildtype (C57Bl/6) and NOX2 deficient (NOX2-/-) mice were treated with lipopolysaccharide (LPS; 10ng/ml), interleukin-4 (IL-4; 10ng/ml), or combined LPS/IL-4 to investigate signal transduction pathways associated with M1-/M2-like activation using Western immunoblotting and qPCR analyses. Signaling pathways and activation markers were evaluated in ipsilateral cortical tissue obtained from adult male wildtype and NOX2-/- mice that received moderate-level controlled cortical impact (CCI). A neutralizing anti-IL-10 approach was used to determine the effects of IL-10 on the NOX2-dependent transition from M1- to M2-like activation phenotypes.

Results: Using an LPS/IL-4-stimulated BMDM model that mimics mixed M1-/M2-like phenotypes of the posttraumatic brain, we show that NOX2-/- significantly reduces STAT1 signaling and M1-like activation in BMDMs. In addition, NOX2-/- BMDMs have increased M2-like activation; IL-10-mediated STAT3 signaling, but not STAT6 signaling, appears to be the critical pathway regulating M2-like activation. Following moderate-level CCI, IL-10 is significantly increased in microglia/macrophages in the injured cortex of NOX2-/- mice. These changes are associated with increased STAT3 activation, but not STAT6 activation, as well as increased M2-like marker expression in the injured cortex. Neutralization of IL-10 in NOX2-/- BMDMs and CCI mice blocks STAT3 signaling and M2-like activation, thereby identifying an important role for IL-10 in regulating NOX2-dependent transitions between M1- to M2-like activation states.

Conclusion: Collectively, our in vitro and in vivo studies indicate that NOX2 deficiency promotes an M2-like anti-inflammatory activation response in macrophages/microglia that is mediated by an IL-10/STAT3-dependent mechanism. Thus, therapeutic interventions that inhibit macrophage/microglial NOX2 activity may improve TBI outcomes by not only limiting pro-inflammatory neurotoxic responses, but also enhancing IL-10-mediated anti-inflammatory responses that are neuroprotective.

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TRSL/BS 78 (1997)

The Human Metabolite of a Bioactive Ginger Phytochemical Relaxes Human Airway Smooth Muscle: Potential Novel Therapeutics for Bronchoconstriction

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Introduction: Asthma, characterized by chronic airway inflammation, wall remodeling, and pathologic bronchoconstriction, poses a continuous challenge in perioperative medicine [1]. In addition to traditional medications of inhaled corticosteroids and Î²-agonists, many asthmatics utilize complimentary therapies, including ginger root, a popular medicinal herb [2]. Previously, we demonstrated that 6-shogaol (6S), the primary bioactive component of thermally treated ginger, relaxes pre-contracted human airway smooth muscle (hASM) [3, 4]. However, oral 6S is extensively metabolized [5] and it is unknown if the resulting products remain bioactive. Herein, we hypothesize that despite undergoing diverse biotransformations, the major human metabolites of 6S, namely M2, M6, and M14 (Fig. 1A), retain the ability to relax hASM and inhibit Gq-coupled stimulation of intracellular calcium levels [Ca2+] i.

Methods: To measure the relaxant effect of 6S metabolites, hASM strips were suspended in organ baths and contracted with an EC 50 concentration of acetylcholine (Ach) followed by treatment with vehicle (0.1% DMSO) or M6 (100 Î¼M). To study the effect on [Ca2+] i, immortalized hASM cells stably expressing the M3 muscarinic receptor were loaded with a Ca2+-specific fluorophore, Fura-2 AM (5 Î¼M), then pretreated (10 min) with vehicle (0.1% DMSO) or 50 Î¼M of either S6, M2, M6, or M14 followed by a challenge with Ach. Fluorescence was recorded in the FlexStation 3 plate reader. The [Ca2+] i dose responses to 6S (0.1-500 Î¼M) were obtained in a similar manner.

Results: In hASM the major human metabolite of 6-shogaol (M6, 100 Î¼M) significantly relaxes an Ach EC 50 contraction (36 Â± 13% of the initial Ach-induced contraction remaining at 30 min compared to control 97Â± 7.1%, $p < 0.01$, $n = 7$) (Fig. 1B). As our prior studies have suggested that the relaxation of hASM by bioactive components of ginger is caused by inhibition of phospholipase C (PLC)-mediated increases in [Ca2+] i, we measured 6-shogaol metabolites' effect on Ach-induced increase in [Ca2+] i. Pretreatment of hASM cells with 6-shogaol (3.6 Â± 16.1%, $p < 0.001$, $n = 4$), M2 (19.2 Â± 7.4%, $p < 0.001$, $n = 4$), M6 (-2.8 Â± 21.1%, $p < 0.001$, $n = 4$), and M14 (-12.6 Â± 18.2%, $p < 0.001$, $n = 4$) significantly reduced increases in [Ca2+] i compared to vehicle control (0.1% DMSO, 100 Â± 29.4%, $n = 4$) (Fig. 1C). This response is dose-dependent (6-shogaol EC 50 = 17.2 Â± 5.8 Î¼M, $n = 3$).

Conclusion: Prior studies have shown that 6-shogaol relaxes hASM [3, 4]. Here we show that a primary 6-shogaol metabolite (M6) is also able to relax hASM ex vivo. Furthermore, the cell-based studies with 6-shogaol metabolites indicate that the relaxation is related to an inhibition of Ach-induced [Ca2+] i increases. Metabolic biotransformation of the parent compound by thiol conjugation (M2), ketone reduction (M6), or olefination (M14) does not negatively affect their bioactivity. This may lead to the development of a novel class of drugs for treatment of bronchoconstriction.

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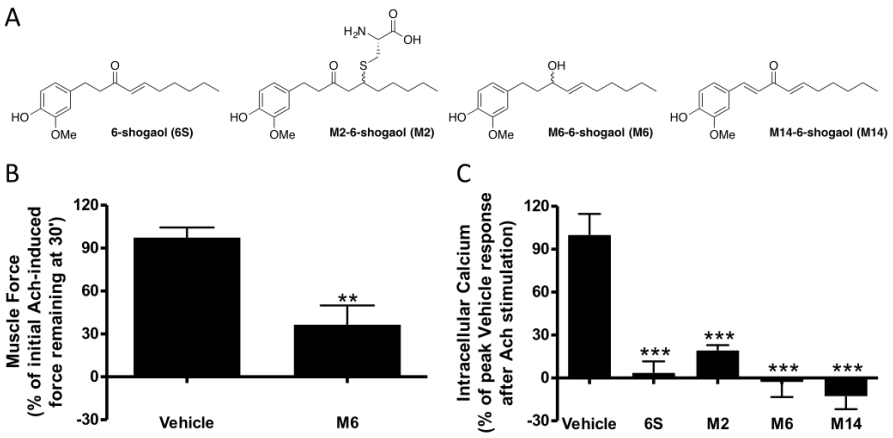

Fig.1. A natural ginger phytochemical 6-shogaol (6S) and its primary human metabolites as potential therapeutics for bronchoconstriction. A: Structures of the parent compound, 6-shogaol (6S), and its human metabolites: M2-6-shogaol (M2), M6-6-shogaol (M6) and M14-6-shogaol (M14). B: *Ex vivo* human airway smooth muscle (hASM) contractile force. Strips of tracheal hASM suspended in organ baths were contracted with an EC_{50} concentration of acetylcholine (Ach, 10 μM) and were then subjected to vehicle (0.1% DMSO) or the primary human metabolite of 6-shogaol (M6, 100 μM). ** $p < 0.01$, n = 7. C: Inhibition of $[Ca^{2+}]_i$ increase in hASM cells that were pretreated with either vehicle (0.1% DMSO), 6S (50 μM), M2 (50 μM), M6 (50 μM), or M14 (50 μM) and then stimulated with Ach (10 μM). *** $p < 0.001$ compared to vehicle, n = 4.

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TRSL/BS 79 (1779)

Idebenone Bypasses Impaired Mitochondrial Respiration in Primary Rat Cortical Neurons or Astrocytes Only When it is Enzymatically or Chemically Reduced

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Introduction: Idebenone is a drug in clinical trials for a number of diseases with a mitochondrial dysfunction component [(1)]. Unfortunately, completed trials for Alzheimer's disease and Huntington's disease found no significant benefit [(2,3)]. When idebenone is in its reduced form idebenol, it is proposed to have neuroprotective properties both as an antioxidant and as an electron donor for mitochondrial Complex III to support cellular respiration [(1)]. However, idebenone is administered to patients in its oxidized form due to the poor solubility and bioavailability of idebenol. NAD(P)H:quinone oxidoreductase 1 (NQO1) is an enzyme that can reduce idebenone to idebenol. Ascorbate can chemically reduce idebenone. We tested the hypothesis that NQO1 or ascorbate enables idebenone to bypass impaired mitochondrial respiration resulting from either in vitro simulated ischemia-reperfusion injury or direct mitochondrial Complex I inhibition in primary rat cortical neurons and astrocytes.

Methods: Primary rat cortical neurons or astrocytes were cultured from embryonic day 17 or postnatal day 1 animals, respectively. Ischemia-reperfusion injury was simulated in vitro by transiently depriving cells of glucose for one hour in the presence of the glycolysis inhibitor 2-deoxyglucose and the mitochondrial Complex IV inhibitor azide. At one hour after drug washout and glucose replenishment, cellular oxygen consumption due to mitochondrial respiration was measured using the Seahorse XF24 Extracellular Flux Analyzer (Agilent). Data were analyzed using one or two-way analysis of variance (ANOVA) followed by Tukey's post-hoc analysis to compare individual groups. A p value of less than 0.05 was considered significant.

Results: Idebenone stimulated mitochondrial oxygen consumption in astrocytes and enabled respiration in the presence of the Complex I inhibitor piericidin A. In contrast, idebenone impaired respiration in neurons. NQO1 was expressed by astrocytes but not by neurons. The NQO1 inhibitor dicoumarol prevented the respiratory stimulation by idebenone in astrocytes and blocked the rescue of piercidin A-inhibited respiration. Conversely, delivery of recombinant NQO1 enzyme and substrate to neurons prevented the inhibitory effect of idebenone on respiration. Simulated in vitro ischemia-reperfusion injury caused an attenuation of the maximal respiration rate of neurons. Mitochondrial respiration was partially rescued by idebenone when added with ascorbate to enable idebenone reduction but not by idebenone alone.

Conclusion: Idebenone cannot rescue impaired mitochondrial respiration unless active NQO1 enzyme or a chemical means of reduction is present. The extent of idebenone reduction in target cells may limit the success of idebenone in clinical trials. Because NQO1 is an inducible enzyme that responds to drugs targeting the Nrf2 antioxidant response pathway, combination therapy should be considered in future idebenone trials.

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TRSL/BS 80 (2257)
Fatty Acid Metabolism is Pivotal for Maintained Post-Ischemic Cardiac Function in Arctic Ground Squirrel Isolated Hearts

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Introduction: Intralipidâ„¢ (IL), a clinically used fat emulsion, has been shown to have a profoundly greater cardioprotective effect in hearts isolated from summer-active Arctic Ground Squirrel (AGS) when given before and after prolonged global ischemia/reperfusion (I/R) compared to hearts isolated from the best protected rat strain, the Brown Norway (BN). We hypothesized that this effect is due to better mitochondrial fatty acid oxidation in AGS.

Methods: Langendorff-prepared BN and AGS hearts were perfused with balanced Krebs solution containing 7.5 mM glucose (control) Â± 1% IL Â± 5 ÂµM Etomoxir, an inhibitor of carnitine palmitoyltransferase (CPT)-1. This was followed by cardioplegic I/R for 45/60 min, respectively. Spontaneous heart rate, left ventricular pressure, its derivatives, and coronary flow before, during and after I/R were measured. Statistcs: 2-way ANOVA with SNK post-hoc test, alpha 0.05 (two-tailed).

Results: Etomoxir abrogated all observed functional cardioprotective effects of IL in AGS.

Conclusion: Even under non-hibernating euthermic conditions, AGS hearts are better protected against stunning following I/R than the best-protected rat strain. IL perfusion leads to a remarkable improvement in return of function in AGS, but not in BN rats, suggesting that year-round endogenous mechanisms involved in myocardial lipid utilization without the production of harmful metabolites contribute to improved outcome, independent of decreased metabolism during hibernation. Our results suggest that fatty acid oxidation is a critical element of cardioprotection in AGS. The role of metabolic fuel selection during I/R warrants further investigation.

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TRSL/BS 81 (1210)
Isoflurane Effects on Pro-Inflammatory Interleukin-23 Activity in Mice

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Introduction: Although perioperative stress pre-exposes patients to immune vulnerability, general anesthetics also modulate the immune system.[1] Whether exposure to anesthetics causes an elevated sensitivity to inflammation is an important clinical question, especially considering the recent implications linking volatile anesthetic exposure to the early onset of certain neurodegenerative diseases, which are possibly associated with neuroinflammation. In this study, we focus on isoflurane's modulation of IL-23, a key pro-inflammatory cytokine essential for both acute and chronic inflammation.

Methods: The bone-marrow-derived dendritic cells (BMDCs) were exposed to 1.5% isoflurane for 4 h with or without lipopolysaccharide (LPS) challenge. The gene expression of inflammatory cytokines was quantified by quantitative reverse transcription PCR. The effects of isoflurane on the LPS-induced signaling pathways were also analyzed using Western blot. In parallel in vivo experiments, the levels of inflammatory cytokines and downstream signaling in the spleen and lung were quantified in CD1 mice treated with 1.5% isoflurane for 4 h with and without LPS. Analysis of variance followed by Fisher's least-significant difference post hoc test was performed to determine the effects of isoflurane. A $p < 0.05$ was considered statistically significant.

Results: As expected, 0.1 and 1 ng/ml LPS enhanced IL-23 mRNA level in BMDCs. Isoflurane further increased IL-23 mRNA expression ($p < 0.001$). Even in the absence of LPS, isoflurane exposure increased the IL-23 mRNA level by twofold. Isoflurane increased levels of phosphorylated p38 (p-p38) regardless of LPS treatment. In contrast, levels of p-ERK, p-JNK, IRF3, p-IRF3, IÎºB, or p-IÎºB were not affected by isoflurane. Pretreating BMDCs with 5 ÂµM SB203580, a specific p-p38 inhibitor, abolished LPS- and isoflurane-induced IL-23 mRNA, suggesting that the isoflurane-induced enhancement of IL-23 expression is dependent on p-38 MAP kinase. Consistent with ex vivo results, in vivo measurements showed that isoflurane administration increased levels of IL-23 mRNA and p-p38 in splenic tissue.

Conclusion: A clinically relevant dose of isoflurane modulates the function of dendritic cells by increasing the expression of the pro-inflammatory cytokine IL-23, likely through p38 MAPK activation. Similar elevation of splenic IL-23 mRNA and p-p38 protein expression in isoflurane-anesthetized animals suggested the possibility of adverse immune modulation by isoflurane. Further clinical investigations are warranted to determine whether an isoflurane-induced increase in IL-23 expression occurs in humans and, if so, what impact this might have on the short- and long-term outcomes of surgical patients.

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TRSL/BS 82 (1612)
Plasma Exosome miRNAs Mediate Inflammation in a Mouse Model of Sepsis

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Introduction: MicroRNAs (miRNAs) are a group of small non-coding RNAs. We have recently reported that a group of host cellular microRNAs (miR-34a, -122, - 145, -146, -210) are released into the circulation during severe sepsis (as determined by miRNA array and qRT-PCR) and play an important role in innate immune activation, such as complement activation and cytokine production(1). Exosomes have been proposed as vehicles for miRNA-mediated intercellular communication and a source of miRNA biomarkers in the blood and tissue fluid. However, the exact role of the blood exosomes and miRNAs loaded in the exosomes in sepsis is largely unknown. In this study, we tested the hypothesis that during bacterial sepsis, plasma exosomes play an important role in inflammation and miRNAs contribute to the exosomes-induced inflammation.

Methods: A mouse model of polymicrobial sepsis was created by cecal ligation and puncture (CLP). Sham mice were subjected to laparotomy but without CLP. EDTA anti-coagulated plasma was prepared at 24 hours after CLP and sham procedures. Plasma exosomes were isolated by ultracentrifugation, characterized by electron microscopy and the exosome markers, acetylcholinesterase activity and CD81 protein expression, and quantified by Nanosight. Exosome RNA was isolated by miRNeasy kit and specific miRNA levels were determined by qRT-PCR. To test the ability of exosomes to induce inflammation, bone marrow-derived macrophages (BMDM) were treated with exosomes and IL-6, TNFÎ±, IL-1Î² and MIP-2 in media were measured by ELISA. Data were expressed as means Â± SEM. Statistic significance was determined by Student t test, and ANOVA used to determine differences within groups. A $P<0.05$ was considered statistically significant.

Results: Electron microscopy visualized exosomes with sizes between 100-200 nM (Fig. 1A). Compared with those of sham mice, the exosomes isolated from CLP mice were slightly smaller (157.2Â±2.2 vs. 190.5Â±6.03 nm, $P<0.0001$) (Fig. 1B), possessed higher acetylcholinesterase activity and CD-81 expression, but contained the same amount of total proteins (Fig. 1C-D, F). Interestingly, CLP mice had more abundant exosomes in the plasma compared with sham mice [(3.99Â±0.34) Ã— 1010 vs. (2.31Â±0.35) Ã— 1010, $P<0.003$] (Fig. 1E). qRT-PCR analysis indicated that septic mice had more miR-34a, miR-122, miR-146a and miR-210 loaded in their plasma exosomes than sham mice (data not shown). Septic exosomes also possessed potent pro-inflammatory properties with robust productions of IL-6, TNFÎ±, IL-1Î² and MIP-2 in BMDM (Fig. 2A). The effects of exosomes were resistant to polymyxin B (an endotoxin inhibitor) treatment, but significantly inhibited by anti-miR inhibitors (against miR-34a, -122, -146a) (Fig. 2B-C).

Conclusion: Septic mice had increased numbers of exosomes in their plasma compared with sham animals. The septic exosomes are highly pro-inflammatory and carry increased amount of miRNAs (miR-34a, -122, -146a). These exosomes-associated miRNAs likely contribute to the septic exosomes-induced cytokine productions in macrophages.

References:

1. J Immunol., 2016; 196(6):2788-98

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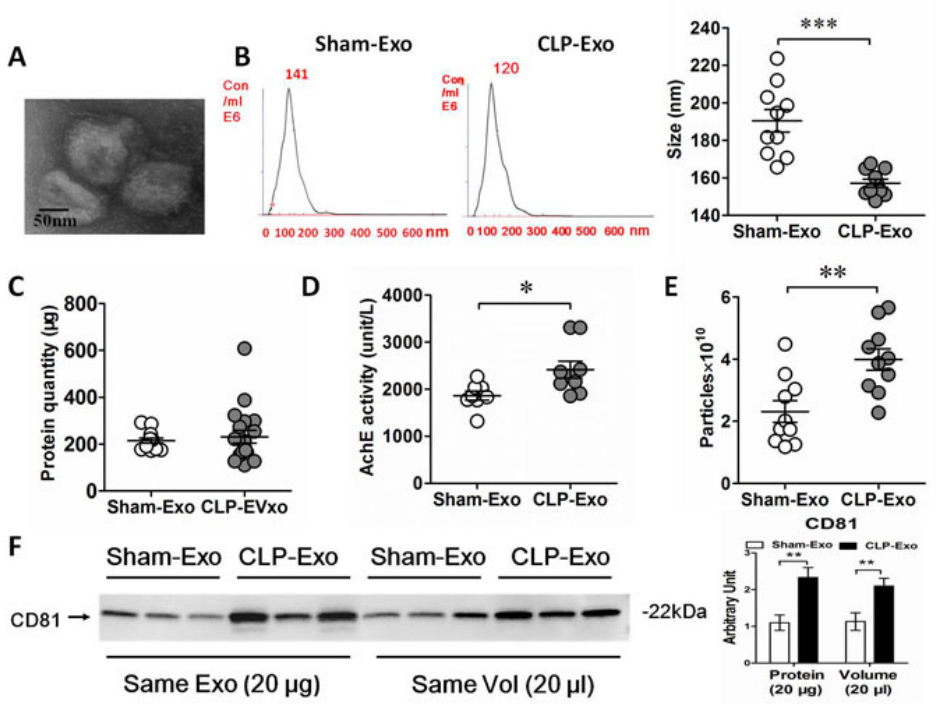

Figure 1. Characterization of exosomes isolated from the plasma of CLP and sham mice. A. Representative EM image of exosomes. B. Exosome size distribution as measured by Nanosight. C. Exosome protein quantification by Bradford assay. D. Exosome acetylcholinesterase (AchE) assay. E. Exosome particle numbers as quantified by Nanosight. F. CD81 protein expression in exosomes was quantified by WB. * P<0.05, ** P<0.01, *** P<0.001.

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