


ASCCA
American Society of
Critical Care
Anesthesiologists

American Society of Critical Care Anesthesiologists
23rd Annual Meeting and Critical Care Update

Syllabus

Friday, October 15, 2010 • Hilton San Diego Bayfront • San Diego, California

American Society of Anesthesiologists™

This CME meeting is jointly sponsored by the American Society of Anesthesiologists (ASA).

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Program Information

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

Needs Assessment
Topics for this meeting were derived from evaluations from the 2009 and previous annual meetings. Suggested topics were discussed and developed by educators who attended previous Annual, Board meetings and by other authorities in the field of Anesthesiology.

Faculty Disclosure
The American Society of Critical Care Anesthesiologists adheres to ACCME Essential Areas, Standards, and Policies regarding industry support of continuing medical education. Disclosures of faculty and commercial relationships will be made known at the activity. Speakers are required to openly disclose any limitations of data and/or any discussion of any off-label, experimental, or investigational uses of drugs or devices in their presentations.

Accreditation Statement and Credit Designation
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the American Society of Anesthesiologists and the American Society of Critical Care Anesthesiologists. The American Society of Anesthesiologists is accredited by the ACCME to provide continuing medical education for physicians.

The American Society of Anesthesiologists designates this educational activity for a maximum of 8.0 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclaimer
The information provided at this CME/CE activity is for continuing education purposes only and is not meant to substitute for the independent medical/clinical judgment of a health care provider relative to diagnostic and treatment options of a specific patient's medical condition.

Learning Objectives
Upon completion of this learning activity, participants should be able to:

- Discuss and apply current concepts in the care of critically ill obstetric patients
- Manage the challenges posed by the obese patient in the perioperative period
- Describe pharmacologic agents for use in hematologic disorders
- Explain the indications for, the benefits of, and the side-effects from recently developed cardiovascular pharmaceuticals
- Discuss the pharmacology and use of prothrombotic and antithrombotic agents
- Outline molecular mechanisms of regional lung dysfunction in ventilator-associated lung injury
- Summarize the ethical considerations in cardiac donation after death
- Identify emerging trends in the management of infectious disease in the ICU
- Evaluate and manage patients presenting with pulmonary thromboembolism
- Apply the principles of competency-based education and continuous performance assessment to ICU training and practice
- Evaluate the appropriate application of regional analgesic techniques in unique/austere environments and their novel application to intensive care unit settings.

ASCCA Breakfast Panel at the ASA Annual Meeting

"Management of the Septic Patient in the Operating Room: State of the Art"
Tuesday, October 19, 2010, 7:00 – 8:15 a.m.
San Diego Convention Center, Upper 10

Objectives: Upon completion of this learning activity, participants should be able to: 1) Review altered physiology present in sepsis patients; 2) Discuss practical approaches to assessing perfusion pressure and organ function in septic patients; 3) Describe currently recommended management of the septic patient and implications for intraoperative care.

Clinical Trials in Critical Ill Patients:
How Should They Impact Intraoperative Care?
Daniel R. Brown, M.D., Ph.D., FCCM - Mayo Clinic
Rochester, Minnesota

Practical Approaches to Assessing Perfusion Pressure and Organ Function in Septic Patients
Andrea Gabrielli, M.D. - University of Florida
Gainesville, Florida

Sepsis Pathophysiology and Anesthesia:
Why The Septic Patient is Different
Stephen D. Surgenor, M.D. - Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire

Awards

Lifetime Achievement Award

Attendees of the ASCCA 23nd Annual Meeting will honor **M. Christine Stock, M.D., FCCP, FCCM** as this year's Lifetime Achievement Award recipient. This award recognizes Dr. Stock's distinguished service and outstanding contributions to critical care medicine.

Young Investigator Award

This award is presented annually to the individual whose research exemplifies the Society's mission to educate anesthesiologists in the care of critically ill patients and to foster the knowledge and practice of critical care medicine by anesthesiologists. The recipient of the Young Investigator Award will make an oral presentation of their work at the ASCCA Annual Meeting. ASCCA is proud to announce the 2010 Young Investigator Award recipient as **Marina Yamada, Ph.D.** for her paper entitled ***iNOS Inhibition Prevents Muscle Wasting, Apoptosis and Decreased Akt Activity in Burned Rodents.***

Program Committee and Faculty Disclosures

Each presenter is required to disclose the existence of any financial interest and/or other relationship(s) (e.g. employee, consultant, grant recipient/research support) he/she might have with either the manufacturer(s) of any commercial product(s) to be discussed during his/her presentation and/or the commercial contributor(s) of the activity.

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ASCCA 23rd Annual Meeting Schedule

6:30 a.m. – 5:30 p.m.	Registration	Sapphire North Foyer
7:00 – 7:25 a.m.	**Continental Breakfast**	Sapphire Ballroom E/F
7:25 – 7:30 a.m.	**Welcome and Introduction** Laureen L. Hill, M.D.; Andrew L. Rosenberg, M.D.	Sapphire Ballroom M/N/I/J
7:30 – 9:00 a.m.	**SESSION I** Moderator: Ross Blank, M.D.	
	7:30 – 8:00 a.m. **Obstetrical Critical Care Update** Arvind Palanisamy, M.B.B.S., M.D.	
	8:00 – 8:30 a.m. **Obesity in the ICU and Post Operative Care for the Bariatric Patient** Charles Weissman, M.D.	
	8:30 – 9:00 a.m. **ICU Pharmacology: What's New in 2010?** Andrew Patterson, M.D.	
9:00 – 9:20 a.m.	**Break and Exhibits**	Sapphire Ballroom E/F
9:20 - 10:00 a.m.	**Facilitated Poster Session**	Sapphire Ballroom E/F
10:00 – 10:25 a.m.	**ASCCA-FAER-Hospira Physician Scientist Award Lecture** **"Molecular Mechanisms of Regional Lung Dysfunction in Ventilator-Associated Lung Injury"** R. Blaine Easley, M.D.	
10:25 – 10:35 a.m.	**Introduction of ASA President-Elect** Todd Dorman, M.D., FCCM	
10:35 - 10:55 a.m.	**ASA President-Elect Address** Mark A. Warner, M.D.	
10:55 – 11:05 a.m.	**Burchardi Award** Recipient: Heidi B. Kummer, M.D., M.P.H. Presenter: Todd Dorman, M.D., FCCM; William E. Hurford, M.D.	
11:05 – 11:35 a.m.	**Lifetime Achievement Award:** **"We've Come a Long Way (Baby)!"** Recipient: M. Christine Stock, M.D., FCCP, FCCM Presenter: William Peruzzi, M.D.	
11:35 – Noon	**Young Investigator Award and Abstract Presentation:** **"iNOS Inhibition Prevents Muscle Wasting, Apoptosis and Decreased Akt Activity in Burned Rodents"** Recipient: Marina Yamada, Ph.D. Presenter: Michael F. O'Connor, M.D.	
Noon – 1:00 p.m.	**Lunch and Lecture: "Regional Anesthesia in Austere Environments and Battlefields. Lessons Learned From Iraq and Afghanistan"** Chester C. Buckenmaier, III, M.D.	Sapphire Ballroom A/B

ASCCA 23rd Annual Meeting Schedule *(cont.)*

1:00 – 2:00 p.m. **Ethics Debate: Interactive Session on Donation After Cardiac Death (DCD)**
Moderator: Robert N, Sladen, M.D.
Nicholas Sadovnikoff, M.D.; Michael F. O'Connor, M.D.

2:00 – 3:00 p.m. **SESSION II**
Moderator: Steven A. Deem, M.D.

2:00 – 2:30 p.m. **Infectious Disease Update**
Sylvia Y. Dolinski, M.D.

2:30 – 3:00 p.m. **Perioperative Care of the Patient for Pulmonary Thromboembolism**
William C. Wilson, M.D.

3:00 – 3:30 p.m. **Break and Exhibits**

3:30 – 4:10 p.m. **Education and Competencies in the ICU**
Neal H. Cohen, M.D., M.P.H., M.S.

4:10 – 5:15 p.m. **Interactive ICU "Rounds" with Junior Faculty**
Moderator: Douglas B. Coursin, M.D.

5:15 – 6:00 p.m. **ASCCA Annual Business Meeting** Sapphire Ballroom M/N/I/J

6:00 - 7:15 p.m. **Welcome Reception** Sapphire Ballroom E/F

SESSION I

Moderator: Ross Blank, M.D.

7:30 – 8:00 a.m. **Obstetrical Critical Care Update**
Arvind Palanisamy, M.B.B.S., M.D.

8:00 – 8:30 a.m. **Obesity in the ICU and Post Operative Care for the Bariatric Patient**
Charles Weissman, M.D.

8:30 – 9:00 a.m. **ICU Pharmacology: What's New in 2010?**
Andrew Patterson, M.D.

Obstetrical Critical Care Update

Arvind Palanisamy, M.B.B.S., M.D.

Though pregnant patients are generally healthy, profound changes in maternal physiology places them at a high risk for potentially devastating complications such as hemorrhage and thrombo-embolism. With changing demographic trends, i.e., increased maternal age at childbearing and co-existing medical illnesses, it is likely that such complications will rise and potentially necessitate critical care intervention. Currently, the prevalence of obstetric patients requiring critical care ranges from 100 to 900 per 100,000 gestations.[1] The most common reasons for ICU admission are predictable: hypertensive diseases (30.8%), peripartum hemorrhage (20.3%), and pulmonary complications (either secondary to the abovementioned, or specific diseases such as asthma, amniotic fluid embolism etc) (13%).[2] In general, obstetric patients admitted to the ICU have lower mortality rates than the general population. A detailed discussion of the physiological changes of pregnancy and its impact on critical care management is beyond the scope of this update; only recent trends in the management of critically ill obstetric patients will be analyzed as outlined below.

ICU Scoring Systems for Pregnant Women:

The existing scoring systems (APACHE, SAPS) are not designed for use in obstetric patients and hence it is difficult to assess illness severity or predict outcomes.[3,4] Normal physiologic variables in obstetric patients are often scored as abnormal, and tests that are important in the assessment of preeclamptic patients (platelet count, liver function tests) do not influence the scores. In general, with the currently existing scoring systems, the predicted mortality rate is more often higher than the observed mortality rate. In addition, the Injury Severity Score (ISS) does not predict the risk of placental abruption and fetal death following trauma during pregnancy.[5]

Sedation Practices:

Currently, there is no data to guide choice of sedative agents in critically ill pregnant women. However, worrying evidence from preclinical studies indicates that early brain development may be impaired by $GABA_A$ (gamma amino butyric acid type A) receptor modulation; both apoptotic neurodegeneration of the developing brain and behavioral maldevelopment have been reported.[6,7] Since GABA functions mostly as a trophic factor during early neurodevelopment (and not as a neurotransmitter), it is plausible that prolonged and unphysiological stimulation of the developing fetal brain with maternally administered GABA-ergic sedative agents (benzodiazepines, propofol) can have significant adverse effects. Because of minimal transplacental transfer[8] and the lack of appropriate receptor mechanisms in the fetal brain, dexmedetomidine appears to be a useful alternative and, hence, its use should be further investigated in this setting.

Strategies in Mechanical Ventilation:

Though the need for mechanical ventilation in pregnancy is rare, anatomical and physiological changes of pregnancy mandate modifications to standard ventilatory approaches. [9] Hyperventilation should be avoided as it adversely affects uterine blood flow. Permissive hypercapnia, that accompanies ventilatory strategies to minimize iatrogenic pulmonary injury, has not been evaluated in pregnancy. Despite the mild respiratory alkalosis seen at term, maternal hypercapnia up to 60 mmHg in the presence of adequate oxygenation does not appear to be affect the fetus.[10] Because chest wall compliance is reduced, higher inflation pressures may be required to achieve adequate tidal volumes. Unlike maternal hypoxia, the effects of maternal hyperoxia on the fetus are unclear; nevertheless, optimization of maternal oxygenation and acid-base status can be considered as appropriate surrogate end points to ensure fetal well-being. Ventilation in the prone position is unfeasible in this population, and hence simple measures such as left uterine displacement and/or left lateral decubitus position must be considered to improve ventilation-perfusion mismatch.

Pharmacotherapy:

An overarching principle of obstetric critical care management is that care of the mother takes precedence over the fetus. However, the impact of such interventions on the fetal status needs to be ascertained, and if possible, alternative and equally effective therapies with minimal effect on the fetus be considered. In addition, drugs commonly used in pregnancy, such as beta agonists and magnesium can have a profound impact on maternal cardiac and respiratory status. Early goal-directed therapy for sepsis, fluid management, and transfusion practices are similar to non-obstetric patients. The choice of vasoactive agents needs to be made with utmost care; most vasopressors at high doses affect uteroplacental perfusion, and commonly used vasodilators such as nitroglycerin and sodium nitroprusside can induce uterine atony and potentially increase the risk of hemorrhage in a recently

postpartum patient. Evidence-based guidelines for thromboprophylaxis of pregnant women are currently available.[11] Because of the risks of fetal teratogenicity, coumadin derivatives are not recommended between 6-12 weeks of gestation and unfractionated heparin and LMWH remain the agents of choice. Most prevailing practices, however, are guided by consensus, common sense, and expert opinion and may not necessarily reflect the best evidence.

Radiation Dose Considerations in Diagnostic Imaging:

Because treatment of the mother takes precedence over the fetus, important diagnostic studies should not be withheld for fear of radiation exposure. The estimated fetal radiation exposure during most radiologic studies that use ionizing radiation is < 0.05 Gy, and risk of malformations is increased only at doses that exceed 0.15 Gy.[12,13] Specifically, the radiation dose is low if the fetus is outside the field of view (CT of the head, cervical spine, and extremities). Even chest CT is considered a low-dose exposure if the fetus is excluded from the primary beam, and radiation exposure from CT angiography is within the upper limits of acceptable exposure. Nevertheless, every effort must be made to reduce radiation exposure such as use of alternatives that employ non-ionizing radiation (USG, MRI) and shielding of the uterus. In non-emergent scenarios, the pregnant patient must be counseled and the radiation dose to the fetus must be documented.

Fetal Monitoring in the ICU:

Establishing the viability of the fetus (using antenatal records, USG) is important in deciding the need for fetal surveillance.[14] A pre-viable fetus (< 23-24 weeks depending on institutional practice) may not need fetal monitoring. Since the fetal heart rate (FHR) is a direct reflection of the adequacy of uteroplacental perfusion, new-onset late decelerations and absence of baseline variability should prompt a thorough reevaluation of maternal cardiorespiratory status. In addition, care must be taken to exclude maternally administered sedative and analgesic drugs as the cause for altered fetal heart rate tracing. Because of the nuances of FHR monitoring, it may be prudent to have a labor and delivery nurse continually available at the bedside.

Fetal Outcomes after Maternal ICU Admission:

The data on fetal outcomes after maternal ICU admission are sparse. Recent retrospective evidence from non-obstetric causes of ICU admission during pregnancy, however, seems to indicate that maternal shock, blood transfusion, and lower gestational age are associated with an increased risk of fetal, but not neonatal, death.[15] The reported fetal mortality rates (30-35%) are comparable to results from another retrospective study that included both obstetric and non-obstetric causes in pregnant women.[16] However, in this study, fetal outcomes were not separately evaluated for obstetric and non-obstetric indications for ICU admission. Most of the available studies assess only macroscopic indicators of neonatal health. Subtle changes in cognition and non-cognitive behavioral development, however, need to be assessed in children born of critically ill mothers who required ICU admission while pregnant.

Cardiopulmonary Resuscitation (CPR) of the Pregnant Patient:

Cardiac arrest in pregnancy is a rare event and the estimated incidence is approximately 1:30,000 pregnancies.[17] Though basic principles of resuscitation are similar between pregnant and non-pregnant subjects, certain modifications are recommended. These include early and aggressive airway management (to ensure adequate ventilation and minimize pulmonary aspiration risk), use of lateral decubitus position (to improve venous return and hence, cardiac output), cautious use of sodium bicarbonate (because of the risk of fetal acidosis), and early consideration of perimortem cesarean delivery (to facilitate effective CPR by relieving aortocaval compression). The current recommendation is to perform perimortem cesarean delivery within 4 minutes (and ensure fetal delivery within 5 minutes) of unsuccessful resuscitative efforts.[17,18] This is only a guideline as successful neonatal outcomes have been reported even after 15 minutes of maternal cardiac arrest. However, perimortem cesarean delivery must be promptly considered in a setting with experienced obstetricians, as speed and decisiveness are keys to success. The procedure must not be delayed because of a lack of consent, and CPR must be continued during delivery.

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Obesity in the ICU and Post Operative Care for the Bariatric Patient

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Obesity

- Obesity has increased worldwide over the past two decades.
- In the United States the prevalence (2007-2008) of overweight individuals was estimated to be 34%, while 34% (32.2% - men, 35.5% - female) were obese [1].
- Recently published statistics indicate a continued increase in obesity in the United States with 9 states reporting a rate greater than 30% [2].
- This epidemic of obesity is occurring in many other counties, including Mexico and Great Britain.
- The obesity epidemic includes children and adolescents.
- This “obesogenic” tendency has been ascribed to a sedentary lifestyle (web surfing vs sports) and increased consumption of fast and prepared foods. .
- Along with this increase in obesity has been an increase in Type II diabetes mellitus even among adolescents.
- Definitions of obesity (Table 1).

Obesity and the ICU Patient

It is has been estimated that one in four adult ICU patient is obese. These estimates are based upon a number of studies performed in Medical and Surgical ICUs and are in line with the prevalence of obesity in the population.

Does obesity affect the morbidity and mortality of ICU patients?

There is controversy whether obesity is a determinant of increased mortality among ICU patients. Alternately, a number of studies have shown that being underweight is associated with increased mortality. Two meta-analyses showed that obesity (as defined using BMI) was not a risk factor for mortality, however, other studies differ especially when abdominal adiposity is used as the marker of obesity [3,4,5].

ICU morbidity is often higher in obese patients associated with greater difficulty in tracheal intubation and a higher incidence of extubation failure [6,7].

Obese patients sustain different types of blunt trauma than non-obese patients [8]. Obese blunt trauma patients have increased ICU morbidity, but not mortality [9].

How do the metabolic changes associated with obesity (“The Metabolic Syndrome”) affect the care of the ICU patient?

Adipose tissue does not only store fat but is also an endocrine organ [10]. The “Metabolic Syndrome” is a concept that associates several cardiovascular and type 2 diabetes mellitus risk factors – central obesity, hypertension, dys-lipidemia, hypercoagulability, proinflammatory state and insulin resistance [11]. This cluster of underlying associated pathological entities is the baseline metabolic state in many obese patients who undergo surgery, have critical illness and become trauma victims. Therefore, the metabolic responses to stress and sepsis might be modified secondary to this underlying state. What is known about this interaction will be discussed.

What should the nutritional support strategy be in obese patients?

With much stored fat and with the shift to fat oxidation during stress, the question arises whether the nutrition support strategy in obese patients should be a hypocaloric, yet protein-rich, diet. The aim would be to utilize this endogenous source of non-protein calories for some of the non-protein calories while trying to achieve as positive nitrogen balance as possible. In other words, the aim would be to utilize fat stores while preserving muscle mass. A secondary benefit would be weight loss that favors loss of fat stores over muscle mass, a situation that could assist in the overall care of the patient. The downside to this strategy is the argument that the stress state is not a time for a “reducing diet” since it might add the metabolic consequences of semi-starvation to an already stressed state. Another point is that endogenous lipid might not be utilized in the same way as exogenous lipids [12].

Postoperative Care of Bariatric Surgery Patients

Among the contemporary treatments of obesity is bariatric surgery (Table 2). The aim of such surgery is to limit the intake and/or absorption of food. Modern surgical and endoscopic techniques; better selection and preoperative preparation of patients; and earlier surgery have increased the number and success, while reducing the risks, of such procedures. Preoperative evaluation for Obstructive Sleep Apnea is essential to reduce postoperative respiratory complications.

Do patients undergoing bariatric procedures require routine post-procedure ICU care?

In many institutions bariatric patients are not routinely admitted to the Intensive Care Unit [13,14]. However, some are cared for in an intermediate setting (intermediate care unit or extended stay in the PACU), especially if they have risk factors such as obstructive sleep apnea or active ischemic heart disease.

When and why do bariatric surgery patients require ICU care?

In the immediate postoperative period elective bariatric patients are often electively admitted to the ICU because of severe sleep apnea or super obesity. Others are admitted unexpectedly because of respiratory failure and surgical complications. Emergency admissions are often due to emergent surgery for surgical complications and revision surgery [15].

Conclusions

The weight loss resulting from bariatric surgery has beneficial effects, such as reduced glucose intolerance, improvement in type 2 diabetes mellitus, regression of hypertension induced cardiovascular dysfunction and lower blood pressures. In light of improved short- and long-term outcomes bariatric surgery is being performed more readily in patients who fail to loose weight with more conservative therapies. Therefore, the number of bariatric procedures will continue to increase.

With the continuous rise in overweight and obese individuals it is necessary to ascertain whether ICU treatment strategies need to be modified to improve their care. More research is needed to determine whether the metabolic state associated with obesity necessitates a different approach to nutritional support the treatment of perioperative and ICU hyperglycemia. Furthermore, additional refinements of bariatric surgical techniques are needed to further reduce postoperative complications.

Table 1 – Definition of Obesity

BMI – Body Mass Index

Underweight	BMI: <18.5
Normal Weight	BMI: 18.5–24.9
Overweight:	BMI: 25.0-29.9
Obese:	BMI: 30.0-39.9
Morbid Obesity	BMI: >40.0

Central (abdominal) adiposity: waist circumference ≥102 cm (>40 in.) in men and ≥88 cm (>35 in.) in women; waist to hip ratio of greater than 0.9

Table 2 – Examples of Bariatric Procedures

Endoscopic intra-gastric balloon placement
Gastric sleeve resection
Sleeve gastrectomy with duodenal switch
Gastric banding (vertical banded gastroplasty; adjustable-band)
Gastric bypass (Roux-en-Y gastric bypass)

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ICU Pharmacology: What's New in 2010?

Andrew Patterson, M.D.

Objectives:

1. Consider the indications for, the benefits of, and the side-effects from recently developed cardiovascular pharmaceuticals.
2. Discuss new agents for the treatment of hematology disorders.

Overview

What's new in 2010 in terms of Intensive Care Unit (ICU) pharmacology? Two cardiovascular agents, a medication used for the management of tumor lysis syndrome, a plasma-derived factor concentrate preparation, and two second generation thrombopoietic agents. Actually, not all of these agents are new. Some of these agents (such as clevidipine and dronedarone) have been used in the acute care setting for at least two years. However, several recent studies focused on how and to whom these not-so-new agents can be administered in the ICU make these agents worthy of discussion today.

Atrial Fibrillation and Flutter

Atrial fibrillation and flutter occur frequently in patients undergoing cardiac surgery (1), in patients undergoing major non-cardiac surgery (2), in patients experiencing sepsis, (3) and in patients with other forms of critical illness (4). Atrial fibrillation is associated with an increased risk of mortality and stroke as well as higher cost of care (5). Markedly elevated levels of circulating catecholamines (6), autonomic imbalance (7), and inflammation (6, 8, 9) are implicated in the development of cardiac dysrhythmias. Management of atrial fibrillation involves rate control, prevention of thromboembolic events, and restoration of normal sinus rhythm. Pharmacologic options for restoration of normal sinus rhythm include class Ia, class Ic, and class III antiarrhythmic agents (10).

Dronedarone

Dronedarone is an orally administered benzofuran derivative with properties of all four Vaughn Williams antiarrhythmic classes. It is an amiodarone analogue, and like amiodarone it decreases heart rate and prolongs the PR interval. It also causes moderate and dose-dependent increases in the QT interval. Unlike amiodarone, dronedarone is non-iodinized. Dronedarone is also less lipophilic than amiodarone due to the presence of a methane sulphonyl group. Dronedarone also has a shorter half life than amiodarone (11). Dronedarone is hepatically metabolized. Heart failure and renal dysfunction have not been shown to impact dronedarone pharmacokinetics (10). The impact of severe hepatic impairment on the pharmacokinetics of dronedarone has not been determined (12).

Although clinical trials evaluating dronedarone have not focused on critically ill patients per se, results from several investigations have important implications for the use of dronedarone in the ICU. For example, dronedarone has been found to interact with numerous pharmaceutical agents commonly administered to critically ill patients. Dronedarone administration has also been associated with higher mortality in patients with severe and unstable congestive heart failure.

Dronedarone is a substrate for and a moderate inhibitor of the liver enzyme CYP3A4. Consequently, potent CYP3A inhibitors like ketoconazole, itraconazole, voriconazole, macrolides, protease inhibitors, and cyclosporine should not be administered to patients receiving dronedarone. Diltiazem, verapamil, and simvastatin are less potent CYP3A inhibitors. Doses of these agents should be reduced for patients receiving dronedarone. Sirolimus is also metabolized by a CYP3A isoenzyme. Patients receiving both sirolimus and dronedarone can experience sirolimus toxicity and excessive immunosuppression (13). Like amiodarone, dronedarone interferes with the metabolism of digoxin, but not with the metabolism of warfarin (12).

The ANDROMEDA study suggested that dronedarone should not be administered to patients with severe or unstable congestive heart failure. In fact, ANDROMEDA was terminated prematurely when it was determined that significantly greater numbers of patients receiving dronedarone (versus placebo) died and that the deaths were caused (predominantly) by worsening heart failure (10, 14).

Dronedarone may cause fetal harm and should be avoided during pregnancy (Category X). It is unknown whether dronedarone or its metabolites enter human breast milk at significant concentrations. The safety and efficacy of dronedarone have not been established for children (10).

In 2010, it was determined that dronedarone is less effective than amiodarone for decreasing atrial fibrillation recurrence. The DIONYSOS study investigators compared the efficacy and safety of amiodarone and dronedarone in patients with persistent atrial fibrillation. The authors randomized five hundred four patients to receive dronedarone 400 mg twice daily or amiodarone 600 mg once daily for twenty eight days then 200 mg daily for at least six months. The primary composite endpoint of the study was recurrence of atrial fibrillation or premature study

discontinuation due to adverse events. The investigators concluded that over the short term, dronedarone is less effective than amiodarone in decreasing atrial fibrillation recurrence but has a better safety profile and does not interact with oral anticoagulants (15).

Acute Hypertension

In the outpatient setting, specific antihypertensive agents have been shown to convey benefit to definable patient populations. However, it is unclear whether a similar situation exists for the acute care setting. A variety of intravenous agents are available for blood pressure control in the acute care setting. Some of these agents decrease systemic vascular resistance. Others decrease cardiac output. Some agents do both. In the absence of adequate outcome data, a rational approach is to match the mechanisms of action of antihypertensive agents to the patient's physiological needs. During the past five years, the ultra-short acting intravenous dihydropyridine calcium channel blocker clevidipine became available. Of interest to intensivists, the recent VELOCITY trial suggests that clevidipine is safe and effective for blood pressure control in patients with moderate to severe renal failure as well as heart failure.

Clevidipine

Clevidipine is a third generation intravenous dihydropyridine calcium channel blocker that reduces blood pressure by decreasing arterial vascular tone. It inhibits transmembrane calcium influx through voltage-dependent L-type calcium channels (16, 17, 18). Clevidipine has minimal negative inotropic effects and maintains or even increases cardiac output (in contrast to first generation dihydropyridine calcium channel blockers which have negative inotropic effects). Clevidipine does not induce bradycardia. It has an onset of action within two minutes and an initial half-life of less than three minutes (though the half-life increases with decreasing blood temperature). Pharmacokinetic studies have shown a 50% decrease in clevidipine concentration one minute after termination of infusion (18). Clevidipine is rapidly hydrolyzed by red blood cell and extravascular tissue esterases (19). It is also insoluble in water. Clevidipine is, therefore, dissolved in a 20% lipid emulsion (made with soybean oil and egg yolk phospholipids) (18, 20). Consequently, clevidipine has the potential to support bacterial growth. The manufacturer recommends disposal of any drug remaining in the vial four hours after opening due to limited stability. The manufacturer also advises that clevidipine should not be administered through an intravenous line with any other medications. Clevidipine is considered pregnancy category C. In animal studies, it was associated with increases in maternal and fetal mortality. The safety and efficacy of clevidipine for children has not been established (18).

Although most studies of clevidipine have focused on cardiac surgery patients, recent studies have included other patient populations. For instance, the VELOCITY trial and its subset analyses involved evaluation of 126 patients who presented to either the emergency department or the ICU with acute hypertension. Based upon the results of the VELOCITY trial, the investigators concluded that clevidipine is safe and effective for reduction of blood pressure in patients with severe hypertension and that continuous infusions could be utilized for 18 hours or more (21, 22). Based upon VELOCITY trial subset analyses, the investigators concluded that clevidipine is safe and effective for blood pressure reduction in patients with moderate to severe renal failure as well as in patients with acute heart failure (22). These results are important when considering which critically ill patients might be candidates for blood pressure reduction using clevidipine.

Hyperuricemia in Tumor Lysis Syndrome

Tumor lysis syndrome occurs after abrupt release of large amounts of cellular components into the systemic circulation during rapid lysis of tumor cells (23, 24). The release of cellular components leads to hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. Hyperuricemia occurs because nucleic acids are degraded into uric acid. Uric acid can precipitate in renal tubules and cause acute renal failure. Hypocalcemia is a secondary effect caused by phosphate binding to calcium. Tumor lysis syndrome can result in cardiac arrest, and it occurs most frequently after initiation of chemotherapy for high grade lymphomas (e.g., Burkitt lymphoma) and acute lymphoblastic leukemia (23, 24, 25, 26).

Rasburicase

Intravenous hydration, allopurinol, and rasburicase are recommended for prevention of hyperuricemia in patients at high risk for tumor lysis syndrome. Allopurinol is effective because it blocks the metabolism of purines to urate. However, allopurinol has no effect upon preformed urate in the blood (27). Rasburicase is effective for lowering uric acid concentrations (24). Rasburicase catalyzes the oxidation of uric acid to allantoin (which is more water soluble than uric acid). Rasburicase was approved by the United States Food and Drug Administration (U.S. FDA) as a multi-dose regimen over five days (which costs about $22,000). Recently, a single dose rasburicase regimen based upon ideal body weight was developed for the treatment of tumor lysis syndrome in adults. 0.15 mg/kg of rasburicase was shown to be effective for reduction of urate levels to within normal limits for up to 48 hours (27). This regimen may serve as a preferred approach for intensivists due to its clinical effectiveness and reduced cost.

Intracranial Hemorrhage

Hemostatic abnormalities can exacerbate the impact of intracranial hemorrhage. Patients receiving anticoagulants, patients with acquired or congenital coagulation factor deficiencies, and patients with platelet abnormalities are at significant risk for hematoma expansion (28). For patients receiving warfarin at the time of an intracranial hemorrhage, current recommendations are to correct the internal normalization ratio (INR) as rapidly as possible (29, 30). Vitamin K and fresh frozen plasma have historically been administered for this purpose. However, prothrombin complex concentrates and recombinant factor VIIa are now being utilized (28).

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) are plasma-derived factor concentrates traditionally used to treat factor IX deficiency. However, they also contain factors II, VII, and X. Consequently, they are also useful for warfarin reversal. The advantages of PCCs are: 1. They can be rapidly prepared and administered. 2. They have high concentrations of factors in small volumes, which reduces the probability of fluid overload. 3. They have a rapid impact (normalizing the INR within minutes in patients receiving warfarin). A disadvantage of PCCs is that they may increase the risk of thrombotic events. Commercially available PCCs include Bebulin VH and Profilnine SD (28).

Thrombocytopenia

Thrombocytopenia can be caused by platelet destruction as well as by inadequate platelet production and distribution. It is associated with numerous medical disorders, including liver cirrhosis, human immunodeficiency virus (HIV) infection, autoimmune diseases, chemotherapy-induced myelosuppression and bone marrow disorders. Platelet transfusion is the primary treatment option for thrombocytopenia. However, the impact of platelet transfusion can be limited by transient effects upon the platelet count and by production of anti-platelet antibodies (31).

Idiopathic thrombocytopenic purpura (ITP) is an immune-mediated disorder that affects approximately 1 in 10,000 Americans. The primary treatment strategy for ITP is prevention of platelet destruction. Azathioprine, danazol, dapsone, cyclosporine, and rituximab have all been used to achieve this goal, with modest success. Recently, two second generation thrombopoietic agents have been approved by the U.S. FDA for the treatment of refractory ITP (32).

Romiplostim and Eltrombopag

Romiplostim and eltrobopag are second generation thrombopoietic agents. In contrast to first generation thrombopoietic agents (which were recombinant forms of human thrombopoieten - TPO), romiplostim and eltrobopag have no sequence homology to endogenous TPO. Clinical studies indicate that they do not induce production of antibodies that cross react with endogenous TPO, the primary limitation of the first generation thrombopoietic agents. Phase II and phase III clinical trials investigating romiplostim and eltrombopag are currently being conducted for patients with chemotherapy-induced thrombocytopenia, chronic liver disease, and myelodysplastic syndromes (31). These agents may soon provide intensivists with effective alternatives to blood product transfusion for the management of thrombocytopenia caused by a variety of disorders.

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ASCCA-FAER-Hospira Physician Scientist Award Lecture "Molecular Mechanisms of Regional Lung Dysfunction in Ventilator-Associated Lung Injury"

R. Blaine Easley, M.D.

Objectives:

The attendee will learn the following:

1. the definition of ventilator associated lung injury (VALI).
2. the relevant background of VALI from rodent and human studies.
3. how functional lung imaging and large animal models have increased our understanding of regional lung dysfunction in VALI.
4. the discovery of pre-colony enhancing factor (PBEF) and its correlation with regional lung dysfunction to the initation and/or propagation of VALI.

Summary of Content:

Mechanical ventilation can contribute to the extension and propagation of lung tissue damage in critically ill patients, a process called ventilator–associated lung injury (VALI). Many of the specific cellular and molecular events linking mechanical and biochemical stresses to lung injury remain unknown. **Our group has hypothesized that increased mechanical strain results in increased molecular expression of regional markers of "strain" indicative of injury and these contribute to worsening lung injury severity.** Specifically, this has led to the discovery and exploration of pre-B cell colony enhancing factor or PBEF. The purpose of this presentation will be to demonstrate the application of high-resolution computerized tomographic (HRCT) functional lung imaging and large animal models to understanding regional lung dysfunction and the molecular responses that are attributable to VALI.

Background: Acute Lung Injury (ALI) is a common and life threatening critical illness, with a mortality of 25-50% in children and adults [2]. Treatment for ALI is primarily supportive, sustaining the patient with mechanical ventilation until the cascade of injury subsides and the lung tissues recover. Over the past decade, computed tomographic (CT) imaging has revealed the mechanically heterogeneous nature of ALI in animals and humans, demonstrating coexisting regions of alveolar atelectasis (collapse) and flooding, overdistension, and a wide range of intermediate states within the same lung [3, 4]. These observations have resulted in the "open lung" approach to mechanical ventilation, with the goals of recruiting and maintaining the lung in the "open" intermediate range and avoiding the injurious extremes of overdistension and collapse [5]. This concept is the basis of the "lung protective" ventilator strategy of small tidal volume ventilation combined with positive end expiratory pressure (PEEP) that resulted in reduced mortality when applied to adult patients with ALI [6].

Ventilator-associated lung injury: In humans, the pathogenesis of ALI is thought to involve an initiating insult, such as infection, inflammation, trauma, etc. (Figure 1), compounded by further lung injury brought on by the necessary use of life-sustaining mechanical ventilation- the concept of ventilatorassociated lung injury (VALI) [7]. The mechanism of VALI is multi-factorial but clearly involves inflammation, as Stuber et al. [8] demonstrated by measuring reversible changes in circulating inflammatory mediators in ALI patients when changed from a high to a low PEEP strategy for only a brief period of time.

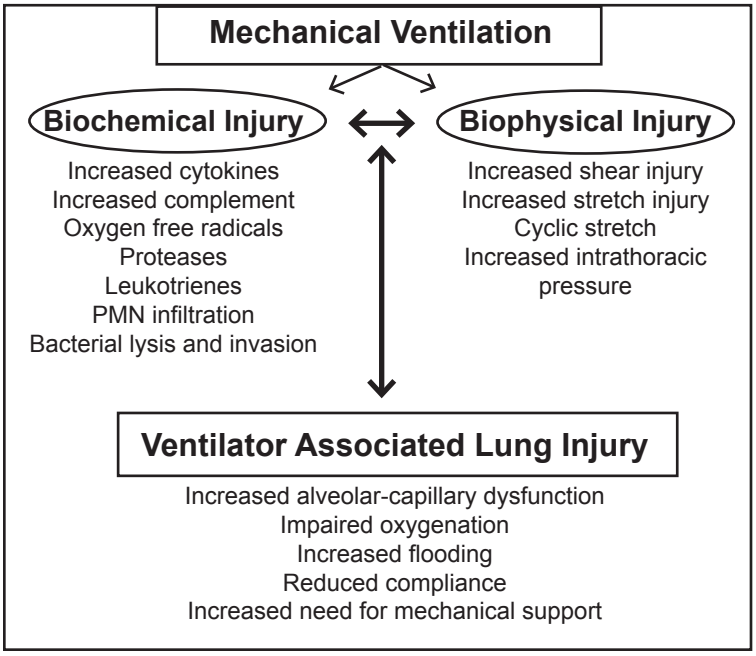

Figure 1:
Complex Mechanisms contributing to VALI.

In vivo Canine Model of VALI: Our ability to identify the earliest mechanisms of tissue strain and subsequent molecular expression of damaged tissue in vivo relies on using a primarily noninflammatory model. We have developed this model using a saline lavage injury to create moderate canine lung injury that results in reduction of the PaO2/FiO2 (P/F) ratio and a doubling of plateau pressure (Pplt) that is stable for the 6-hour experimental period (Figure 2). This moderate lavage injury was chosen for investigating the mechanisms behind early VALI in order to avoid overwhelming injuries which may activate other acute processes. The lavage removes surfactant, amplifying the effect of stretch and destabilizing peripheral airspaces, predisposing them to endexpiratory collapse and increased mechanical strain.

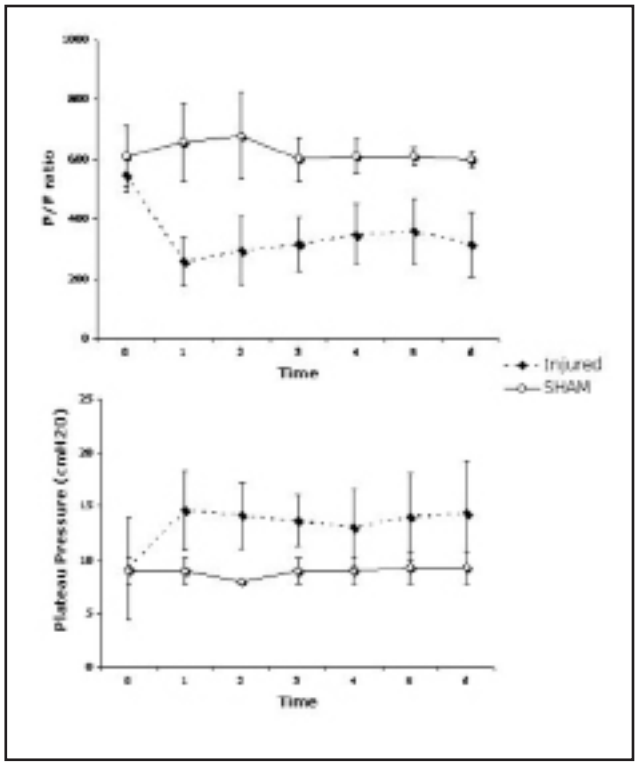

Figure 2. Pplt and P/F ratio in canine ALI after lavage injury (n=20) or sham (n=20). Means ± std.

Physiologic CT imaging: Quantification of regional mechanical tissue strain in vivo in our canine model of VALI will use novel physiologic imaging techniques developed by our laboratory. Static CT imaging approaches use density distributions and histograms to describe regional aeration patterns and changes between inspiration and expiration (Figure 3, from Simon et al.). Figure 4 illustrates our method for quantifying regional specific volume change (sV) from regional changes in CT density.[23] This method directly measures regions of increased strain during mechanical ventilation to target for sampling of BAL and tissue specimen.

In this canine injury model of unilateral lavage injury we found significant differences in patterns of regional gene expression, including important gene pathways such as inflammation, cell adhesion, coagulation, and apoptosis [26, 27]. These experiments identified pre-B cell colony enhancing factor (PBEF), a pro-inflammatory molecule not previously described in the lung, as one of the most up-regulated genes with significant regional variation (note: dependent vs. nondependent expression in Figure 5).

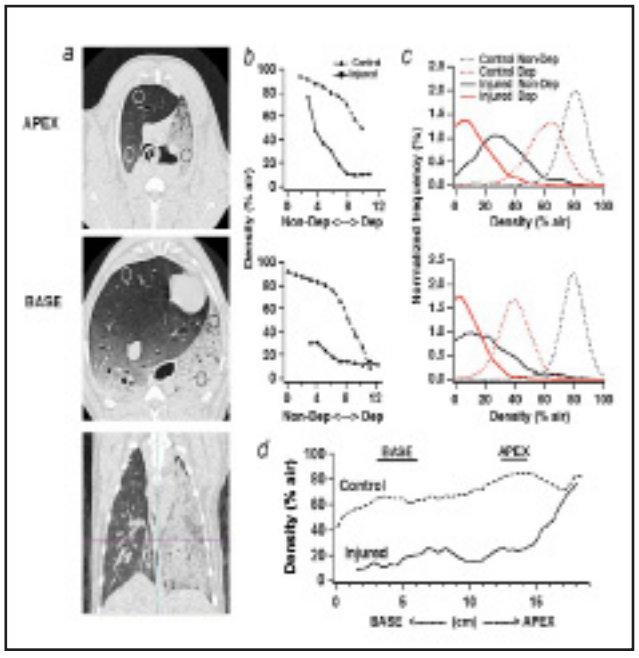

Figure 3: CT imaging data from unilateral lung injury model. a) end-expiratory images demonstrating normal and injured lung. b) vertical gradient of density distribution for the injured and uninjured lungs. c) histograms of air distribution in the dependent and non-dependent regions comparing endinspiration (above) to end-expiration (below). d) axial profile of density from Base to Apex comparing normal and injured lungs.

Future Directions: Hyperoxia and oxidative stress in VALI: Free radicals and other reactive oxygen species have been shown to increase in the setting of critical illness and inflammation creating increased oxygen exposure (hyperoxia) which results in tissue injury to alveolar cells in culture. In a variety of ALI models, hyperoxia has been demonstrated to be an important element in the biochemical propagation of mechanical injury specifically in stretched alveolar cells and rodent VALI models [29] and impaired function of antioxidant enzyme systems has resulted in progression and worsened severity of rodent ALI. We have performed experiments evaluating the effect of hyperoxic vs. normoxic exposure on canine VALI and have identified patterns of altered gene expression of several genes implicated in ALI.[30]

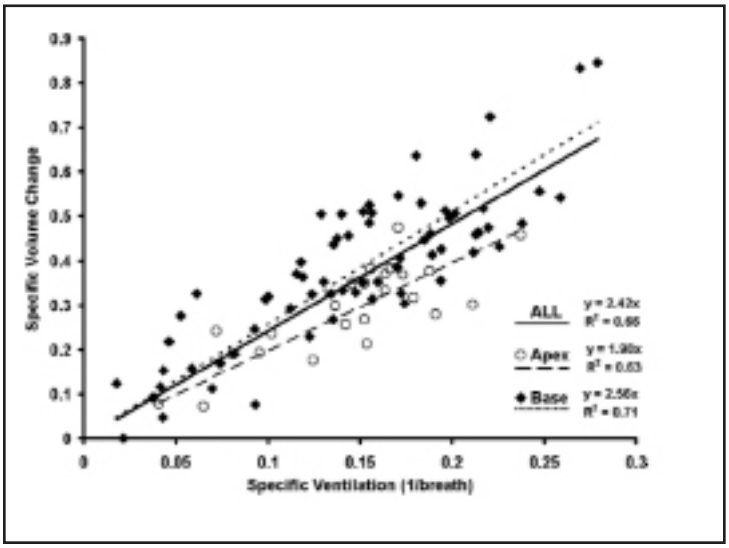

Figure 4: Regional specific volume and correlation with regional ventilation using in vivo CT imaging.

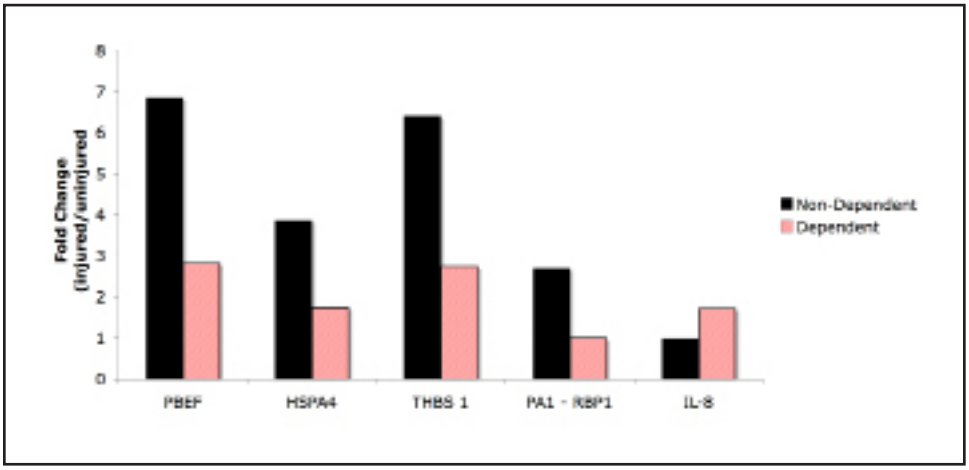

Figure 5: Candidate genes identified through microarray analysis of regional lung tissue comparing altered gene expression between injured and uninjured canine lung. Black is the non-dependent and Pink the dependent lung regions. Gene symbols: PBEF-pre B-cell colony enhancing factor, HSPA4 – heat shock 70KDa protein, THBS 1 –thrombospondin 1, PA1-RBP1 – PA 1 mRNA binding receptor protein 1, IL-8 – interleukin 8.

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Lifetime Achievement Award: We've Come a Long Way, [Baby!]

Recipient: M. Christine Stock, M.D., FCCP, FCCM

This presentation will briefly discuss the history of positive pressure ventilation, tracing its history from 1555 to the advent of its widespread use during the polio epidemic. The talk will explore the use of spontaneous breathing concomitant with positive pressure ventilatory support and the physiologic attributes of spontaneous ventilation for the patient receiving ventilatory support. Various modes of ventilatory support that allow spontaneous breathing will be discussed in the context of these physiologic principles.

Starting with Vesalius, who, in de Humani Corporis Fabrica, published in 1555, was the first to give a detailed description of positive pressure ventilation and what sounds very much like "modern resuscitation":

> *"But that life may in a manner of speaking be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in the air. Indeed, with the slight breath in the case of the living animal, the lung will swell to the full extent of the thoracic cavity, and the heart becomes strong…for when the lung, long flaccid, has collapsed, the beat of the heart and arteries appears wavy, creepy, twisting; but when the lung is inflated, it becomes strong again…And as I do this, and take care that the lung is inflated at intervals, the motion of the heart and the arteries does not stop… "*

And so it began…

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Young Investigator Award

iNOS Inhibition Prevents Muscle Wasting, Apoptosis and Decreased Akt Activity in Burned Rodents

Marina Yamada, Ph.D.

Introduction: Muscle wasting leads to decreased mobilization, difficulties in weaning off respirators, prolonged rehabilitation and hospitalization. Insulin resistance is a major contributor to muscle wasting. Akt promotes hypertrophy and survival of muscle cells, while GSK-3β induces atrophy and apoptosis. Akt inhibits GSK-3β activity by phosphorylation. Inducible nitric oxide synthase (iNOS), a major mediator of inflammation, plays a pivotal role in obesity- and endotoxin-induced insulin resistance. We have previously shown that the inhibition of iNOS prevents burn-induced insulin resistance in skeletal muscle, and that muscle wasting by burn is associated with apoptosis. However, a role of iNOS in muscle wasting in critical illness (e.g., burn) has not yet been studied. Therefore, we examined the effects of iNOS inhibition on apoptosis, fiber size, and basal activities of Akt and GSK-3β in skeletal muscle of rodents.

Methods: Full-thickness third degree burn injury comprising 45% and 30% of total body surface area was produced under anesthesia in male Sprague-Dawley rats, and wild-type and iNOS knockout (-/-) C57BL/6 mice, respectively, by immersing the trunk in 80□ water. Burned and sham-burned rats were treated with a specific inhibitor of iNOS, L-NIL (60 mg/kgBW, b.i.d., IP) or PBS. Apoptosis was assessed by TUNEL assay and ELISA kit. The muscle was stained with hematoxylin eosin for measurement of fiber size. Activities of Akt and GSK-3β were evaluated by phosphorylation of Akt, GSK-3β , and glycogen synthase, an endogenous substrate of GSK-3β , and immune complex kinase assay.

Results: Burn injury induced iNOS expression, apoptosis, and decrease in fiber size in skeletal muscle of rats and mice. iNOS inhibitor, L-NIL, decreased apoptosis in skeletal muscle to 33% of the level in PBS-treated burned rats at 3 days after burn ($p<0.01$). In wild-type mice, muscle fiber size was decreased to 61% of that in sham-burned mice at 7 days after burn ($p<0.01$). Burn-induced decrease in muscle fiber size was significantly attenuated in iNOS/- mice (80% of those in sham-burned wild-type and iNOS-/- mice, $p<0.05$), although fiber size did not differ between in sham-burned wild-type and iNOS-/- mice. Basal (exogenous insulin-nave) phosphorylation of Akt and GSK-3β was decreased in skeletal muscle after burn, indicating decreased Akt activity and activation of GSK-3β. Consistently, phosphorylation of glycogen synthase was increased after burn in rats. L-NIL reversed these alterations in the Akt/GSK-3β pathway in burned rats, although neither burn nor L-NIL altered the protein expression of Akt and GSK-3β. Similarly, phosphorylation of glycogen synthase was increased in muscle of wild-type, but not iNOS-/-, mice after burn.

Conclusions: Our data demonstrate that: (1) the inhibition of iNOS by L-NIL or gene disruption significantly prevented burn-induced muscle apoptosis and atrophy in rodents; and (2) burn resulted in decreased Akt activity and activation of GSK-3β in muscle, which were reverted by iNOS inhibition. Our results clearly indicate that iNOS plays an important role in muscle apoptosis and wasting following burn. These findings suggest that altered activities of Akt and GSK-3β may be involved in iNOS-mediated myopathy in burn injury.

"Regional Anesthesia in Austere Environments and Battlefields. Lessons Learned From Iraq and Afghanistan"

Chester C. Buckenmaier, III, M.D.

Abstract

The current conflicts in Afghanistan (Operation Enduring Freedom; commenced October 2001) and Iraq (Operation Iraqi Freedom; commenced March 2003) have been remarkable due to the more than 90% survival rate among wounded warriors. Although this statistic is a historic achievement by the military's medical services, other medical issues have taken on greater emphasis as more casualties from war survive than ever before. Pain management of United States wounded, in particular, has been a medical issue of increasing importance, as modern understanding of the detrimental effects of pain on recovery and rehabilitation becomes clearer. In this review, a warrior's perspective of military pain management is explored and potential for improvement discussed.

Keywords: Battlefield analgesia. Pain. Regional anesthesia. Acute pain.

Introduction

War and the physical and psychological trauma it causes has been part of the human condition from earliest recorded history. As the weapons of war have improved throughout the conflicts of the 20th century, there has been a concomitant improvement in the survival of wounded soldiers. US military casualties from Afghanistan (Operation Enduring Freedom [OEF]; commenced October 2001) and Iraq (Operation Iraqi Freedom [OIF]; commenced March 2003) currently have a 90% survival rate compared with only 76% during the Vietnam War (1961–1973), 67% during the Civil War (1861–1865), and 58% during the RevolutionaryWar (1775–1783) [1]. The dramatic improvements in casualty survival can be attributed to many factors, including advances in body armor, improvements in far forward trauma surgical and resuscitation techniques, improved battlefield hemorrhage control, enhanced blood product availability, and rapid evacuation to higher medical capability [2, 3]. Unfortunately, as survival rates in the current conflicts achieve new heights, improvements in the management of pain in wounded warriors have been far less dramatic.

Historically, the American military has emphasized opioid-based pain management [3]. Although the success of opioid medications in pain management is without question, their use includes significant side effects that can be lethal in the austere combat environment [4, 5]. The reasons for the delayed development of pain management on the modern battlefield can be categorized into cultural biases and current limits to medical knowledge. Most warriors are familiar with the euphemism, "Pain is weakness leaving the body." The military culture encourages stoic acceptance of pain as a mark of strength and courage in the face of adversity. Even after the discovery of ether, many surgeons considered anesthetic agents unnecessary, or even detrimental, to a patient's recovery [6]. For many military physicians practicing under the harsh realities of combat medicine throughout history, the treatment of pain must have seemed an unrealistic luxury.

Improved understanding of the pathophysiology of pain and its associated morbidity has only recently begun to alter physician attitudes. There is an evolving apprehension that poorly managed pain can develop into a disease of the nervous system with the potential for lifelong disability and morbidity consequences for the patient [7]. Perhaps the most significant change that is occurring within military pain medicine is the realization that pain management must begin at point of injury, extend across the care continuum from battlefield to military medical center in the United States, continue through the Veteran's Administration or civilian rehabilitation facility, and stretch into the rest of the veteran's life if necessary [8].

In this review, the state of pain care is examined utilizing the five levels of care, also known as "roles of care" (Table 1). Levels of care denote the progressive medical capability that a casualty transitions through from point of injury on the battlefield back to the United States [9]. In an effort to convey the reality of this extreme medical environment, a fictional account of a casualty experience, based on actual wounded warrior reports, accompanies the description of pain management at each level of care.

Levels of Care

Note: The casualty story used in this article is a work of fiction based on personal accounts by wounded warriors and the author's experience. It is for illustration purposes only. Any resemblance of characters to actual persons, living or dead, is purely coincidental.

Level I

One of the local police had expressed concern about insurgent activity in front of my camp. Random firing could be heard in my sector all day. I was on patrol, dismounted, with my squad. My squad leader, two other warriors, and I moved onto the objective. My squad leader was hit first and fell with a bullet wound to the face. Another insurgent rushed the squad and detonated himself about 15 feet from my position, this despite having emptied my weapon's magazine into the insurgent. The blast killed the warrior to my left and shredded my left lower leg. The insurgent's vest had been filled with small black ball bearings, which peppered my body. Fortunately, my helmet, goggles, and body armor prevented the ball bearings from hitting vital organs or my eyes. I remember the blast knocking me back and onto my stomach. I tried lifting myself up off the ground but could not; both my arms were broken. I actually started to laugh with shock and disbelief. What was happening?

The medic seemed to arrive instantly. He was very confident and reassured me as I tried to express some last words to my family. The medic would have none of that. He calmed me and gave me some morphine for pain control out of a case he carried. I remembered the case because the medic did weekly checks on the contents. The medic stopped the bleeding from my left leg with a tourniquet and started an IV. That medic saved my life.

One of the single most important advances in military medicine leading to improved survival of combat wounded throughout the 20th and into the 21st century has been the combat medic. Bringing ever greater capability and skill to the point of wounding, these medic warriors are a primary reason for improved survival of American wounded. Tasked, under combat conditions, with initial assessment and stabilization of a wounded warrior's airway, breathing, and hemorrhage control, the management of pain in this setting becomes secondary.

There are situations when effectual management of trauma pain can significantly enhance the effectiveness of the medic in supervision of casualties in the chaotic combat environment. Fear, disorientation, and the inability to focus beyond the pain experienced following trauma can incapacitate a warrior's ability to assist in his/her extraction from the battlefield. Pain and fear, in the most extreme cases, can even cause wounded warriors to become a danger to themselves and the casualty evacuation mission.

Table 1 Levels of medical care in the United States military

Level[a]	Capabilities	Facility
I	Self-aid, combat medic, battalion surgeon; advanced trauma life support	Battalion aid station
II	Resuscitation/stabilization surgery	Forward surgical teams
III	Full operating rooms and specialty care	Combat support hospital
IV	Full service hospital	Regional medical center
V	Reconstructive and restorative care	Tertiary medical center

[a] Levels I to III are located within a war or disaster operational zone. Levels IV and Vare typically located outside the war or disaster operational zone. (Data from Lounsbury and Bellamy [9])

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Since the Civil War, morphine and other opioids have been the standard battlefield pain medications, with morphine remaining the Level I pain medication of choice today. The preeminence and success of opioid medications in the management of combat trauma is without question. However, the exclusive use of opioids for pain care of the wounded has not been without complications. During World War II, a landmark study on combat trauma pain was undertaken from 1943 to 1944. It was observed that increasing numbers of casualties were manifesting signs of morphine overdose that, in many cases, resulted in warrior deaths [10]. Not only did this study heighten awareness of the dangers of opioids in austere medical environments, it also focused attention on the issue of pain following wounding. Unfortunately, pain care was essentially reserved for hospitalized wounded, and further development in far forward pain management remained unchanged until the present conflicts.
In previous American conflicts, wounded warriors were static and cared for within the theater of war until they had recovered from wounds and were sufficiently stable for transport. Many days to weeks might pass before a wounded warrior could be safely transported back to the United States. This reality has changed dramatically in the current conflicts, in which rapid evacuation to higher levels of care capability outside of the war theater has saved many lives. In some cases, a soldier is flown out of the country of confrontation in less than 24 h. This rapid pace of evacuation has rendered conventional battlefield pain care obsolete, as long-established opioid monotherapy fails in the challenging air evacuation environment [11].

Significant enhancements to Level I pain care have been achieved in the present conflicts. The management of pain is now an integral part of the combat medic's curriculum, with specific recommendations that often de-emphasize early and exclusive use of opioids [12]. Some units have explored the use of "wound packs" containing acetaminophen, a cyclooxygenase 2 inhibitor, and a fluoroquinolone that the warrior is instructed to consume following a penetrating extremity wound [13]. Although this approach is too new for comment on efficacy, the concept of prepackaged pain medications for use under defined conditions during war or disaster warrants further research and development. Parenteral preparations of NSAIDs are also available that further the potential utility of these medications in field medicine.

There is a trend in far forward (Levels 1 through 3) medicine to use ketamine as a primary medication for the management of trauma pain [14]. Ketamine produces rapid analgesia, is opioid sparing, reduces nausea and vomiting, and typically does not further reduce blood pressure in hypotensive patients [15]. The dissociative state typical of analgesic doses of ketamine can be a particular advantage as a chemical restraint in combative patients in the confined air evacuation environment. The military is currently in the final stages of testing nasal ketamine delivery devices for use far forward on the battlefield. Nasal delivery of pain medications precludes the need for IV access and enhances the speed of drug bioavailability.

The recognition that poorly managed acute pain can lead to chronic pain syndromes [16] has led to the recent enhanced focus of military medicine on far forward pain management. Combat medics understand that casualties relieved of pain can better assist with medical mission objectives and often be active participants in their own evacuations.

Level II

> I was loaded into a vehicle and driven to the forward operating base. The medical facility was run by Canadians. They removed all my clothes, started another IV, bandaged wounds, and splinted fractures. I do not know what I was given, but I did not have much pain. I was awake but somewhat groggy. I was being packaged for a plane ride to the combat support hospital. I recall my Sergeant Major being there. He wished me farewell, but I don't actually remember leaving. I remember screaming at the medic as we headed for the helicopter, "Don't take off until the other guys get on!" I kept worrying about my squad mates. What had happened to them? I was going in and out of consciousness, I do not recall much before being loaded on the helicopter.

Forward surgical teams (FSTs) are an established component of the military medical response to war. FSTs are designed to provide advanced trauma life support and far forward lifesaving surgical procedures aimed at patient stabilization and packaging for rapid evacuation to the next level of care. A typical FST has two operating rooms, four intensive care beds, and are staffed with 20 health care providers (4 surgeons, 2 anesthesia providers, and support personnel) [17]. Casualties requiring resuscitation and/or damage control surgery to contain hemorrhage and protect against metabolic injury (coagulopathy, hypothermia, and metabolic acidosis) are often anesthetized, mechanically ventilated, and unconscious during Level II care. Pain care principles remain similar to those used by the medic for hemodynamically stable casualties, with particular attention to splinting, bandaging, and padding of

injuries for transport. Exacting attention is given to protecting the patient from hypothermia during transport, which can be a problem even in hot-climate battlefields.

Level III

As I was being loaded onto the Blackhawk helicopter, my shredded left leg fell off the stretcher and I screamed out in excruciating pain. The flight medic quickly re-secured my leg and gave me something through my IV that really eased the pain. I was aware of other casualties on the flight, but everything seemed distant and the flight seemed to pass by quickly. When I arrived at the combat support hospital, there was much activity. I was wheeled into an area with bright lights and many people in gowns, gloves, and masks. It seemed many things were happening to me at once as people stuck me with more needles and handled every inch of my body. I remember being rolled, which was very painful with my injured leg. I was asked about my pain and given something, which again took the edge off. I was moved to another room with a large X-ray to scan my body. I was then told I was going to the operating room to clean up my wounds and splint my fractured arms. The anesthesia guy kept telling me what was happening and a nurse was holding my hand, which helped. I was placed on a hard, narrow table, and they said I was going to sleep.

The next thing I remember I was in a bed, on a ward, with many other wounded. My arms were in casts and I couldn't feel my left leg, which was a blessing. They told me I had lost my left foot. The nurse said I had been given two nerve blocks in the operating room, one in my bottom and one in my thigh. She taught me about the bright orange pumps that were infusing local anesthetic to my left leg and how I could push a flashing green button on the pump if my leg started to hurt. Later, the anesthesiologist visited and explained which pump served which part of my leg and labeled the pumps so I could remember. I was told I could have oral morphine if I needed it, but I was very comfortable with the nerve blocks and the other medications I was getting through my IV. The one dose of morphine I did ask for made me feel sick. I was pretty comfortable and able to call my family in the States that evening.Mymom was upset but happy to hear my voice. That phone call really helped.

The combat support hospital (CSH) is where the first restorative and rehabilitative surgery is performed on the wounded warrior. These facilities are located near major airfields and focus on preparing casualties for evacuation out of the war theater. The CSH has capabilities that are very similar to those of a moderately sized community hospital in the United States with emphasis on trauma management. Fully staffed and equipped operating suites, modern anesthesia machines, full-service blood bank, digital X-ray, CT, fluoroscopy, and ultrasound, among other technologies, are usually present at these facilities. From a pain perspective, this is the first facility where definitive pain management plans can be implemented and managed.

With the preponderance of extremity wounds that have defined the current conflicts in Afghanistan and Iraq, the introduction of continuous peripheral nerve blocks (CPNBs) to battlefield medicine in 2003 has greatly enhanced the pain management capabilities of providers far forward [18, 19]. During these initial efforts to bring the relatively advanced technology of CPNBs to the battlefield, it was recognized that pain management far forward was inconsistently practiced and based almost exclusively on the use of IV morphine. The use of morphine while the patient is static at the CSH was mostly effective, and side effects associated with opioid-based pain management could be handled by CSH health care personnel. Regrettably, morphine as the sole option for pain management on evacuation flights out of the war zone has been failing. Evacuation flights are crowded with patients, light conditions are low, vibration and noise are high, monitoring resources are constrained, and health care personnel are limited. Morphine, as the sole option for pain control in this environment, was inadequate and possibly dangerous [20•]. The requirement for new pain management technologies and strategies, which could safely treat pain in this austere environment without further burdening flight health care personnel, was recognized early in the OEF and OIF conflicts [21•].

In response to this need, the tri-service Defense and Veterans Pain Management Initiative (DVPMI, formally MARAA [Military Advanced Regional Anesthesia and Analgesia]; www.DVPMI.org) was formed. This organization has improved interservice communication and decision making for battlefield and evacuation pain control. DVPMI has been instrumental in coordinating the efforts of the Air Force, Army, and Navy in improving pain management for wounded warriors. The DVPMI is directly responsible for the establishment of battlefield CPNB, epidural, and patient-controlled analgesia (PCA) infusion pump technology on evacuation flights. Most recently, the DVPMI organization published the first handbook on military pain management in the field and air evacuation environments (Military Advanced Regional Anesthesia and Analgesia Handbook; www.bordeninstitute.army.mil). In collaboration

with the DVPMI, the Army has developed a pain management equipment set, designed for the CSH, which has been fielded in Afghanistan.

Despite these advances in the pain care of American wounded warriors, the management of pain within the theaters of war remains inconsistent and fragmented. At the CSH level, there is no medical officer responsible or specifically tasked with pain management. Pain care is often thought of as an assumed or implied duty of CSH anesthesia providers who are often unavailable due to other casualty responsibilities or not trained in acute pain medicine. Recently, the author (C. C. Buckenmaier) deployed to Afghanistan with the British hospital at Camp Bastion, Helmand Province, to determine the advantages and feasibility of having a pain physician asset at Level III. The pain service that was established with this deployment became an integral part of the CSH involved in more than 40% of the trauma cases during a 4-month period. The pain service physician serves as a consultant for pain issues and a proponent of multimodal analgesic approaches (Table 2) that de-emphasized opioid-based analgesia [22]. The consistent availability of a fellowship-trained acute pain consultant quickly resulted in enthusiastic support from surgeons. Data from this first experience demonstrated profound improvements in verbal analogue pain scores and will serve as a basis for establishing pain service requirements for CSH field operations in the near future.

Air Evacuation

The flight medics came that evening and bundled me up on a stretcher. They were very efficient and they explained everything about the coming flight. I was going to have to make one stop before I left country for the military hospital in Landstuhl, Germany. Movement was still pretty uncomfortable for my leg, but I was able to push the buttons on my pump for added medication, which eased any pain in a few minutes. I was also given a third pump with morphine. I could push that button too if I needed more pain medicine.

I was taken by ambulance to the airfield and loaded on a C-130 aircraft. The plane engines never stopped; it was very loud and hard to hear the flight nurse and her instructions. I had my pain pumps, and the flight was uneventful. When we briefly stopped at the next hospital in country, I was examined again by another doctor. There was confusion at this facility about the catheters to my leg, and the doctor said they had to be removed. This was fine at first, but then the block wore off and my amputated foot really began to hurt. The morphine pump was not cutting it. The remaining flight to Landstuhl was very painful and an experience I will not soon forget. I was confused why one plan for my pain that was working was rejected for another that didn't work.

Table 2 Elements of multimodal analgesia

Local anesthetics: epidural, spinal, continuous/single injection peripheral nerve block
NSAIDs: cyclooxygenase enzyme blockers
Acetaminophen
N-methyl-D-aspartate receptor antagonists: ketamine
α2-Adrenergic agonists: clonidine, dexmedetomidine
Anticonvulsants: gabapentin, pregabalin
Antidepressants
Glucocorticoids: dexamethasone
Opioid medications: morphine, hydromorphone
Paracetamol (IV acetaminophen), among others

Inconsistency in the management of pain throughout the evacuation chain continues to be a problem plaguing transportation of wounded warriors. Although techniques and technologies to manage pain have improved greatly since the beginning of the current conflicts, there remains no consistent policy for pain management throughout the continuum of care. Congress has recently acted to rectify the problem with the passage of the National Defense Authorization Act for 2010, which includes pain management language under subtitle B, Health Care Administration section 711. Not later than March 31, 2011, the Secretary of Defense shall develop and implement a comprehensive policy on pain management by the military health care system. With the establishment of this public mandate, the need for a comprehensive strategy for pain management at all levels of care now carries the force of United States law.

Levels IV and V

When I got to Landstuhl, I had to go back to surgery. I was offered nerve blocks again, and I readily accepted. I was comfortable after surgery at Landstuhl and on the flight back to the United States since I had my continuous blocks and infusion pumps back. I have needed so many operations on my left leg. It is hard to imagine having to withstand all those operations without the nerve blocks and the pain control they provided between operations. The ability to manage your own pain with nerve block infusions or PCA is important. There is considerable anxiety in knowing that a short-acting pain medication is going to wear off soon and having to ask, and then wait, for more medication.

I have been to multiple major military hospitals in the States. Walter Reed Army Medical Center (WRAMC, Washington, DC) stands out because they have an acute pain service with pain nurses who are available any time to deal with pain issues that arise. It really helps to have someone available to come to your room immediately and not have to worry about waiting for an anesthesiologist to come out of the operating room. The pain nurses take the time to explain the medications and equipment, and they listen to your issues. My family and I never mind a daily visit by the pain team. Other facilities lack acute pain nursing and the acute pain service. The difference is apparent and not positive.

One of the key features of any successful pain management program is available and trained pain personnel who are motivated to aggressively treat pain. From the patient's perspective, timely access to acute pain services in the perioperative period is vital. At WRAMC, skilled acute pain nurses are available to respond to calls for pain issues immediately. These nurses are backed up by an acute pain medicine physician who is available for consultation and adjustment of pain care plans. WRAMC acute pain nurses also serve as a central educational link between the pain physician, nursing service, the patient's family, and the patient. They provide one-on-one pain teaching for the patient, family, and ward staff, ensuring full understanding of pain management goals established by the pain team with the patient. Although pain physicians can formulate excellent pain care plans for patients, pain nursing makes these plans successful through explanation of treatments to patients and family members and management of patient expectations for pain relief and care. Pain nursing also serves a critical role as the sentinels of the service, alerting the team when treatment plans are failing or a patient's status is changing adversely. Possibly most significantly they are the gentle touch, the empathetic ear, and the compassionate voice whose impact is resistant to objective measure but whose significance to overall pain management is constantly reaffirmed by the patients. The importance of pain nursing to the overall success of an acute pain service cannot be overestimated.

Conclusions

Poorly managed or untreated pain is maladaptive, detrimental to recovery, and can quickly become a disease process as debilitating as the inciting surgery or trauma [23]. On this key point, civilian and military medicine is not different, and both can benefit from the pain management experience of the other.

The importance of acute pain management services following trauma and surgery is recognized as a fundamental part of modern medical care [24–26••]. Acute pain management plans are necessarily as unique as the patients who require these services. Complex trauma or surgical patients cannot be managed with "one size fits all" protocol-driven pain programs. On the battlefield, during evacuation, and back at major military hospitals in the United States, effective pain care throughout the continuum requires dedicated health care professionals at all levels that are specifically trained, tasked, and responsible for the management of pain. America's military wounded deserve no less for their sacrifice.

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Disclaimer: The views expressed in this article are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, or the United States Government.

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Ethics Debate: Interactive Session on Donation After Cardiac Death (DCD)

Moderator: Robert N, Sladen, M.D.
Nicholas Sadovnikoff, M.D.; Michael F. O'Connor, M.D.

Introduction: DCD and the Dead Donor Rule

For decades organ donation was provided by patients whose clinical picture was characterized as an "irreversible coma", or more colloquially as "brain dead." More recently, a second category of donors of donors has been accepted, namely those patients who have died due to the withdrawal of life-sustaining therapies (LST). Through a process known as Donation after Cardiac Death (DCD), organs may be taken, with the permission of the donor or surrogate decision-maker, once the donor has been declared dead after withdrawal of LST. In order to reassure such devastatingly injured or ill patients' families, and the public in general, that donors are not being deliberately killed for the purpose of obtaining organs, DCD policies abide by the Dead Donor Rule, which simply put, states that no person shall be killed by or for the purpose of obtaining organs. The result is that DCD candidates must be declared dead before organ procurement can take place. This results in a "staged death", with parameters as to how quickly the potential donor must die and how death should be declared varying somewhat from institution to institution. The fact that, unlike the case of donors who have been declared dead by neurologic criteria, organ perfusion is obligatorily absent for a period of time, results in organs of lesser quality, and for the most part rules out the heart and lungs for donation. Further, if the DCD donor fails to be declared dead within the specified window of time, usually 1-2 hours, the donation attempt is abandoned and no organs are taken.

My intent is to propose that there are ethically viable alternatives to current DCD practices that would optimize the potential for benefit to recipients without violating the rights of donors or duties of physicians. Along those lines, I will also call to question the foundation of the principle of "brain death" as death, and I will offer that there may be a more inclusive way of thinking about both types of donors. This proposal does indeed have implications not only for intensivists, but for anesthesiologists as well.

Donation After Cardiac Death: What Every Anesthesiologist Needs to Know

1. Case presentation
2. History of the Definition of Death and the evolution of the Dead Donor Rule
3. Ongoing Shortage
4. Donation After Cardiac Death: A Solution to a growing problem
5. Case presentation
6. ASA and SCCM statements
7. Legal Considerations
8. The Future

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SESSION II

Moderator: Steven A. Deem, M.D.

2:00 – 2:30 p.m. **Infectious Disease Update**
Sylvia Y. Dolinski, M.D.

2:30 – 3:00 p.m. **Perioperative Care of the Patient for Pulmonary Thromboembolism**
William C. Wilson, M.D.

Infectious Disease Update

Sylvia Y. Dolinski, M.D.

Epidemiology

Nearly 30 years have gone by since the first HIV/AIDS cases were identified. It is estimated that worldwide approximately 33.4 million adults and children were living with HIV/AIDS at the end of 2009.1 Since 1981 when the first cases of AIDS were reported in homosexual white men, the demographics have greatly changed and now minority population groups, particularly African-American and Hispanic populations as well as heterosexuals are overrepresented. Infection rates in women and children have been rising. HIV is also becoming more prevalent in adults older than 50 years, but often there is a delay in reaching the diagnosis of HIV which leads to a higher rate of AIDS at the time of diagnosis and death within a month of initial diagnosis.2 In the United States data from 2006 estimated that 1.1 million adults were living with HIV/AIDS. The Centers for Disease Control and Prevention estimates that 21% of those individuals are unaware of their HIV status, and 40% diagnosed with HIV are labeled with the diagnosis AIDS within the following year. 3 Almost 30 years ago, HIV infection was quickly fatal and life-expectancy after overcoming pneumocystis pneumoniae infection was approximately 7 months. Now, HIV infected individuals can live >15 years after seroconversion. During the first 5 years of infection, patient mortality rates among HIV-individuals approximates the death rates of those who are not HIV infected.

Due to improved survival with antiretroviral therapy (ART), HIV infected individuals present to the Intensive Care Units (ICU) less often with opportunistic infections and more commonly with complications from their ART medications or co-morbid conditions: heart, lung, kidney, liver diseases as well as from non-AIDS defining cancers.4

ICU Admission diagnoses

There are primarily 3 reasons that HIV/AIDS patients are admitted to the ICU:
1. Opportunistic Infections
2. Medical and Surgical Non-HIV related conditions
3. Complications related to ART therapy.

1. Opportunistic Infections:

As stated, some patients are unaware of their HIV status and present with an AIDS defining illness. Some have known of their HIV infection, but either chose not to be treated or had no access to care and present with very low CD 4 counts and severe infections related to Pneumocystis jirovecii pneumonia (PCP), cryptococcal meningitis or Tuberculosis. Intensivists need to be able to manage such opportunistic infections and the CDC publishes management guidelines.

2. Medical and Surgical Non-HIV related conditions

Patients undergo surgeries, and present with common medical diseases such as bacterial pneumonia secondary to organisms such as Streptococcus pneumoniae.5 COPD exascerbation, hepatitis or hepatic failure from co-infection with hepatitis B and C occurs, drug overdoses are seen.

Intensivists must know how to manage the ART medications while the patient's condition requires fasting as most anti-retroviral medications are not available parenterally and also must know about frequent drug interactions.

3. Complications related to ART therapy.

a. Premature cardiovascular disease

Patients with HIV on ART medications have an 26% increased risk of myocardial infarction.6 ART promotes hyperlipidemia, hypercholesterolemia, insulin resistance and is thought to accelerate atherosclerotic plaque formation. HIV itself may promote atherosclerosis via chronic inflammation and endothelial cell dysfunction.7 Patients may present with heart failure due to HIV-related cardiomyopathy, severe dyspnea from HIVrelated pulmonary HTN, acute myocardial infarctions or after coronary artery bypass grafting. Cardiovascular disease accounts for 10% of deaths.

b. Lactic acidosis

Hyperlactatemia is a common and asymptomatic side effect. However, patients can become symptomatic with significant lactic acidosis from treatment with any of the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI). It is most commonly associated with stavudine and didansosine. 8 The combination of these two medica-

tions is now advised against due to reports of fatal lactic acidosis. The presumed mechanism is the impaired synthesis of adenosine triphosphate-generating enzymes. With lactate levels in excess of 15 mmol//L, mortality can be > 60%. The offending agent is withdrawn and supportive care is the mainstay of treatment. Riboflavin, L-carnitine, coenzyme Q have been tried for symptomatic improvement.

c. Hypersensitivity syndromes
Abacavir can lead to life-threatening respiratory failure from hypersensitivity pneumonitis and hypotension. Reactions typically occur after two weeks. Patients can improve within 1-2 days after drug cessation and patients should not be rechallenged with abacavir as anaphylactic reactions have been described. Nevirapine can lead to severe hepatotoxic reactions particularly with higher CD4 counts. Stevens-Johnson syndrome can also lead to ICU admission.

d. Pancreatitis
Protease inhibitors may cause pancreatitis and an agent to which this complication developed should not be reintroduced.

e. Liver failure
There is a high prevalence of co-infection of Hepatitis C with HIV which results in a common cause for mortality in patients.

f. Immune Reconstitution Inflammatory Syndrome
Diagnostic criteria for IRIS includes a) the diagnosis of AIDS, utilitzation of anti-retroviral medications, symptoms of an infection/inflammation while being treated with antiretroviral agents that cannot be explained by a new infection, or side effect of therapy.9 It should be considered in a patient who has recently been started on ART medication. It most commonly occurs in patients being treated for PCP, Mycobacterium avium, cryptococcus , CMV, Hepatitis B or C.

Survival in the ICU

In the 1980's, the diagnosis of AIDS was considered a death sentence by both physicians and patients and mortality was around 70% from opportunistic infections. By the end of the decade, zidovudine (AZT) improved the quality of life and extended life expectancy. With the introduction of ART therapy, ICU mortality declined and significantly improved overall life expectancy. In a retrospective study from San Francisco, the lowest survival rates seen were in patients admitted to the ICU with respiratory failure, GI bleeding and PCP.10 Interestingly, survival among HIV patients receiving ART compared to those not receiving ART was not much different 67% vs 70%. In a French study, survival increased from 75% in 1996 to 93.4% in 2005.11 Both studies showed that the most common admission diagnosis was respiratory failure. Due to ART, US Mortality rates overall declined from approximately 45,000 per year to around 14,580 reported in 2007. Life expectancy increased from ca. 10 years in 1996 to 22 years in 2005. 12 Patients now are more often admitted to the ICU for a non-HIV related illness or for complications stemming from ART. It is controversial whether there are short term benefits of ART in ICU patients with critical illness while is well known
that ART has long-term survival benefits.

Summary

HIV status should not alone decide whether a patient ought to receive ICU care. Patients are living longer and aging HIV patients are more likely to present with cardiovascular diseases including coronary artery bypass surgeries, pulmonary diseases, hepatic failure, acute renal failure, neurocognitive disorders, non-AIDS defining cancers. There should be low threshold for testing for HIV in ICU patients.

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Perioperative Care of the Patient for Pulmonary Thromboembolism

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Introduction

Pulmonary thromboendarterectomy (PTE) is a potentially curative procedure for chronic thromboembolic pulmonary hypertension (CTEPH). Although highly debilitating, CTEPH remains an under-diagnosed entity. As both CTEPH and PTE become increasingly recognized, anesthesiologists will increasingly manage these patients during surgery, and anesthesiologist-intensivists will increasingly care for these patients in the intensive care unit (ICU).

PTE is the only viable treatment for CTEPH. In contrast to non-embolic pulmonary artery hypertension (PAH), where effective therapies exist (e.g. PGE_1, PGI_2, NO, endothelin inhibitors), medical management provides only limited and temporary relief of symptoms in CTEPH patients.[1,2] CTEPH is a progressive disorder with a dismal prognosis[3,4], the only alternative to PTE is lung transplantation. Compared to lung transplantation, PTE has a lower surgical mortality, better long-term survival, shorter waiting period, and fewer complications.[5a] Indeed, the perioperative mortality rate for PTE at UCSD is <5%, whereas lung transplantation mortality, including the waiting period, has been reported to be 20%-50%.[5-7]

II. Recognician and Epidemiology of PE and CTEPH

Pulmonary embolism (PE) was first described by Laennec in 1819.[7a] Since then, PE has been increasingly recognized as an important complication of hospitalized patients. Approximately 600,000 patients develop pulmonary emboli (PE) annually in the United States (US).[8] Approximately 150,000 of these patients die leaving 450,000 survivors. The majority of patients who expire following PE die within one hour from cardiovascular collapse or respiratory failure. These figures likely underestimate the true incidence of PE, which can also present sub-clinical. Indeed, one autopsy study revealed that PE was unsuspected in 70-80% of patients in whom it was later deemed to be the principal cause of death.[9]

In patients who survive the initial PE event, anticoagulation therapy with heparin and coumadin usually restores pulmonary blood flow within 1-4 weeks. The vast majority of survivors enjoys complete dissolution of their emboli and subsequently lead a normal life. However, at least 0.1-0.5% of the survivors have unresolved pulmonary emboli. It is these 500 to 2500 patients who go on to develop CTEPH every year in the US.

III. Acute PE Management (Different than Treatment for CTEPH)

Treatment for documented acute PE is very different from management of CTEPH (described below); yet, very similar to treatment for an acute deep venous thrombosis (DVT) and includes anticoagulation, thrombolytic therapy; occasionally, placement of inferior vena cava (IVC) filters, invasive radiology, and rarely, surgical intervention. Untreated PE is associated with a 30% mortality. When timely diagnosis and treatment occurs, mortality is reduced to approximately 5%.[9a]

Thrombolysis, is used only when compromise in pulmonary blood flow is so severe it cannot wait for the body's natural fibrinolytic system to clear the obstruction. Thrombolysis requires PA catheterization and direct infusion of thrombolytic drug, e.g. tissue plasminogen activator (tPA), into, or adjacent to, the embolus.[9b]

IVC filters are placed at UCSD for the prevention of initial or recurrent PE in patients at highest risk (e.g. quadriplegics), and those with contraindications to anticoagulation (e.g. acute traumatic brain injury).

When significant hemodynamic compromise persists from a large embolus, surgical embolectomy, or interventional (catheter-based) techniques can be employed to both fragment and aspirate the clot.[9c] Surgical intervention has historically been reserved as the last option. Trendelenberg reported the first attempt at surgical treatment of massive PE in 1908, as a heroic thrombectomy in a moribund patient, with brief hemodynamic improvement.[15] Long-term survival after acute pulmonary embolectomy remained low throughout the mid 20th century.[16] Success rates for acute pulmonary embolectomy improved in the early 1960s with the advent of cardiopulmonary bypass (CPB), which allowed a more careful and thorough approach.[17] Surgical removal of an acute PE clot is easiest to do on CPB, but has been done without extracorporeal circulation.[17a]

Improved outcomes have been recently reported for urgent surgical embolectomy of acute PE in patients with significant hemodynamic impairment. Indeed, in a retrospective review of 15 patients the 10 who were operated on within the first 24 hours of diagnosis all survived; whereas, those who were operated on >24 hours after diagnosis had a

60% mortality.[17b] A more recent literature review from the team at McGill, report that several major centers have liberalized the use of surgical embolectomy to include patients with PE associated with moderate-to-severe RV dysfunction without hemodynamic compromise, and are showing improved outcomes suing a multidisciplinary approach in this population as well.[17c]

IV. Natural History and Pathophysiology of CTEPH

CTEPH comprises a broad spectrum of disease. Many patients report suffering a major DVT and PE, although often an initial event cannot be identified.[10] The embolus undergoes incomplete resolution, and the patient experiences a "honeymoon" period followed months or years later by progressive cardiopulmonary deterioration. Why some patients (0.1-0.5% of survivors) develop CTEPH while others do not is not well understood, but may partially result from the fact that many of the acute PE episodes go undetected and thus untreated. Morris, et al recently demonstrated a resistance of fibrin (harvested from CTEPH patients) to plasmin-mediated lysis;[10a] however, both the plasminogen activator activity and inhibitor activity are usually normal.[11] Furthermore, antithrombin III (ATIII), protein C, protein S are abnormal less than 1% of patients with CTEPH.[12] The only prothrombotic factor regularly seen in this population is the lupus anticoagulant, which is present in approximately 10% of patients with CTEPH.[13]

V. Clinical Presentation of CTEPH

The majority of patients who develop CTEPH present for medical evaluation late in the course of their illness. This results from two factors: 1) few of these patients recall an obvious history of DVT or pulmonary emboli, and 2) early findings for pulmonary hypertension may be subtle, and the progression of disease is often insidious. Patients typically complain of progressive fatigue and dyspnea on exertion (DOE). When initially seen by physicians they are de-conditioned, and may have concomitant disease (hypertension, CAD or COPD) which can confuse the diagnosis.

VI. Evolution of Invasive Management for Chronic Pulmonary Emboli

It was not until the late 1920s that CTEPH was recognized as a distinct diagnostic entity. The condition remained severely under-recognized as a cause for PAH; by 1963 only 250 cases of CTEPH had been reported. Only 6 of these were diagnosed before death, and only 3 received operative intervention.

The first operative approach to this disorder was undertaken by Alfred Blalock in 1948 (removal of chronic thrombus),18 and the first pulmonary endarterectomy was performed in 1957 (unsuccessful).19 During the 1970s a few isolated cases were reported (including the first case performed at UCSD in 1973),20 and the use of median sternotomy and cardiopulmonary bypass gained popularity. During his time it was recognized that a complete endarterectomy was required (not merely a thrombectomy). In the 1980s and 1990s the UCSD program blossomed, with innovations in patient selection, surgical technique, anesthetic management, and critical care leading to improvements in outcome.

VII. Diagnostic Evaluation and Surgical Selection

Once CTEPH is suspected the diagnostic work-up is straightforward. Major goals are to 1) confirm the presence of thromboembolic disease, 2) quantify the degree of PAH, and 3) search for the etiology or contributing factors (such as hypercoagulability). The evaluation begins with the history, physical examination and laboratory data. It then progresses to radiographic and interventional testing.

A. History

Most CTEPH patients present with progressive DOE. Exercise-induced syncope may be present, particularly in late stages of the disease. A documented history of PE is, helpful, but not necessary. Causes for DVT should be sought (e.g. leg swelling, immobility, venous stasis) as well as history consistent with PE (acute dyspnea, chest pain, hemoptysis).

B. Physical Examination

In the late stages of this disease physical examination typically demonstrates evidence of right ventricle (RV) failure: peripheral edema, hepatomegaly and jugular venous distention (JVD). Precordial examination reveals a RV heave, and a unique systolic murmur often heard upon auscultation of the lung fields.[21] This distinctive murmur of CTEPH results from turbulent flow through partially obstructed pulmonary vessels. Patients with ASD may have less significant JVD and instead may present with cyanosis. Prominent "a" and giant "c-v" waves are seen on the jugular venous pulsations in those with tricuspid valve regurgitation (frequently encountered). Hepatomegaly and ascites develop late in the disease process, along with peripheral edema. Pericardial and pleural effusions are also encountered.

C. Typical Laboratory and Imaging Findings

Secondary polycythemia is typical with hematocrit values commonly in the 45% - 55% range. Liver function tests may be abnormal in a nonspecific pattern reflecting hepatic congestion. Prothrombin Time (PT) and activated partial Thromboplastin Time (aPTT) are usually normal. But, an elevated aPTT may indicate the presence of lupus anticoagulant or other anti-phospholipid antibodies.[22,23]

CXR typically demonstrates clear lung fields (with relative oligemia in affected lobes of the lungs). Evidence of RA and RV enlargement is almost universally noted. Asymmetry in the size of the central PAs are typical, with greater diameter of the left main PA shadow compared to that of the aorta.[24]

The ECG shows evidence of RVH . Pulmonary function test (PFT) reveals a decreased carbon monoxide (CO) diffusing capacity and a moderate restrictive defect.[24] Obstructive patterns may also be present, arising from the bronchial hyperemia (there is a marked increase in bronchial blood flow).

Arterial blood gas (ABG) universally reveals an increased alveolar-arterial (A-a) O_2 gradient, which widens with exercise. Dead space ventilation (V_D) is increased leading to a compensatory increase in minute ventilation. As V_D increases with exercise, hypercarbia may result.[26] Moderate-to-large ventilation perfusion (V/Q) mismatches are universally documented.[26] However, V/Q scans can underestimate central pulmonary vascular obstruction in CTEPH patients.[27]

Transthoracic echocardiogram (TTE) demonstrates massive RA and RV enlargement. Occasionally thrombi are noted in the right atrium , and obstructive material is often found in the pulmonary arteries. There may be severe LV compression due to impingement from the hypertrophic RV, as well as abnormal septal motion.[28] Tricuspid regurgitation (TR) can be found using Doppler color-flow measurements. It is with TTE and V/Q scanning that most cases of CTEPH are first diagnosed. Right heart catheterization demonstrates the severity of pulmonary hypertension. If the pulmonary artery (PA) pressures are only modestly elevated at rest, measurements are repeated during exercise.

Pulmonary angiography demonstrates characteristic patterns, including: 1) irregular arterial contours, 2) abrupt cut-off or narrowing of vessels, 3) pulmonary artery webs and bands, 4) pouch defects, 5) obstruction of lobar or segmental arteries at their point of origin.[29] Coronary angiography is performed in patients at risk for coronary artery disease.

Spiral computerized tomography (CT) scanning and magnetic resonance imaging (MRI) have been investigated for in evaluation of CTEPH.[30] MRI and spiral CT are still less satisfactory in fully characterizing distal pulmonary thromboembolic disease (per UCSD Pulmonlogists). Thus, pulmonary angiogram remains the “gold standard” for evaluating pulmonary vascular obstruction. Although an invasive test, over 600 pulmonary angiograms were completed without a single fatality at UCSD.[10]

D. Selection for PTE Surgery is based on Five Criteria:

1. Hemodynamically significant pulmonary vascular obstruction. The majority of patients have PVR > 300 dynes* sec*cm-5 Values > 1000 dyne*sec*cm-5 and suprasystemic PA pressures are common (No pressure or PVR is too high for PTE)
2. Functional impairment. Most PTE patients are NYHA class III or IV.
3. Absence of active malignancy, and Rule-Out of Competing Diagnosis (i.e. entities that look like, but are not, CTEPH).
4. Patient must desire surgery based upon dissatisfaction with their poor cardiorespiratory function or prognosis.
5. Patient must be willing to accept the mortality rate of the procedure (historically 5-7%10; currently 4.5% at UCSD).

VIII. Preoperative Preparation

Several days prior to surgery an IVC filter is placed to prevent recurrent PE. Immediately prior to surgery a peripheral IV (16 gauge or larger) is placed in an upper extremity, and a radial arterial catheter (A-line) is inserted. The patient may then be given light sedation (e.g. midazolam 1-2 mg) and brought into the OR. Preoxygenation ensues, routine monitors are attached, and the arterial line is transduced. A PA catheter is generally placed after induction rather than before, since the hemodynamic status of the patient is usually known, and the hemodynamic target goals are set (see below).

IX. Operating Room Management

A. Hemodynamic considerations for induction and the pre-CPB period

Less than 10% of patients with CTEPH presenting for PTE have associated LV pathology. Hemodynamic assessment and decision making is thus centered on RV function. Because of the high right-sided pressures, the coronary blood supply to the hypertrophic RV is continuously at risk. Maintenance of adequate SVR, preserving the inotropic state, and maintaining sinus rhythm tends to preserve RV coronary perfusion and systemic hemodynamics. The preoperative catheterization data, including cardiac output, PVR, patency of coronary arteries, and RV end-diastolic pressure (RVEDP) are important. Elevated RVEDP (>14 mmHg), moderate to severe TR, and preoperative PVR>1000 dyne-sec-cm^{-5} are signs of impending decompensation. In such cases inotropes and/or vasopressors should be considered for the induction and pre-bypass period.

B. Induction of anesthesia

Induction is targeted at maintenance of hemodynamic stability. Moderate doses of etomidate (0.1-0.2 mg/kg) or midazolam (0.1 mg/kg) in conjunction with fentanyl 5-50 µg/Kg are given in divided doses while hemodynamic response is assessed. Etomidate is particularly useful in patients with tenuous hemodynamic status. Phenylephrine (50-100µg) is frequently necessary to maintain right coronary artery (RCA) perfusion pressure; mean arterial pressure (MAP) in the 75-85 mm Hg range is usually sufficient. Richet al.[34] documented improved RV performance (increase MAP, coronary artery perfusion pressure, maintained cardiac output) with phenelpherine administration in patients with pulmonary hypertension.

The muscle relaxant is chosen according to airway issues and desired hemodynamic response. Pancuronium, rocuronium, and vecuronium have all been useful in this patient population.

C. Post induction pre-CPB period

If the superior vena cava (SVC) is patent, a Right IJ introducer and PA catheter are inserted. Placement of the PA catheter may be difficult because of low cardiac output, TR, and dilation of the RA and RV.

A femoral A-line is placed after induction. This 2nd A-line is useful in cases involving long re-warming periods, because the systemic arterial pressure is significantly underestimated by the radial A-line in the post-CPB period. This phenomenon has been noticed by our group and others.[35-38] It is not uncommon for a mean arterial pressure (MAP) gradient of 20 mm Hg to develop after CPB during a PTE. The mechanism is unclear; but, probably involves arteriolar vasodilatation following prolonged re-warming from CPB.[35-38]

Next, the TEE is placed to monitor and assess cardiac function and filling during PTE. The TG-mid SAX view demonstrates massive RV enlargement. The ME 4-chamber view is then used to evaluate the RA (for dilatation and thrombi), RV (for dilatation and systolic function) tricuspid valve (for regurgitation), and septal motion. The aortic valve and pulmonary outflow tract are then examined along with the right and left PAs, which may contain thrombus. However, CTEPH patients may not have central thrombus, and present only with dilatation of the main PAs. This dilatation is secondary to distal thromboembolic disease. Attention is then turned to the atrial septum. Agitated saline is administered in a 10 cc bolus through the right atrial CVP port to determine if ASD exists (present in 25-35% of PTE patients).[39]

EEG electrodes are placed and the processed EEG (Neurotrac, Hewlett Packard, inc.) is monitored throughout the procedure. Recently we have begun to use near infrared spectroscopy as an addi-

tional cerebral monitor to study changes that occur with DHCA. Following this, the patients' head is wrapped in a circulating ice cold-water cooling blanket.

Other monitors include a urinary catheter with temperature monitoring capabilities, a rectal temperature probe, and tympanic membrane temperature probe, which provides a fairly reliable estimation of brain temperature.[40] The rectal and bladder probes estimate core temperature, helping quantitate thermal gradients. The pulmonary artery catheter measures the blood temperature, which is allowed to differ no more than 10° C from the core temperature during cooling and warming.
The fluid warmers are turned off in preparation for cooling, and additional fentanyl and/or midazolam is administered as necessary prior to chest incision. Potent inhalational agents are used sparingly.
If the hematocrit and hemodynamics permit, 1-2 units of autologous blood are harvested and reinfused after CPB.

D. Surgical approach and initiating CPB

Surgical approach involves a median sternotomy and the use of CPB with periods of complete circulatory arrest, providing the bloodless operative field necessary to complete meticulous lobar and segmental dissections.[31] Cooling begins immediately after CPB in concert with cooling blankets, present under the patient and around the head. A gradient of ≤ 10°C is maintained between the arterial blood and the bladder/rectal temperature. This allows an even distribution of cooling. The venous O_2 saturation increases during cooling. A saturation of 80% is typical at 25° C, rising to 90% at 20° C. Hemodilution to a hematocrit of 18-25% is utilized to decrease blood viscosity, optimize capillary blood flow and promote uniform cooling.

E. Deep Hypothermic Circulatory arrest (DHCA)

As core temperature approaches 20° C and brain temperature approaches 16-18° C, the aorta is cross-clamped and thiopental is administered to assure EEG isoelectricity (typically 500 to 1000 mg). Complete cooling typically requires 45-60 minutes, depending on the size and perfusion of the patient. Immediately after aortic cross-clamping, cold crystalloid cardioplegia solution is administered into the aortic root. Additional myocardial protection is afforded by placing a cooling jacket around the heart.

F. The surgical technique

An incision is made in the right PA, and an endarterectomy plane is established and dissection continues until bronchial artery back-bleeding impairs good visualization. At this point circulatory arrest is imperative. Bronchial back flow in these patients is frequently substantial and without circulatory arrest complete endarterectomy cannot be accomplished.

Circulatory arrest is limited to 20 minute epochs to prevent neurological damage. An experienced surgeon can usually accomplish the entire unilateral endarterectomy within this time period. If additional arrest time is necessary, reperfusion is carried out at 18° C core temperature for a minimum of 10 minutes. At the completion of the right endarterectomy, perfusion is reestablished while the right PA incision is closed. The left PA endarterectomy is then performed in a similar fashion. Following completion of the left endarerectomy a small incision (approx. 1 cm in length) is made in the RA near the junction of the atrium and IVC. This incision allows inspection of the atrial septum and repair of an ASD, if present. The small incision provides adequate exposure and is associated with less risk of postoperative atrial dysrhythmias compared to larger incisions.31 Additional procedures (e.g. CABG or valve replacement / repair) can be performed during the re-warming period.

G. Anesthetic considerations during DHCA

During DHCA the anesthesiologist ensures that the head cooling blanket is functioning properly, the EEG is isoelectric, and all stopcocks and IV solutions are turned to the off position. This decreases the risk of entraining air into the vasculature during exsanguination. Furthermore, flushing of arterial or venous lines during DHCA is strictly avoided as this may allow air, debris, or warm saline to be infused into the cerebral circulation. Immediately after circulatory arrest the lungs are gently ventilated with unwarmed room air (not oxygen). The purpose of this is to empty remaining blood from the pulmonary veins and bronchial vessels, providing a bloodless surgical field. Room air is preferred for this maneuver because of the theoretical concern that 100% oxygen

during circulatory arrest may lead to bronchial or alveolar injury (involving oxygen derived free radical mediated mechanisms).

H. Post-DHCA Rewarming

Upon rewarming, the head cooling blanket is removed and additional anesthetic (e.g. benzodiazepine or propofol infusion, opioid), and muscle relaxant is administered. The aortic cross clamp is removed and full perfusion is restored. The myocardial jacket is removed and methylprednisolone 500 mg (stabilize cellular membranes and decrease reperfusion pulmonary edema) and Mannitol 12.5 grams (to promote diuresis and free radical scavenging) are administered. Research is ongoing at UCSD to assess the benefit of these theoretically advantageous maneuvers. A 10° gradient between blood and bladder/rectal temperature is maintained but not exceeded during rewarming. Warming more quickly (>10°C gradient) promotes systemic gas bubble formation (decompression sickness) and uneven warming. Rewarming times are variably related to the patient's weight and systemic perfusion; 90 to 120 minutes are usually required to achieve a core temperature of 36.5° C. In the event the systemic vascular resistance is elevated, additional anesthetics are administered first, then a vasodilator such as nitroprusside is administered. The heart generally begins to beat spontaneously with a bradycardiac rhythm as the blood temperature approaches 25°-30°C; defibrillation is occasionally necessary.

I. Separation from Cardiopulmonary Bypass

Prior to separation from CPB the checklist used for most cardiac anesthetics is applied. This includes adequate ventilation, acceptable potassium and hematocrit levels, adequate cardiac rhythm (normal sinus rhythm or paced), and satisfactory myocardial function. We use a generous tidal volume (12-15 ml/kg) to provide adequate lung expansion, and 5 cm of positive end-expiratory pressure (PEEP). End-tidal carbon dioxide (ETCO2) is a poor measure of ventilation adequacy in these patients both pre and post-CPB, since VD ventilation is an integral to the disease process. After successful surgery, the Pa-PETCO2 gradient may be decreased compared to preoperative values, but the time course for this improvement varies. Most patients paradoxically have transient increase in this gradient immediately following CPB.

While still on CPB, the TEE is used to detect intracavitary air as well as to evaluate left and right ventricular function. The femoral A-line pressure is monitored (better reflection of aortic pressure than the radial A-line pressure following re-warming. The anesthesiologist checks the airway for frothy sputum or bleeding because reperfusion pulmonary edema and airway bleeding at this time. Separation from CPB occurs as the venous return line is clamped and the heart is allowed to fill. The CVP in typically in the 10-12 range at time of Separation; the TEE is used to further assess function & volume.

Dopamine (3-5 µg/kg/min) is routinely infused for its mild inotropic activity. In patients with particularly poor ventricular function epinephrine 0.4 -1.5 µg/Kg/min. is added. If the surgery has been successful, the TEE reveals immediate post PTE improvements in the left and right-sided geometry,28,42 The distention of the RA and RV is greatly decreased, resulting in improvement of function of both ventricles. If TR was present before the endarterectomy, it is usually greatly decreased or resolved; it is for this reason that tricuspid valve repair is generally not performed as part of this operation. Significant improvement in hemodynamic status is noted, including a doubling of the cardiac index, dramatic decrease in pulmonary artery (PA) pressures, and a drop in the PVR to 25% of the preoperative value.10

J. The post-CPB period

If autologous blood was harvested before CPB, it is now reinfused. Frothy sputum, if present, likely indicates the onset of reperfusion pulmonary edema. In this case, the endotracheal tube (ETT) is suctioned and increasing amounts of PEEP are applied beginning with 5 cm H_2O escalating to 7.5 and 10 cm H_2O.

If frank blood is returning from the ETT, surgical bleeding is the probable culprit. Although it may not be of much benefit, PEEP is increased and aggressive suctioning of the blood ensues, and fiberoptic bronchoscopy is employed to evaluate the source of bleeding. Lung isolation maneuvers

(e.g. bronchial blockers, double lumen ETT) are considered.
Following heparin reversal, the pericardium and thoracic cavity is inspected for bleeding sources. The anesthesiologist verifies heparin reversal with an activated clotting time (ACT). A cell-saver is utilized to recover shed blood and process blood remaining in the bypass circuit. Mediastinal tubes are placed and the chest is closed. Bleeding diathesis is rare, and transfusion requirements are usually minimal.[10] Anti-fibrinolytic agents such as ε-amino-caproic acid and aprotinin are not used for fear that the resulting hypercoagulable state will facilitate platelet aggregation on the newly endarterectomized surfaces.

X. POSTOPERATIVE MANAGEMENT
Postoperative management of the PTE patient is similar to that following most other types of CPB. The patient tends to awaken in 2-6 hours after high dose opioid/midazolam techniques (or 1-2 hours after more propofol based techniques). The mediastinal drains protect against of pericardial tamponade.[10] Two major postoperative complications unique to PTE are reperfusion pulmonary edema and PA steal.

Reperfusion pulmonary edema is a localized form of high permeability (non-cardiogenic) lung injury, localized to the area of lung which received the endarterectomy. It usually occurs within the first 24 hours but may appear up to 72 hours following PTE.[43] In most cases it is mild; reperfusion edema resulting in clinically significant morbidity occurs in < 10% of cases. In its most severe form, it begins immediately post CPB, in the OR. These patients are often extremely ill, requiring aggressive ICU and ventilator management. Pressure control, PEEP, inverse ratio and airway pressure release ventilation (APRV) are used judicially in an effort to improve V/Q matching, minimize shunt and further pulmonary injury.

Pulmonary arterial steal represents a postoperative redistribution of pulmonary arterial blood away from the previously well-perfused segments into the newly endarterectomized segments.[44] Whether the cause is failure of autoregulation in the newly endarterectomized segments or secondary small vessel changes in the previously open segments has not been clarified. However, long term follow-up has documented a decrease in pulmonary vascular steal in the majority of patients, suggesting a remodeling process in the pulmonary vascular bed.[45]

XI. OUTCOME
As mentioned above, there has been steady improvement in mortality rate at UCSD since 1980. We believe this results from improvements in surgical skill, anesthetic care, perfusion technique, and postoperative management. The positive effect of experience, in the form of case volume, on outcome has been well documented for other types of complicated surgery, such as liver transplantation.[46]

The long-term hemodynamic and systematic outcomes have been equally encouraging. Systematic improvement has been documented for as long as 12 months following the surgery with every indication that the improvements are essentially permanent. A study of UCSD patients having received pulmonary endarterectomy between 1970 and 1995 indicates that most patients experience a sustained improvement in functional status indefinitely.[47] The majority of patients who were initially NYHA class III and IV status returned to NYHA class I and II and are able to resume normal activities.

The long term improvements result from a combination of improved autoregulation in the reperfusion pulmonary edema segments, as well as a decrease in pulmonary artery steal. In addition, resolution of hypertensive changes within pulmonary vascular bed occur and remodeling of the right ventricle continues over weeks to months.[12]

All patients are maintained on life-long anticoagulation therapy with coumadin. Although thromboembolic recurrence has been detected in a few patients in whom anticoagulation therapy was discontinued or allowed to fall below therapeutic levels, there have been no documented occurrences of recurrent thrombobolic events in patients who have been maintained on adequate anticoagulation. The neurologic outcome is generally good, although occasionally patients exhibit neuropsychiatric changes which can include paranoia, euphoria, and, rarely, focal deficits. There has been a decrease in the frequency and magnitude of neurologic deficits in the last 10 years at UCSD.[12, 31] This improvement has been attributed to decreased circulatory arrest times and improved cerebral protection.

XII. FUTURE
There remain many unanswered questions about CTEPH and PTE. Research continues to further elucidate the etiology of CTEPH, as well as the mechanisms and factors leading to reperfusion pulmonary edema, vascular steal, and ischemic neurologic injury. Projects designed to determine the physicochemical changes which occur in the lungs and brain after DHCA, as well as the geometric response of the right side of the heart to CTEPH and its relief

are ongoing. In addition, further study of the coagulation system, hypercoagulability, and abnormal responses to heparin are of continued interest.

XIII. CONCLUSION

PTE is a potentially curative procedure for CTEPH. Patients with CTEPH who do not undergo PTE have a uniformly poor prognosis with their only alternative being lung transplantation. Compared to lung transplantation, PTE offers less surgical mortality, better long term survival, and fewer complications. The majority of the world experience in PTE has been obtained at UCSD Medical Center (nearly 2,500 cases), where there has been progressive improvement in operative outcome. Mortality rate for PTE at UCSD is now 4.5% with documented sustained functional improvement in the vast majority of survivors.

This success results from the efforts of a multi-disciplinary team with experience in the preoperative evaluation, intraoperative anesthetic and surgical management, and postoperative critical care of these patients.

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Education and Competencies in the ICU

Neal H. Cohen, M.D,, M.P.H., M.S.

Introduction

This discussion will address some of the educational goals for ICU training for both residents and fellows and define some of the challenges associated with achieving them. It will also address some of the changes in duty hours for residents and fellows that are being proposed by ACGMe and describe the impact on critical care training. Finally, we will discuss the implications of competency-based training on credentialing and scope of practice for critical care anesthesiologists.

Competency Based Practice

Over the past few years, ACGME and the Anesthesiology RRC have reevaluated the curricular expectations for each level of training and modified the program requirements accordingly. One of the primary goals for this reassessment is to ensure that at each level of training, the resident and fellow achieve specifically defined competencies, gain appropriate clinical skills and decisionmaking ability and have graded levels of responsibility and supervision to prepare them for independent practice. For critical care medicine, defining the appropriate content and curriculum that will ensure that a fellow has the skills consistent with the scope of practice is challenging because there are so many different models of care and patient populations that are served under the umbrella of “critical care”. These same challenges exist for critical care anesthesiologists in both academic and community hospitals. They must be able to document continued competence to provide care to the patient population served in the ICU in which they practice.

Critical Care Medicine Curriculum

One of the primary challenges for developing a competency-based curriculum is the diversity of practice opportunities, expectations and needs that encompass “critical care medicine”. While a review of the content outlines for critical care training programs in each of the specialties that has an accredited fellowship reveals significant overlap in the curriculum, the actual components of practice vary considerably from one ICU (and hospital) to another. There are some general curricular expectations that encompass the scope of practice for critical care – and there is significant overlap between the content outlines for critical care training in anesthesiology, medicine, surgery, and other specialties that provide critical care training. However, the practice of critical care medicine is diverse, so it is essential that we define the core curriculum and ensure a consistent educational program that will prepare any critical care anesthesiologist for whatever practice opportunities that are available. The current curriculum in anesthesiology critical care medicine includes basic pathophysiology, pharmacology, organ specific pathology, life support measures, fluid, electrolyte and transfusion therapy, and other general topics relevant to the practice. Compared to the curriculum for critical care training in surgery, medicine or other specialties, the anesthesia curriculum emphasizes pharmacology and respiratory and cardiovascular management strategies. At the same time, many critical care anesthesiologists work side-by-side with other critical care physicians and have the same scope of practice and must maintain the same standards of care. As a result, the critical care curriculum must be extensive – often more diverse than can be provided in an individual ICU rotation. It is therefore incumbent upon the program director to ensure exposure to a diverse patient population and to provide clinical and technical experience that addresses all aspect of critical care medicine. We have to provide the core educational experience that is needed to allow our graduates to practice in a surgical ICU, a medical-surgical ICU, a neurologic ICU and any other ICU. To accomplish this diverse training requires close cooperation with other critical care faculty and training programs, something that has been difficult to accomplish for some programs. A number of approaches are being taken to foster interdisciplinary critical care training and practice – and these efforts will hopefully improve educational opportunities for our fellows and practice opportunities for critical care anesthesiologists.

ACGME Duty Hours

In 2003 the ACGME enacted standards on resident duty hours, limiting residents to 80 hours of work per week. Since that time, anesthesia training programs have successfully incorporated these changes into the residency and fellowship programs. Over the past few years, the current standards have been challenged. In 2008, the Institute of Medicine (IOM) convened a group to evaluate resident duty hours, the impact on patient safety and make recommendations regarding work hours. The IOM recommendations included significant additional restrictions to resident work hours and mandated increased supervision. In response to the IOM report, ACGME appointed a Task Force on Duty Hours to consider the IOM recommendations and possible changes in the duty hour requirements

and other aspects of training. The Task Force recently published its proposed recommendations [Nasca TJ, Day SH, Amis ES Jr; ACGME Duty Hour Task Force. N Engl J Med. 2010 Jul 8;363(2)]. The changes include modest restrictions on work hours, but, perhaps of greater impact on critical care training, they propose significant changes in the supervision required at each level of training and the requirement to provide fellows will graded levels of responsibility based on documented milestones. The need to document competence throughout the training will be difficult, particularly since the clinical experiences are dependent upon the ICU in which the fellow rotates, the patient population and the clinical care requirements. The critical care faculty and program directors will have to closely monitor clinical experiences and document competencies in determining call schedules, level of supervision of residents by fellows and the clinical situations in which fellows can function relatively autonomously. These changes will also affect faculty roles and responsibilities and may require greater faculty presence than is currently provided in some ICUs.

Credentialing in Critical Care Medicine

All of the challenges confronting the educational programs related to clinical skills and scope of practice in critical care medicine must also be addressed for physicians practicing critical care medicine. The generic credential to practice "critical care medicine" is no longer an acceptable way for credentials committees to ensure competence in all aspects of critical care. In addition, the credentialing requirements are more complicated in critical care than many other specialties because of the multidisciplinary nature of critical care medicine. Since critical care providers have varying backgrounds and may work in different intensive care environments, credentials committees, with mandates from The Joint Commission (TJC), CMS and other regulatory bodies are requiring that critical care credentials become more "granular" with specifically delineated procedural and cognitive skills. They are also requiring that each practitioner with a specific credential have the same level of skill, same expectation for clinical activity and outcomes associated with care, no matter what the background or previous training. As a result, the critical care physicians must define the scope of practice and the credentials that are essential to their individual practice. This differentiation of privileges and credentials raises a number of questions we must address. For example, should a critical care physician who practices in a cardiac surgery ICU have the same privileges (and skill set) as a critical care physician working in a medical or medical surgical ICU? Should every critical care physician, no matter what the primary specialty have the same airway management credentials? Should every ICU physician have the same ability to provide palliative care? Does it matter if an institution has a separate palliative care service? Should every critical care provider be expected to perform the same procedures – and provide the same level of care across the spectrum of critical illness? The answer to some of these questions is obvious, but for others the response is not so clear. If an individual physician does not maintain skills in a procedure, that physician should not maintain the privilege to perform it. However, if the procedure is done rarely, but is essential to good patient care, how can the physician document clinical competence? For example, should every critical care physician be expected to insert and manage a pulmonary artery catheter? If not, what happens when (if?) a patient *requires* one? More importantly, if each critical care provider has a different set of skills and different clinical privileges, how can an ICU – or a hospital guarantee the same level of care to all ICU patients 24 hours a day, 7 days a week. How do the differing credentials impact call coverage? These are critical questions that are becoming more commonplace and require our attention. We will have to define alternative methods for ensuring clinical competence *for each privilege* by not only monitoring outcomes, but also providing opportunities demonstrate competence through simulation and other methods and by allowing individual physicians to "retrain" to demonstrate competence in rarely exercised credentials or to regain credentials that were relinquished in the past when the clinical needs require it, such as with a reorganization of ICUs in a hospital.

Conclusion

The practice of critical care medicine is exciting and diverse. Along with the incredible opportunities that critical care medicine provides, as a specialty, we must ensure that each provider has the skills and competence to fulfill the needs of an ever-expanding, complex patient population. As is true for most of us, our individual practices have evolved and the scope of practice has changed throughout our careers. As educators, we must ensure that our residents and fellows have the training and experience they need to begin their careers in critical care medicine, but also provide opportunities to maintain competence as well as develop new skills as their own practices evolve. By addressing these challenges in education and credentialing, we can ensure that critical care physicians will have rewarding careers and, most importantly that our patients will continue to have access to high quality and safe care.

Poster Presentations

(Note: Bold name represents poster presenter)

#1 **Closed-Loop System Automatically Up- and Down-Regulates Pressure Support Ventilation Appropriately**
N. Al-Rawas, M.D.; M. Banner, Ph.D.; N. Euliano, Ph.D.; D. Martin, Ph.D.; A.J. Layon, M.D.; A. Gabrielli, M.D.

#2 **Intraoperative Glycemic Control with Intravenous GLP-1 in Cardiac Surgery**
Benjamin A. Kohl, M.D.; Mary S. Hammond, BSN; Stanley Schwartz, M.D.; Edward A. Ochroch, M.D.

#3 **SOFA Scores Predict Outcome in Elderly Mechanically Ventilated Patients**
Alexander F. Bautista, M.D.; Ozan Akca, M.D.; Rainer Lenhardt, M.D.; Matthew Kuestner, M.D.; Michael Heine, M.D.

#4 **Incorporation of a Critical Care Curriculum in Undergraduate Medical Education: A Design Perspective**
Shahriar Shayan, M.D.; **Michael Ault, M.D.;** Thomas Corbridge, M.D.

#5 **Does Peri-Operative Transfusion of Fresh Blood Reduce Post-Operative Mortality?**
Alaa A. Abd-Elsayed, M.D., MPH; Patricia M. Carey, M.D.; Anna Boyd, B.S.; Judith Strong, Ph.D.; Steven Lisco, M.D.

#6 **Does Stress Ulcer Prophylaxis With Proton Pump Inhibitors Increase The Risk Of Ventilator-Associated Pneumonia In Critically Ill Neuroscience ICU Patients?**
Ozan Akca, M.D.;Yusuke Kasuya, M.D.; James L. Hargett, M.D.; Susie Crowe, Ph.D.; Rainer Lenhardt, M.D.

#7 **A Novel Pathway for Anesthesiology Intensivists to Achieve Competency in Focused Cardiac Ultrasound**
Peter Schulman, M.D.; Michael Hutchens, M.D.; Matthew Griffee, M.D.; Kevin Wei, M.D.; Matthias Merkel, M.D.

#8 **Elevated PPV Predicts an Increased Length of Stay and Morbidity During High Risk Abdominal Surgery**
Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., M.B.A.; Thomas M. Dodds, M.D.; Maxime Cannesson, M.D., Ph.D.; Matthew D. Koff, M.D., M.S.

#9 **Intensivist M.D./NPCCP Collaborative Model for ICU Care**
Chad E. Wagner, M.D.; Joshua Squiers, ACNP, Ph.D.(c); Lee Parmley, M.D., J.D.

#10 **Isoflurane Protects Against Renal Ischemia-Reperfusion Injury Induced Liver and Intestine Dysfunction via Intestinal Sphingosine Kinase Activation**
Minjae Kim, M.D.; Sang Won Park, Ph.D.; Jinu Kim, Ph.D.; Mihwa Kim, B.S.; Vivette D'Agati, M.D.; H. Thomas Lee, M.D., Ph.D.

#11 **The Agreement Assessment of Search Strategies to Identify Postoperative Acute Lung Injury Risk Factors**
Anas Alsara, M.D.; Guangxi Li, M.D., THDCC; Vitaly Herasevich, M.D., Ph.D., THDCC; Ognjen Gajic, M.D., THDCC; Osama Alsara, M.D.; Daryl J. Kor, M.D.

#12 **Administration of Cell Saver Blood Increases Activated Clotting Time in Cardiac Surgery Patients**
Jennifer E. Hofer, M.D.; Michael O'Connor, M.D.; Avery Tung, M.D.; Mark Nunnally, M.D.

#13 **Increased Activated Clotting Time After Cell Saver Administration in Cardiac Surgery Does Not Correlate with the Volume of Cell Saver Transfused**
Jennifer E. Hofer, M.D.; Michael O'Connor, M.D.; Avery Tung, M.D.; Mark Nunnally, M.D.

#14 **Estrogen Renoprotection After Cardiac Arrest is Ablated by Novel Estrogen Receptor GPR30 Deletion**
Michael P. Hutchens, M.D., MA; Yasuhara Kosaka, M.D.; Paco S. Herson, Ph.D.; Halina Offner, M.D.; Patricia D. Hurn, Ph.D.

#15 ***Young Investigator Award***
iNOS Inhibition Prevents Muscle Wasting, Apoptosis and Decreased Akt Activity in Burned Rodents
Marina Yamada, Ph.D; Kazuhiro Ishimaru, M.D., Ph.D; Nobuo Yasuda, Ph.D; Masao Kaneki, M.D., Ph.D; J.A.Jeevendra Martyn M.D., F.R.C.A.

#16 **Perceptions and Attitudes of Anesthesiology and Surgical Residents Regarding Critical Care Training: An Educational Assessment**
Jeremy M. Huff, D.O.; Samuel M. Galvagno, D.O.; Todd Dorman, M.D., FCCM; Pamela A. Lipsett, M.D., FCCM, FACS; Theresa L. Hartsell, M.D., Ph.D.

#17 **Local Fractal Analysis of Cardiac Interbeat Intervals During Hypovolemia in Healthy Volunteers**
Christopher C. Young, M.D.; Eugene W. Moretti, M.D.; Nicola Scafetta, Ph.D.; Stephanie McGuire, M.D.; Richard E. Moon, M.D.

#18 **Mortality of Patients with Respiratory Insufficiency and Adult Respiratory Distress Syndrome After Surgery: The Obesity Paradox**
Anna Maria Bombardieri, M.D., Ph.D.; Stavros G. Memstoudis, M.D., Ph.D., FCCP; J. Matthias Walz, M.D., FCCP; Yan Ma, Ph.D.; Ya Lin, M.S.; Madhu Mazu, M.D., Ph.D.

#19 **TEE Monitoring With a Miniaturized Disposable Probe Influences Post-Operative Management of Cardiac Surgery Patients**
Chad E. Wagner, M.D.; John H. Selby, M.D., J.D.; Clifford L. Parmley, M.D.,J.D.

#20 **Blood Product Administration is Associated with Postoperative Infectious Complications in Patients Undergoing Esophageal Resection Surgery: A Retrospective Cohort Study**
Arun Subramanian, M.B.B.S.; Elie F. Berbari, M.D.; Michael J. Brown, M.D.; Anas Alsara, M.D.; Mark S. Allen, M.D.; Daryl J. Kor, M.D.

#21 **Increased IL-6 and NGAL with Transaminitis after Laparoscopic Donor Nephrectomy**
Steven C. Yap, M.D.; Sang Won Park, Ph.D.; H. Thomas Lee, M.D., Ph.D.

#22 **Risk Factors for Seizures in Cardiac Surgery ICU Patients**
Rizwan A. Manji, M.D., Ph.D., MBA; Hilary P. Grocott, M.D.; Jill A. Leake, CAE; Jacqueline S. Manji, Ph.D.; Alan H. Menkis M.D.; Eric Jacobsohn M.D.

#23 **Central Venous Pressure Measurement Correlates with 3 Dimensional Assessment of Right Ventricular Volume and Function**
Daniel S. Rubin, M.D.; Avery Tung, M.D.

#24 **Effects of Denervation and Consecutive Reinnervation on the Expression of the Fetal and Adult Acetylcholine Receptor**
Christopher Kramer, M.D.; Manfred Blobner, M.D.; Saida Zoubaa, M.D.; Alexander Kretschmer, M.D.; Veronika Lehmeyer, M.D.; Heidrun Fink, M.D.

#25 **Thrombosis Risk in Cardiac Surgery ICU Patients Suspected of Having Heparin Induced Thrombocytopenia**
Rizwan A. Manji, M.D., Ph.D., MBA; Hilary P. Grocott, M.D.; Chee-loong Saw, Ph.D.; Peter Nickerson, M.D.; Alan H. Menkis, M.D.; Eric Jacobsohn, M.D.

#26 **Correlation of the 4T Test, Enzyme Linked Immunosorbent Assay and the Serotonin Release Assay in Post Cardiac Surgical ICU Patients Suspected of Heparin Induced Thrombocytopenia**
Rizwan A. Manji, M.D., Ph.D., MBA; Hilary P. Grocott, M.D.; Chee-loong Saw, Ph.D.; Peter Nickerson, M.D.; Alan H. Menkis, M.D.; Eric Jacobsohn, M.D.

#27 **Non-Invasive Measurement of Oxygen Delivery Index: Is This the Future of Goal Directed Therapy?**
Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., MBA; Thomas M. Dodds, M.D.; Randall W. Loftus, M.D.; Matthew D. Koff, M.D., MS

#28 **Functional Hemodynamics During High Risk Abdominal Surgery: Are All Monitors Created Equal?**
Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., MBA; Timothy J. Quill, M.D.; Maxime Cannesson, M.D., Ph.D.; Matthew D. Koff, M.D., MS

#29 **Reduction in Healthcare Associated Infections by a Novel Hand Hygiene System in a Mixed Patient ICU**
Matthew D. Koff, M.D., MS; Howard Corwin, M.D.; Ingrid Mroz, R.N.; Stephen D. Surgenor, M.D.; Randall W. Loftus, M.D.; Kathleen M. Richard, M.D.

#30 **Pediatric Delirium: Validation of the Pediatric Confusion Assessment Method for the ICU**
Heidi A.B. Smith, M.D., MSCI; D. Catherine Fuchs, M.D.; Pamela Berry, R.N.; Svetlana K. Eden, M.S.; Pratik P. Pandharipande, M.D., MSCI; E. Wesley Ely, M.D., M.P.H.

#31 **Outcomes Following Therapeutic Hypothermia After Perioperative Cardiac Arrest: A Case Series**
Thomas W. Rinehart, M.D.; Matthias J. Merkel, M.D.; Michael P. Hutchens, M.D.

Group 1 - Respiratory and Outcomes

Moderator: William E. Hurford, M.D.

#1 **Closed-Loop System Automatically Up- and Down-Regulates Pressure Support Ventilation Appropriately**
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#31 **Outcomes Following Therapeutic Hypothermia After Perioperative Cardiac Arrest: A Case Series**
Thomas W. Rinehart, M.D.; Matthias J. Merkel, M.D.; Michael P. Hutchens, M.D.

Closed-Loop System Automatically Up- and Down-Regulates Pressure Support Ventilation Appropriately

N. Al-Rawas, M.D.[1]; M. Banner, Ph.D. [1]; N. Euliano, Ph.D. [2]; D. Martin, Ph.D. [1]; A.J. Layon, M.D. [1]; A. Gabrielli, M.D. [1]
University of Florida College of Medicine [1], Convergent Engineering [2]

A closed-loop mechanical ventilation system can control one or more output treatment variables, like pressure support ventilation (PSV), based on measurements of one or more input variables and can make changes automatically without physician intervention. If engineered properly and validated for clinical use, such systems have the potential for assisting physicians and improving patient care (1).

The purpose of this study was to evaluate the operation of a PSV closed-loop system, which uses work of breathing per minute (WOB/min), determined non-invasively using an artificial neural network obviating the need for an esophageal balloon (2), and spontaneous breathing frequency (f) and tidal volume (VT) as input variables in a computerized, fuzzy-logic algorithm to automatically regulate the output variable PSV.

The system (Esprit ventilator and NICO monitor, Respironics, and control software and laptop computer, Convergent Eng.) was attached to a Human Patient Simulator (HPS) (METI) intubated with an 8 mm endotracheal tube. Respiratory system compliance and resistance were set at 0.05 L/cm H20 and 15 cm H20/L/sec, respectaively, simulating an adult with respiratory failure. Data from a combined pressure and flow sensor, positioned between the endotracheal tube and ventilator, were directed to the monitor and laptop computer. By changing the HPS endogenous carbon dioxide minute production rate (VCO2), this acted as a stimulus to produce variations in the breathing pattern and WOB/min. VCO2 values of about 600 ml/min have been reported in adults recovering from inhalational anesthesia (3). By automatically varying PSV, the closed-loop system seeks to maintain the following: WOB/min 7-10 Joules/min, f 10-30 breaths/min, and VT 5-8 ml/kg. Data were analyzed with ANOVA, alpha was set at 0.05.

As WOB/min increased, PSV increased automatically and proportionately to maintain WOB/min, as well as f and VT in clinically acceptable ranges (2). The closed-loop system operated in a predictable manner by automatically applying PSV to appropriately unload the simulated patient's inspiratory muscles while limiting inflation pressure and VT to safe ranges, thus protecting against barotrauma / volutrauma. The potential clinical use of this system is that it is automatic and continuously operational. This would be important in clinical situations where experts may not always be available to perform patient assessment and timely decisions for setting PSV.

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Extra Files:

VCO_2 (ml/min)	WOB/min max (Joule/min)	WOB/min final (Joule/min)	PSV (cm H_2O)	f max (breaths / min)	f final (breaths / min)	V_T max (ml / kg)	V_T final (ml / kg)
260	7.21 ± 0.13	7.21 ± 0.12	4 ± 0.1	18.3± 0.3	18± 0.2	5.2± 0.6	5.2± 0.5
330	7.95 ± 0.14	7.95 ± 0.11	4 ± 0.12	21.3±0.2	21± 0.4	5.0± 0.2	5.0± 0.3
450	10.40* ± 0.15	8.43 ± 0.14	8 ± 0.18	23.8± 0.3	22.3± 0.2	5.8± 0.16	5.8±0.5
560	12.21* ± 0.15	10.0 ± 0.2	18 ± 0.19	22.4± 0.2	18± 0.3	8.65± 0.5	7.2± 0.4
620	12.64* ± 0.2	8.76 ± 0.3	20 ± 0.18	21.0± 0.5	18.6± 0.4	7.38± 0.6	7.7± 0.5

Data are mean ± SD, $p < .05$ compared to WOB/min final (*)

SOFA Scores Predict Outcome in Elderly Mechanically Ventilated Patients

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Introduction: Organ failure is the leading cause of morbidity and mortality in patients admitted to intensive care units (ICU), and can be characterized by different degrees and combinations of organ dysfunction or failure. Studies of patients with organ failures have been hampered by the lack of objective criteria for defining the clinical syndrome, although the ICU mortality rate has been correlated with the number of failing organs and with the degree of organ dysfunction. [1]There have been numerous studies done that validated different severity scoring instruments including SOFA amongst critically ill patients. [2-4]We aimed to assess the prognostic value of SOFA scores in mechanically ventilated elderly patients.

Methodology: After IRB approval, in a retrospective cohort, we assessed patients older than 64 years and mechanically ventilated for more than 48 hours. Demographic data, diagnosis, duration of mechanical ventilation, and survival outcome were recorded. Severity scores including SOFA, APACHE II, and GCS were collected at admission and daily. SOFA scores were determined by the worst value found during the initial 24 and 72 hours after ICU admission. The extrapolated SOFA scores for each patient were correlated with patient's outcome. Areas under receiver operating characteristic curves (AUROC) were calculated in order to analyze the discrimination of the scores using mortality as an independent variable. Both univariate and multivariate statistics were performed to assess the contribution of severity scores. All statistical tests were two-tailed and a p value less than 0.05 was considered as significant

Results: The study included 295 patients with a mean (SD) age of 79 (1.4) years. Median day of mechanical ventilation was 8 [4-14]. An initial SOFA score of ≤ 7 predicted a mortality of < 37% while an initial SOFA score ≥8 predicted a mortality rate of > 50%. Likewise day 3 SOFA score of ≤ 7 predicted a mortality of < 42% and SOFA -3 of ≥8 predicted a mortality of > 63% (Figure 1). Regardless of the initial score, a mortality rate of 44.26% when the score increased, 27.12% and 33.0% mortality were noted when it did not change and decreased respectively. SOFA scores at admission day as well as day 3 were higher in the patients who eventually died (Day#1 5.3±2.2 vs. 4.8±2.1, p-univariate: 0.049, p-multivariate: 0.041; Day#3 6.45±2.0 vs. 4.7±2.2, p-univariate: <0.001, p-multivariate: 0.027). AUROC for SOFA day #3 was 0.728(Figure 1).
[Figure 1]

Conclusions: SOFA scores at admission and day 3 were found to be higher in patients who eventually died. The data showed day 3 SOFA score has a good value in predicting mortality.

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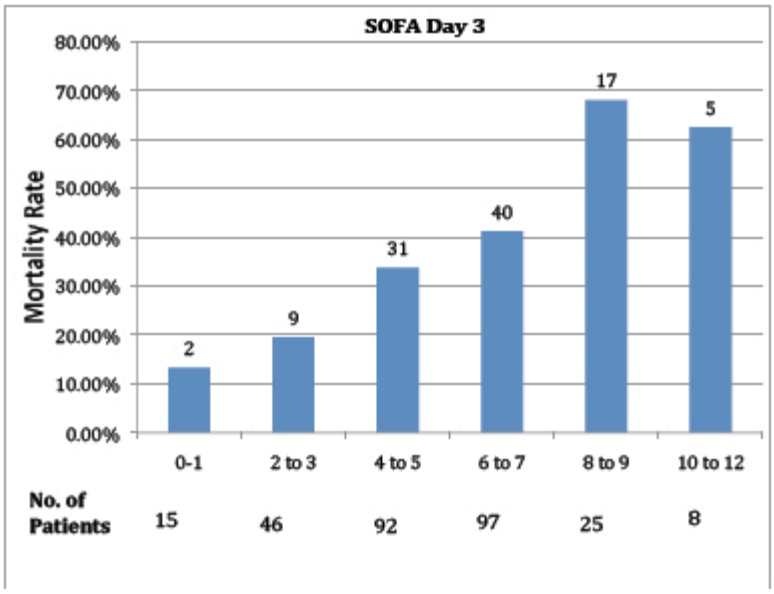

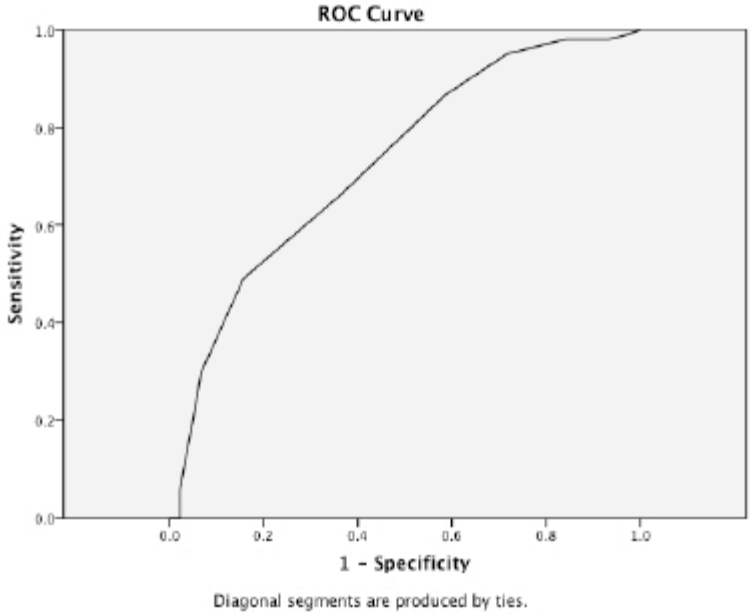

ROC Curve for SOFA Day #3 – Area Under Curve=0.728

Does Stress Ulcer Prophylaxis With Proton Pump Inhibitors Increase The Risk Of Ventilator-Associated Pneumonia In Critically Ill Neuroscience ICU Patients?

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Introduction: Stress ulcer prophylaxis is one of the four established ventilator bundle items,(1) which is widely accepted to be used in mechanically ventilated patients. Surviving Sepsis guidelines supports stress ulcer prophylaxis, and presents H-2 receptor blockers as the agents of choice, and addresses limited available data on the use of proton pump inhibitors (PPI) in critically ill patients. Recent evidence shows a strong link between PPI use and community-acquired pneumonia.(2,3) Therefore, we aimed to assess the effect of stress ulcer prophylaxis with PPI agents in ventilator-associated pneumonia (VAP) formation in mechanically ventilated patients.

Methods: After obtaining IRB approval, we performed a retrospective cohort study in Neuroscience ICU patients who required mechanical ventilation for more than 4 days. Choice of stress ulcer prophylactic agent (H-2 receptor blocker versus PPI) was done randomly by the admitting intensivists throughout the 4-year study period. Patients' demographic characteristics and admission severity status were assessed. First, univariate statistics (Chi-square) were used to compare patients who received H-2 blockers versus PPI. Contribution of stress ulcer prophylaxis in developing VAP outcome was then assessed with multivariate logistic regression analysis.

Results: Patients receiving H-2 blockers and PPI showed similar baseline characteristics and disease severity indices. VAP rate in patients receiving two different stress ulcer prophylaxis agents were as follows: H-2 blockers 10.5% (20/191 patients), PPI 19.8% (21/106 patients). These results were both univariately ($p=0.034$) and multivariately (OR: 1.73, 95% CI: 1.21-3.61, $p=0.025$) statistically significant.

Conclusions: Stress ulcer prophylaxis is one of the very important care standards of the critically ill. Currently, there is no strong evidence to influence the choice of prophylactic agent. Recently, ulcer treatment with PPI agents was shown to increase the risk of community-acquired pneumonia. In this retrospective cohort, we showed that PPI agents independently contributed to developing VAP in mechanically ventilated neuroscience-ICU patients.

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The Agreement Assessment of Search Strategies to Identify Postoperative Acute Lung Injury Risk Factors

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Introduction: Acute Lung Injury (ALI) is a leading cause of postoperative respiratory failure. Timely identification of risk factors associated with postoperative ALI is a key element of its prevention. We aimed to assess the agreement between the automated electronic strategies and manual data extraction in identifying risk factors for postoperative ALI. We also aimed to evaluate the performance characteristics for both search strategies.

Methods: Our study population included 249 patients (83 patients with ALI-associated respiratory failure after high-risk surgery at a tertiary care center and 166 their matched controls). The variables of interest were extracted from the medical record (Table1). These variables were chosen due to existing or preliminary data suggesting an association with postoperative ALI. We compared two techniques for extracting the variables of interest. The first entailed a manual chart review by a trained critical care study coordinator. This was compared to automated electronic search strategies using an institutional electronic database query tool (Data Discovery and Query Builder). To evaluate the performance characteristics we considered the presence of a physician's documentation of the variable of interest in the medical record as a reference standard. This reference standard was determined via an exhaustive "super-review" of the medical record by a trained critical care research physician.

Results: The numbers of concordant and discordant search results when comparing the two search strategies, the overall agreement and Kappa value of these search strategies are shown in Table 1. The agreement between the 2 search strategies was excellent (Kappa ≥ 0.75) for 5 out of the total 11 variables, and good (Kappa ≥ 0.45) for 6 variables, When comparing the two strategies using a thorough super-review, we found that the automated electronic search is more sensitive for 11 variables out of the total 12 and more than or as specific as for 10 out of 12

Conclusion: Evaluating risk factors associated with postoperative ALI using automated electronic search strategies displayed a good or excellent agreement with manual data extraction. These findings suggest that the automated electronic search provides an efficient, reliable alternative to the historic standard of manual chart review.
Table1. Comparison of automated electronic search strategies and manual chart review for identifying pertinent preoperative risk factors for postoperative ALI.

Predictor	Concordant and Discordant				Percent Agreement (%)		0.95 Confidence Interval
Intersitial Lung Disease	12		4	1	98		0.6583-0.9757
Chronic Obstructive Lung Disease	34		6	6	95		0.7227-0.9199
Diabetes Mellitus	53		8	6	94		0.7681-0.9245
Cirrhosis	6		2	0	99		0.6503-1
Gastroesophageal reflux	23		18	9	89		0.4137-0.7217
H2-receptor antagonists	12		6	2	97		0.5512-0.915
Proton Pump Inhibitors	61		26	15	91		0.2184-0.6724
HMG-CoA reductase inhibitors			10	21	87		0.6695-0.8333
Amiodarone	10		16	5	83		0.5225-0.7313
Chemotherapy	2		3	0	99		0.0789- 1
Immunosuppressants	3		2	3	98		0.1321-0.9385

[#]CP = concordant positive, [+]CN = concordant negative, *D(EP) = discordant (electronic search positive, manual search negative), [++]D(MP) = discordant (manual search positive, electronic search negative)

Mortality of Patients with Respiratory Insufficiency and Adult Respiratory Distress Syndrome After Surgery: The Obesity Paradox

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Background: Although obesity has long been considered a risk factor for the development of various pathologies, evidence supporting increased risk of perioperative mortality in obese developing complications after surgery is limited. Recent studies have described the phenomenon of the “obesity paradox” suggesting that morbidity and mortality decrease with increasing body mass index(1).

Therefore we sought to characterize demographics of obese and non-obese patients developing postoperative respiratory insufficiency (RI)/ Adult Respiratory Distress Syndrome (ARDS) and to quantify the impact of obesity on in-hospital mortality among this patient population utilizing data collected from the National Inpatient Sample (NIS). We hypothesized that obese who developed RI/ARDS after major surgery had a reduced postoperative rate and risk of in-hospital mortality compared to their non-obese counterparts.

Methods: NIS data for each year between 1998 and 2007 were accessed. Entries included in our analysis had to fulfill two criteria: 1) indication of the performance of a surgical procedure and 2) contain a diagnosis of RI/ARDS following surgery. Procedure types included were: open abdominal, laparoscopic abdominal, hip and knee arthroplasty, spine, cardiac, thoracic, major vascular and those of the head and neck. Discharges with a diagnosis code for RI/ARDS following surgery were identified. In a third step, patients with this diagnosis code were divided into groups with and without the diagnosis of obesity. In-hospital mortality in postoperative patients with RI/ARDS was the primary outcome. A logistic regression model was fitted to elucidate if obesity was associated with independently increased odds for the outcome while controlling for age, gender, admission and procedure type, and comorbidity index.

Results: We identified 9,149,030 admissions which underwent the defined surgical procedures between 1998 and 2007. Of those, 5.48% had a diagnosis of obesity. The incidence of RI/ARDS was 1.82% among patients with obesity and 2.01% ($P<0.0001$) among those without the diagnosis. The average comorbidity burden was higher among patients with obesity (Deyo index 1.38 versus 0.89, $P<0.0001$). Patients with obesity whose postoperative course was complicated by RI/ARDS had a significantly lower incidence of the need for mechanical ventilation. In-hospital mortality was significantly lower compared to non-obese patients (5.45% versus 18.72%, ($P<0.0001$)). In the regression analysis after controlling for age, gender, race, admission status, hospital characteristics, type of surgery and comorbidity burden, obesity was associated with a 69% reduction in the odds of in-hospital mortality in postoperative patients with RI/ARDS (OR 0.31). Factors associated with increased risk were increasing age, male gender and black race.

Conclusion: In our analysis obesity was associated with a decreased incidence and adjusted odds for in-hospital mortality in patients after surgery. Our results support the emerging concept of the “obesity paradox”. Further studies are warranted to explore possible mechanisms.

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Risk Factors for Seizures in Cardiac Surgery ICU Patients

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Background: Seizures (SZ) after cardiac surgery (CS) is a potentially serious complication. Recently, tranexamic acid (TA), which has proconvulsant properties, has been implicated in postoperative SZ. We sought to determine the association of TA and other risk factors for postoperative SZ in CS ICU patients.

Methods: A prospectively collected database of all consecutive patients having CS from Apr 2003 – Jan 2010 was analyzed. Multivariate logistic regression analysis was used to determine the risk factors for SZ.

Results: SZ occurred in 56/5958 patients (incidence = 0.94%). TA became the sole antifibrinolytic used in 2007 after which the SZ rate increased 8 fold (0.19% pre- vs. 1.54% post-TA, p<0.001). Patients who had SZ received on average 81 mg/kg of TA vs. 64 mg/kg in patients that did not have SZ (p<0.001). The univariate and multivariate analysis for SZ are outlined in the table. In SZ patients (compared to non-SZ patients), the postoperative neurologic complication (delirium/confusion and stroke) rate (19.6% vs. 3.2%, p<0.001), ICU length of stay (4.7 days vs. 1.0 day, p < 0.001) and ICU mortality (7.1 % vs. 1.4 %, p = 0.001) were higher.

Conclusions: Our data suggest that multiple risk factors (preoperative morbidities, open heart procedures with inherent risks of cerebral embolization, and TA with its proconvulsant effects) may be associated with postoperative SZ. The impact of TA on seizures warrants further prospective study.

VARIABLE:	No SZ Group (N= 5902)	SZ Group (N=56)	p-value
UNIVARIATE ANALYSIS:			
Age (yrs) - mean (SD)	64.7 (15.7)	70.9 (11.6)	<0.001
Preop neurological disease	12.4%	29.4%	<0.001
Preop cardiac arrest	0.4%	5.9%	<0.001
Preop congestive heart failure	10.2%	25.5%	<0.001
Peripheral vascular disease	16.2%	25.5%	0.072
Preop renal dysfunction	8.9%	19.6%	0.022
APACHE Score -mean (SD)	14.4 (4.6)	20.8 (7.1)	<0.001
Tranexamic acid	56.8%	90.7%	<0.001
Open heart procedure	27.5%	70.6%	<0.001
Previous cardiac surgery	1.8%	11.8%	<0.001
CPB time (min) - mean (SD)	113.5 (68.1)	156.5 (79.7)	<0.001
MULTIVARIATE ANALYSIS:			
Variable:	**Odds Ratio**	**95% CI**	**p-value**
Tranexamic acid	8.507	3.181 - 22.749	<0.001
APACHE score > 20	7.845	4.304 - 14.298	<0.001
Preop cardiac arrest	16.385	3.893 - 68.954	<0.001
Preop neurological disease	2.325	1.215 - 4.449	0.011
Open heart procedure	5.172	2.675 - 9.999	<0.001
Previous cardiac surgery	6.360	2.410 - 16.787	<0.001

Outcomes Following Therapeutic Hypothermia After Perioperative Cardiac Arrest: A Case Series

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Background: Therapeutic hypothermia (TH) has been well established as an effective treatment for preserving neurological function in survivors of cardiac arrest occurring outside of the hospital. The applications of this attractive therapy have been rapidly expanding, but use of TH has been limited in cardiac surgery patients because of concern about adverse effects. No case series or reports have been published regarding efficacy and safety of TH in cardiac surgical patients who suffer unintentional cardiac arrest. This population has a high risk of postoperative bleeding and arrhythmia and therefore use of therapy that may increase the risk of these complications is controversial.

Objective: To report a series of three patients in our institution's cardiac surgery intensive care unit who suffered unintentional cardiac arrest during or within 48 hours of cardiac surgery and were treated with TH.

Methods: After institutional ethical review board approval, study patients were identified from our institution's cardiac surgery intensive care unit database by a diagnosis of intraoperative cardiac arrest or arrest on ICU days 1-2, as well as the presence of documentation of controlled hypothermia between April 2007 and April 2010. After identifying patients, the institution's electronic medical record and the Society of Thoracic Surgeons database were retrospectively reviewed for demographic information, co-morbid diagnoses, surgical procedure and other information, and outcome including hemorrhage, laboratory abnormalities, re-warming dysrhythmias, infection, in-ICU and in-hospital mortality, length of stay, and neurologic outcome. Use of TH was determined by the bedside attending physician based on circulatory arrest time and other clinical parameters. TH was initiated and monitored using active cooling pads according to written protocol.

Results: Four patients received TH after perioperative arrest. One patient was inadequately cooled, and therefore excluded from the review. The remaining three patients had pre-op Euroscores averaging 14.6, and were all cooled effectively for 17.6±4.04 hours after cardiac arrest. Average chest tube output was 310.3±76.64 ml per day, with one patient requiring transfusion totaling 3 units of packed red blood cells. Hypovolemia, severe electrolyte abnormalities, and re-warming dysrhythmias were not identified in any patient. Average ICU length of stay was 13±7.1 days, with average overall length of stay being 23±9.2 days. 2/3 patients were discharged home and 1/3 discharged to a long-term care facility.

Conclusion: There are currently no prospective, randomized, controlled trials case reports, or case series regarding TH in patients suffering unintentional cardiac arrest during or after cardiac surgery. The small size of our series precludes recommendations regarding use of TH in this population. However, this hypothesis-generating study suggests that further investigation of this therapy may be warranted. We believe that our result may support the notion that clinical equipoise regarding TH in cardiac surgery patients exists and we suggest that further study may offer these challenging patients the benefit of this powerful therapy.

Group 2 - Hematology and Transfusion Medicine

Moderator: Aryeh Shander, M.D., FCCM, FCCP

#5 **Does Peri-Operative Transfusion of Fresh Blood Reduce Post-Operative Mortality?**
Alaa A. Abd-Elsayed, M.D., MPH; Patricia M. Carey, M.D.; Anna Boyd, B.S.; Judith Strong, Ph.D.; Steven Lisco, M.D.

#12 **Administration of Cell Saver Blood Increases Activated Clotting Time in Cardiac Surgery Patients**
Jennifer E. Hofer, M.D.; Michael O'Connor, M.D.; Avery Tung, M.D.; Mark Nunnally, M.D.

#13 **Increased Activated Clotting Time After Cell Saver Administration in Cardiac Surgery Does Not Correlate with the Volume of Cell Saver Transfused**
Jennifer E. Hofer, M.D.; Michael O'Connor, M.D.; Avery Tung, M.D.; Mark Nunnally, M.D.

#20 **Blood Product Administration is Associated with Postoperative Infectious Complications in Patients Undergoing Esophageal Resection Surgery: A Retrospective Cohort Study**
Arun Subramanian, M.B.B.S.; Elie F. Berbari, M.D.; Michael J. Brown, M.D.; Anas Alsara, M.D.; Mark S. Allen, M.D.; Daryl J. Kor, M.D.

#25 **Thrombosis Risk in Cardiac Surgery ICU Patients Suspected of Having Heparin Induced Thrombocytopenia**
Rizwan A. Manji, M.D., Ph.D., MBA; Hilary P. Grocott, M.D.; Chee-loong Saw, Ph.D.; Peter Nickerson, M.D.; Alan H. Menkis, M.D.; Eric Jacobsohn, M.D.

#26 **Correlation of the 4T Test, Enzyme Linked Immunosorbent Assay and the Serotonin Release Assay in Post Cardiac Surgical ICU Patients Suspected of Heparin Induced Thrombocytopenia**
Rizwan A. Manji, M.D., Ph.D., MBA; Hilary P. Grocott, M.D.; Chee-loong Saw, Ph.D.; Peter Nickerson, M.D.; Alan H. Menkis, M.D.; Eric Jacobsohn, M.D.

Does Peri-Operative Transfusion of Fresh Blood Reduce Post-Operative Mortality?

Alaa A. Abd-Elsayed, M.D., MPH [1]; Patricia M. Carey, M.D. [2]; Anna Boyd, B.S. [3]; Judith Strong, Ph.D. [3]; Steven Lisco, M.D. [3]
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Background: More than 14 million units of blood are transfused in the United States annually. Several studies have reported that transfusing old packed red blood cells(RBC) increased post-operative morbidity and mortality. A recent study found a trend toward increased risk of death in patients receiving blood older than 30 days. We examined the effect of perioperative transfusion of old blood (14 days storage or greater) on post-operative mortality.

Methods: Following institutional review we examined an administrative database of 630 patients transfused during surgery from 2003 to 2008 at a Level 1 Trauma Center. All patients remained intubated post-operatively and were admitted to an Intensive Care Unit. Data collected included storage age and number of RBC units transfused, patient age, ASA classification, volume of crystalloid and colloid solutions administered, and units of fresh frozen plasma, cryoprecipitate, platelets, and cell saver RBC transfused. Two groups were defined a priori. Fresh blood was defined as RBC less than or equal to 14 days old; old blood was defined as RBC older than 14 days. In our preliminary review of the patients, we evaluated the groups for hospital mortality as well as previously noted variables. For patients with multiple RBC transfusions, the mean unit age was used to define the age of the blood transfusion administered to each patient.

Results: To date, our study includes 1785 transfusions in 276 patients; 77 patients received old blood and 199 patients received fresh blood. The median age of the transfused blood to all study subjects was 11.6 ± 0.5 days. The median age for the transfused fresh blood and old blood was 7 ± 0.2 days versus 23.2 ± 0.9 days, respectively. There was no significant difference in hospital mortality between both groups ($p=0.33$). When patients were classified according to whether or not any old blood units were received, instead of by average blood age, there were still no significant differences in hospital mortality ($p = 0.77$). Patients who received fresh blood received significantly greater amounts of platelets, cryoprecipitate and fresh frozen plasma ($p<0.05$). Age, ASA classification, amount of crystalloid solutions, colloid solutions, and cell saver RBC were not significantly different between the two groups ($p>0.05$).

Conclusion: Transfusion of fresh packed red blood cells during the perioperative period does not reduce the development of post-operative in hospital mortality. The contribution of the old blood to perioperative inflammation and immunomodulation is insignificant when compared to the need for surgery and the surgery itself.

Administration of Cell Saver Blood Increases Activated Clotting Time in Cardiac Surgery Patients

Jennifer E. Hofer, M.D.; Michael O'Connor, M.D.; Avery Tung, M.D.; Mark Nunnally, M.D.
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Introduction: Although cell saver technology is commonly used, the hemostatic effect of cell saver infusion remains poorly characterized. While some studies report no change in coagulation parameters with use of cell saver blood, decreased hemostasis is often observed clinically. This change in hemostasis has been named Salvaged Cell Syndrome (SCS). We hypothesized that Activated Clotting Time (ACT) might characterize the coagulopathy associated with the infusion of cell saver blood in cardiac surgery patients.

Methods: After obtaining IRB approval and written informed consent, patients undergoing cardiac surgery with cardiopulmonary bypass were enrolled in this study. ACT measurements were taken post-induction/pre-sternotomy, post reversal of systemic heparinization with protamine, and approximately 30 minutes after administration of cell saver blood. Patients were excluded from analysis if their post-protamine ACT suggested residual heparin effect (post-protamine ACT > 20% higher than baseline). These ACT measurements were compared to pre-operative lab results, post-operative lab values, and transfusion requirements for the first 24 hours in the ICU. Data analysis was performed using a paired t-test in Microsoft Excel, with statistical significance taken at $p < 0.05$.

Results: We enrolled 19 patients including CABG (7), valve (6), CABG-valve (2) and device placement (4). Baseline ACT measurements ranged from 109 to 160. The ACT rose a mean of 7.7 (range = -2 to 24) following the infusion of cell saver blood ($p < 0.0001$). The volume of cell saver transfused ranged from 485-1000cc.

Conclusion: Administration of cell saver blood was associated with an increase in ACT levels compared to baseline and post-protamine ACT measurements. This suggests that the decreased hemostasis on the surgical field following cell saver infusion may correlate with this inexpensive test. Possible causes for increased ACT values include dilutional thrombocytopenia, fibrinogen and clotting factor dilution, residual heparin, and anti-coagulant elements of the inflammatory cascade. Further investigation is needed to elicit the specific causes of coagulopathy associated with cell saver.

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Increased Activated Clotting Time After Cell Saver Administration in Cardiac Surgery Does Not Correlate with the Volume of Cell Saver Transfused

Jennifer E. Hofer, M.D.; Michael O'Connor, M.D.; Avery Tung, M.D.; Mark Nunnally, M.D.
The University of Chicago Hospitals

Introduction: The hemostatic effect of cell saver infusion remains poorly understood. Some studies report no change in coagulation parameters with use of cell saver blood, however decreased hemostasis is often clinically observed. We hypothesized that the increase in Activated Clotting Time (ACT) after cell saver administration would not correlate with the volume of cell saver administered.

Methods: After institutional review board approval and informed consent, patients undergoing cardiac surgery with cardiopulmonary bypass were enrolled in this study. ACT measurements were taken post-induction/pre-sternotomy, post reversal of systemic heparinization with protamine, and approximately 30 minutes after administration of cell saver blood. Patients were excluded from analysis if their post-protamine ACCT suggested residual heparin effect (post-protamine ACT > 20% higher than baseline). These ACT measurements were compared to pre-op lab results, post-operative lab values, and transfusion requirements for the first 24 hours in the ICU. Data analysis was performed using a paired t-test in Microsoft Excel, with statistical significance taken at $p < 0.05$.

Results: We enrolled 19 patients including CABG (7), valve (6), CABG and valve (2) and device placement (4). Baseline ACT measurements ranged from 109 to 160. The ACT rose a mean of 7.7 seconds from -2 to 24 following the infusion of cell saver blood ($p < 0.0001$). The volume of cell saver transfused ranged from 485-1000cc, median 546cc, mean 654cc. 16 of 19 patients received allogeneic blood products. The mean and median numbers (in units) of red cells were 4, 3.73: FFP 2,2.61; and platelets 0,0.82. The mean and median volume of albumin transfused was 250cc, 500cc. The mean and median volume of mediastinal drainage was 430cc, 692cc. The correlation between the change in ACT (post cell saver ACT-post protamine ACT) and the volume of cell saver transfused was 0.31.

Conclusion: Administration of cell saver blood was associated with an increase in ACT levels. This increase did not correlate with the volume of cell saver transfused. This suggests that the decrease in hemostasis observed with cell saver is not secondary to a dilution, or that our study was too small to detect this. Other possible causes for the significant increase in ACT after cell saver administration may include thrombin activation, the presence of inflammatory mediators, and residual heparin. Further investigation is needed to elicit the specific causes of coagulopathy associated with cell saver.

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Djaiani G. Continuous –flow cell saver reduces cognitive decline in elderly patients after coronary bypass surgery. Circulation 2007; 116: 1888-1895.
Sharp, WV. Modern autotransfusion. The Amer J. of Surg 1981; 142:522-524.

Blood Product Administration is Associated with Postoperative Infectious Complications in Patients Undergoing Esophageal Resection Surgery: A Retrospective Cohort Study

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Introduction: Esophageal resection surgery is a major procedure with substantial morbidity. Postoperative infections including surgical site infection (SSI), pneumonia, and blood stream infection (BSI) are major causes of morbidity and mortality in this population[1]. Recent estimates suggest a 38% incidence of blood transfusions in this population[2]. Increasingly, blood product administration is being recognized as a risk factor for postoperative infection[3]. This study tests the hypothesis that perioperative blood product administration to patients undergoing esophagectomy will increase the risk of postoperative infections.

Methods: After IRB approval, all consenting patients who underwent esophageal resection over a four-year period (2005-2009) were retrospectively evaluated. Pertinent baseline characteristics were recorded. The timing of RBC, FFP and platelet transfusions were then determined. Postoperative SSI, pneumonia, and BSI were defined using CDC criteria. Onset times were recorded as follows: for SSI, the date of onset of clinical symptoms was recorded; for pneumonia, date of onset was the date on which the patient's clinical pulmonary infection (CPIS) score was greater than six; for BSI, the date on which blood cultures turned positive was used. The association between blood product administration and postoperative infections was evaluated with both univariate analysis (unadjusted) and multivariate logistic regression (adjusted). The multivariate models adjusted for age, sex, diabetes mellitus, preoperative chemotherapy, non-chemotherapeutic preoperative immunosuppression, preoperative hemoglobin, preoperative INR, and preoperative platelet count. To avoid cause-effect inversion, only transfusions administered before the onset of an infectious complication were considered.

Results: Four hundred seventy one patients met inclusion criteria. A total of 139 patients received a perioperative blood product transfusion. Postoperative infections occurred in 89 patients. Results of the analyses are presented in Table 1.

Conclusions: In patients undergoing esophageal resection surgery, blood product administration was associated with the combined outcome of postoperative SSI, pneumonia and BSI. This association was significant for all blood component therapies evaluated and persisted after adjusting for multiple pertinent baseline variables. Transfusion of FFP and platelets were more strongly associated with risk for infection than was transfusion of red blood cells. These results suggest that more conservative perioperative transfusion practices may reduce the risk of postoperative infectious complications in patients undergoing esophagectomy.

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Variable	Infection (n=89)	No infection (n = 382)	Unadjusted OR	Adjusted OR*	p- value
Any Transfusion#	45 (51)	94 (25)	3.1 (1.9 - 5.0)	2.5 (1.5 - 4.3)	< 0.01
RBC #	45 (51)	94 (25)	3.1 (1.9 - 5.0)	2.5 (1.5 – 4.3)	< 0.01
FFP transfusion#	6 (7)	2 (1)	13.7 (2.7 – 69.3)	12.1 (2.5 – 89.6)	< 0.01
Platelet Transfusion#	8 (9)	3 (1)	12.5 (3.2 – 48.1)	13.3 (3.3 – 67.3)	< 0.01

= Number (%).

Table 1. Analysis of the association between blood product administration and postoperative infectious complications.

Thrombosis Risk in Cardiac Surgery ICU Patients Suspected of Having Heparin Induced Thrombocytopenia

Rizwan A. Manji, M.D., Ph.D., MBA [1]; Hilary P. Grocott, M.D. [1]; Chee-loong Saw, Ph.D. [2]; Peter Nickerson, M.D. [2]; Alan H. Menkis, M.D. [1]; Eric Jacobsohn, M.D. [1]
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Background: Heparin induced thrombocytopenia (HIT) and thrombosis (HITT) is an important cause of morbidity/mortality/cost after cardiac surgery (CS). Thrombotic complications include deep venous thrombosis (DVT), pulmonary emboli (PE) and arterial occlusion (AO). The rapidly available ELISA (positive if the optical density is ≥ 0.4) is sensitive but non-specific. The serotonin release assay (SRA) is specific but generally not immediately available. If HITT is clinically suspected (positive ELISA), a non-heparin based anticoagulant should be started which is associated with increased cost and risk of bleeding. If there were known pre- and intraoperative factors associated with thrombosis, this would assist in clinical decision making with regard to starting a non-heparin anticoagulant.

Objective: To determine pre- and intraoperative factors associated with increased risk of DVT, PE and AO post CS in patients suspected of HIT.

Methods: The CS patients having a HIT ELISA between 2008 - 2010 were divided into 2 groups: the high risk thrombosis (HRT) group had a positive ELISA with a positive SRA, or positive ELISA with evidence of DVT/PE/AO (but negative SRA); the low risk thrombosis (LRT) group had a negative ELISA, a negative SRA, or a positive ELISA with negative SRA. Regression analysis was performed to determine factors associated with thrombotic risk.

Results: Of the 269 patients having ELISA assays, 47 (17.4%) were positive. Of these 47, 11 had a positive SRA, and 6 had negative SRA but evidence of thrombosis - i.e. 17 patients in HRT group. The remaining 252 were the LRT group. (See table for univariate analysis). Multivariate analysis revealed aortic surgery to be associated with HRT (OR 4.9, 95% CI 1.3 – 17.8, p=0.017). ICU length of stay was longer in HRT group – 4.8 (3.8 – 8.0) vs. 3.8 (2.2 – 6.8) days in LRT group, p=0.05.

Conclusion: Our data suggest that there appears to be an increased risk of thrombosis in patients having aortic surgery and who have a positive HIT ELISA.

VARIABLE	LRT GROUP (N= 252)	HRT GROUP (N=17)	p value
PREOPERATIVE VARIABLES			
Age (yrs) - mean (SD)	67.5 (12.8)	63.8 (13.2)	0.26
Female	30.6%	52.9%	0.15
Hypertension	72.1%	66.7%	0.77
Hyperlipidemia	45.0%	40.0%	0.79
Myocardial infarction	36.0%	40.0%	0.79
Peripheral vascular disease	20.3%	46.7%	0.03*
APACHE Score - mean (SD)	16.8 (5.1)	16.5 (3.0)	0.79
OPERATIVE VARIABLES			
Open heart procedure	69.0%	70.6%	1.00
Aortic procedure only	9.9%	41.2%	0.001*
Total heparin/kg body weight during surgery (U/kg) - mean (SD)	670.0 (205.9)	721.9 (236.8)	0.34
Minimal temperature (°C) during CPB - median (IQR)	34.9 (34.2 - 35.3)	34.1 (18.2 - 35.3)	0.07
Total cross clamp time (min) - mean (SD)	94.8 (52.1)	94.5 (71.4)	0.99
Total CPB time (min) - mean (SD)	150.6 (73.1)	176.8 (99.2)	0.32

* statistically significant

CPB = cardiopulmonary bypass

Correlation of the 4T Test, Enzyme Linked Immunosorbent Assay and the Serotonin Release Assay in Post Cardiac Surgical ICU Patients Suspected of Heparin Induced Thrombocytopenia

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Background: Heparin induced thrombocytopenia (HIT) and thrombosis (HITT) is associated with significant morbidity/mortality and cost. If one has a high suspicion of HIT, then non-heparin anticoagulants ideally should be started to prevent thrombosis realizing that in cardiac surgery patients, these non-heparin anticoagulants may increase the risk of bleeding and cardiac tamponade. Thrombocytopenia, timing of the platelet decrease, thrombosis, and the consideration of other causes for thrombocytopenia (the 4 T test) is used clinically in non-cardiac surgery patients to determine the pretest probability of HIT and to guide further diagnostics. A score > 3 (out of 8) is intermediate risk of HIT, and a score >6 is high risk for HIT. The 4T test can be performed quickly and is free. However, thrombocytopenia is common after cardiac surgery and being able to accurately perform a 4T test may be difficult. The enzyme linked immunosorbent assay (ELISA) for heparin-platelet factor 4 complex is a readily available test which is highly sensitive but less specific giving a high rate of false positives - an ELISA optical density (OD) greater than 0.4 is considered positive. The highly specific serotonin release assay (SRA) is currently used to confirm HIT. The SRA is difficult to do, is costly and is not readily available often taking many days to get a result. It would be useful for clinicians to know how the 4T test, ELISA, and SRA correlate to aid clinical decision making such as weighing the benefits vs. risks/costs of starting a non-heparin anticoagulant in post cardiac surgery ICU patients.

Objective: To correlate the 4T test to the SRA as well as to correlate the ELISA to the SRA in post cardiac surgical patients.

Methods: We retrospectively analyzed cardiac surgical patients who had been investigated for HIT with an ELISA and SRA. The 4T test was applied, using the postoperative day 1 platelet count as the baseline platelet count from which thrombocytopenia and timing were determined. Thrombosis (for the 4T test) was documented deep venous thrombosis, pulmonary emboli or arterial occlusion (excluding stroke). A receiver operator characteristic (ROC) curve was created and the sensitivities/specificities were determined for the 4T test vs. SRA as well as the ELISA vs. SRA.

Results: There were 47 patients who had both the ELISA and SRA. The area under the curve for the ROC curve for 4T test vs. SRA was poor at 0.56 (p=0.56). The sensitivity of having a positive SRA with a 4T score greater than 3 was less than 65%, with a specificity of less than 45%. The area under the curve for the ROC curve for ELISA vs. SRA was excellent at 0.97 ($p < 0.001$). An ELISA OD > 1.58 was associated with a sensitivity of 100% and a specificity of 94% when compared to the current standard SRA suggesting this was a useful cut off point to use clinically in post cardiac surgery patients.

Conclusions: Our results suggest the 4T test may not be a useful clinical tool in post cardiac surgery patients. An ELISA OD > 1.58 has a high likelihood of having a positive SRA, and therapeutic non-heparin anticoagulantion should be started in this group of patients. Further study is needed in patients with an OD of 0.4-1.58.

Group 3 - Education/Competencies/Administration

Moderator: Brenda Fahy, M.D., FCCM

#4 **Incorporation of a Critical Care Curriculum in Undergraduate Medical Education: A Design Perspective**
Shahriar Shayan, M.D.; **Michael Ault, M.D.;** Thomas Corbridge, M.D.

#7 **A Novel Pathway for Anesthesiology Intensivists to Achieve Competency in Focused Cardiac Ultrasound**
Peter Schulman, M.D.; Michael Hutchens, M.D.; Matthew Griffee, M.D.; Kevin Wei, M.D.; Matthias Merkel, M.D.

#9 **Intensivist M.D./NPCCP Collaborative Model for ICU Care**
Chad E. Wagner, M.D.; Joshua Squiers, ACNP, Ph.D.(c); Lee Parmley, M.D., J.D.

#16 **Perceptions and Attitudes of Anesthesiology and Surgical Residents Regarding Critical Care Training: An Educational Assessment**
Jeremy M. Huff, D.O.; Samuel M. Galvagno, D.O.; Todd Dorman, M.D., FCCM; Pamela A. Lipsett, M.D., FCCM, FACS; Theresa L. Hartsell, M.D., Ph.D.

#29 **Reduction in Healthcare Associated Infections by a Novel Hand Hygiene System in a Mixed Patient ICU**
Matthew D. Koff, M.D., MS; Howard Corwin, M.D.; Ingrid Mroz, R.N.; Stephen D. Surgenor, M.D.; Randall W. Loftus, M.D.; Kathleen M. Richard, M.D.

#30 **Pediatric Delirium: Validation of the Pediatric Confusion Assessment Method for the ICU**
Heidi A.B. Smith, M.D., MSCI; D. Catherine Fuchs, M.D.; Pamela Berry, R.N.; Svetlana K. Eden, M.S.; Pratik P. Pandharipande, M.D., MSCI; E. Wesley Ely, M.D., M.P.H.

Incorporation of a Critical Care Curriculum in Undergraduate Medical Education: A Design Perspective

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Designing an undergraduate critical care medicine (CCM) curriculum is an arduous task given the lack of a formalized frame-work at national level (1). Knowledge acquisition and retention is key in CCM. The most meaningful method of its acquisition and retention is the experiential learning that has come through real life scenarios (2). We present a simple curriculum combining high fidelity simulation (HFS), with modified Problem based learning discussions (PBLDs) that may enhance medical students experience during their clinical rotation in ICU.

Methods: Medical students are assigned to clinical rotations among various Medical and Surgical Intensive care Units (ICU) and divided into two broad groups A & B (table 1). We use Shock as the pathophysiology to build the basis of our curriculum. It is comprised of lectures, HFS & PBLDs. Simulation session is divided into hands-on patient care on a physiological mannequin and PBLDs

Written Examination: The questions are created using the specification table method, previously described as a validated model of designing equally weighted questions (3). Individual Simulation examination: Students are assigned to one of the four Shock Simulation scenarios (cardiogenic, distributive, hypovolemic and obstructive). The overall Score is made of Checklist and Global scores. They are constructed using a modified Delphi method & have been validated as a measuring tool through calibration as described previously (4).
-*Checklist Score:* The students are evaluated on completion of clinical actions, through a binary checklist
-*Global Score:* The students are globally assessed on the following categories: Information/fact gathering, Integration of information, Self confidence/mastery, Communication, Time to treat. Course Grade: Clinical evaluation, written & simulation examinations contribute equally to the grade.

ConIcusion: Here we present a design for a compulsory medical school curriculum combining HFS, lectures, PBLD and clinical duties providing an enhanced critical care experience 2.

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A Novel Pathway for Anesthesiology Intensivists to Achieve Competency in Focused Cardiac Ultrasound

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Background: Echocardiography is an invaluable tool for the evaluation of hemodynamic instability in the critically ill. Unlike traditional echocardiography a focused cardiac ultrasound (FoCUS) is both performed and interpreted by the intensivist at the bedside. Hence, its purpose is to provide rapid and specific information about cardiac structure and function that can be used to answer focused clinical questions and help to guide therapeutic interventions. Although training courses in FoCUS have started to emerge, the best method for intensivists to learn FoCUS has not been established. Courses generally offer didactic lectures and a chance for hands-on practice with live models, but do not provide the opportunity for ongoing supervision and mentoring, or the opportunity to image actual patients. To address these limitations, we developed a multidisciplinary, proctored training program to achieve measured competency in FoCUS including the following five pathologies: global LV dysfunction, global RV dysfunction, hypovolemia, pericardial effusion and tamponade.

Methods: The program includes a formal lecture series, scanning practice, a proctoring phase, and is completed with a final evaluation by a level III, board-certified echocardiographer.

1. The introductory lecture series includes basics of ultrasound physics and system controls, cardiac anatomy, structure and standard views, assessment of volume status and responsiveness, assessment of LV function including use of contrast agents, assessment of RV size and function, assessment of tamponade and acute pericardial disease, and basic hemodynamics.

2. Image acquisition is jointly taught by a board-certified echocardiographer and sonographers. Participants learn to acquire seven typical views in a standard sequence: parasternal (long axis, RV Inflow-outflow, short axis), apical (four chamber, two chamber, three chamber), and subcostal (including assessment of IVC size and variability). Participants are initially taught to scan using live models, but then scan actual patients with the guidance of sonographers.

3. Successful completion of the proctoring phase requires a minimum of 25 studies, including at least one study of each of the five pathologies. The images are archived and an interpretation of the study is documented by the trainee. A pre- and post-scan diagnosis and a brief recommendation for clinical action are recorded based on the findings. The studies are then validated by the mentor, including comparison of the FoCUS images with those from a formal 2D echocardiogram (if available).

4. The proctoring process is completed after passing a practical and written examination.

Conclusion: This program provides a structured, feasible and safe approach to achieve competency in FoCUS. Thus far, all participants entering the program have successfully completed it over 6-9 months. Other institutions could consider adopting a similar program.

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Intensivist M.D./NPCCP Collaborative Model for ICU Care

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Purpose: To develop comprehensive 24/7 coverage for a cardiovascular intensive care unit (CVICU) in a tertiary care hospital utilizing intensivist physicians and non-physician critical care providers (NPCCP).

Specific Aims: The aim of this project was to develop a multidisciplinary ICU team expanding the capacity of the intensivist by participation of NPCCPs in a manner providing high quality critical care services, staffed consistently throughout the day, and meeting Leap Frog criteria.

Methods: Over a three year period a multi-disciplinary ICU teams was developed to cover a tertiary care center CVICU. This team's core consists of two NPCCPs covering 8 patients each for 12 hour shifts and one intensivist physician, present 10-12 hours per day and available by phone and to return to the ICU throughout the remainder of the day/night. This team rounds twice daily, with the NPCCPs acting as the first call for any clinical issues. The NPCCPs, in collaboration with the intensivist physician, are responsible for collaborating to develop and execute the daily medical plan, bedside procedures, and emergency responses

Results: Currently the Vanderbilt CVICU utilizes this "Intensivist M.D./NPCCP Model" within a multi-disciplinary team which also includes a dietitian, pharmacist, respiratory therapist and case manager. The 24/7 coverage requires 9.6 full-time NPCCPs or the equivalent. The 8 patients to 1 NPCCP ratio allows an average 1.5 patient contact hours per patient during the 12 hour shift. With NPCCPs as billing providers, charges need not be lost for services provided in the absence of the intensivist physician. To provide this level of care with only intensivists would not only be cost prohibitive, but also virtually impossible with the intensivist shortage projected.

Conclusions: In conclusion, the development of multi-disciplinary critical care teams led by an intensivist whose capacity is expanded by employment of NPCCPs may serve as a means to partially alleviate the current shortfall of intensivists and may represent a cost effective means for expanding ICU coverage and increasing ICU bed availability while maintaining Leap Frog compliance. Recognizing the need for training for NPCCPs in tertiary care ICUs, Vanderbilt School of Nursing now offers an Acute Care Nurse Practitioner Intensivist specialty to provide NPs for this type of specialized multi-disciplinary ICU care.

Perceptions and Attitudes of Anesthesiology and Surgical Residents Regarding Critical Care Training: An Educational Assessment

Jeremy M. Huff, D.O.; Samuel M. Galvagno, D.O.; Todd Dorman, M.D., FCCM; Pamela A. Lipsett, M.D., FCCM, FACS; Theresa L. Hartsell, M.D., Ph.D.
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Objective: To understand the factors that motivate and discourage residents in their choice of a critical care career.

Methods: An online survey was distributed electronically via an email to all ACGME anesthesiology and general surgery program directors in the U.S. Resident responses to the survey were gathered between March 22, 2010 and May 17, 2010. Descriptive statistics were used to summarize the survey responses, and multiple logistic regression was performed to assess the relationships between variables and interest in critical care fellowship.

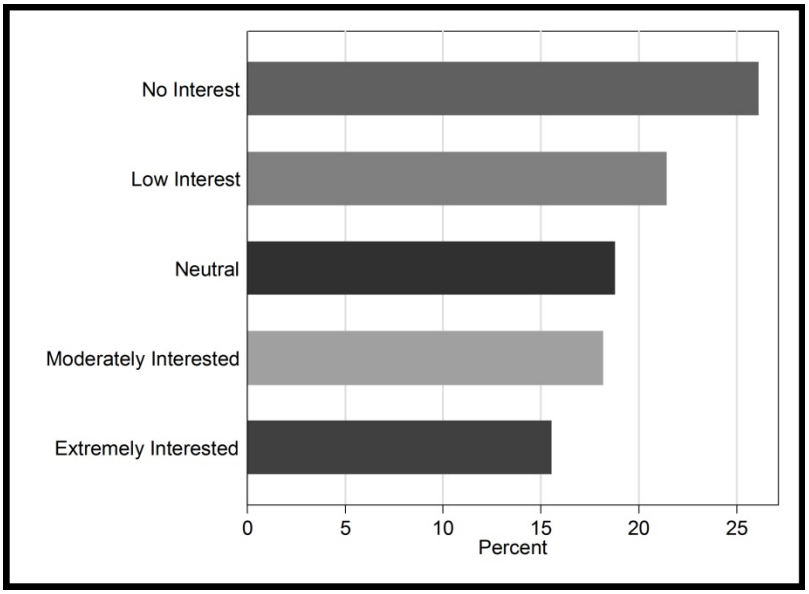
Results: 720 residents initiated and 596 (82.7%) completed the survey. Results of the 340 anesthesiology trainees are reported here. Of the anesthesia respondents, 33.5% indicated either moderate or high current interest in pursuing a critical care medicine (CCM) fellowship. 57.3% reported completing more than 4 months (the current ACGME anesthesiology requirement) of ICU rotations at the time of the survey, and 42% anticipated rotating 6 or more months in the ICU prior to completing residency. As residents spend more time in the ICU, they were significantly more likely to have greater interest in CCM fellowship training (OR 1.27, 95% CI 1.07-1.50, p = .007). However, 27.6% indicated that additional fellowship training would not be necessary to independently practice CCM after residency.

78.8% of respondents reported an active CCM fellowship program at their institution, but only 33% reported having a mentoring relationship with a CCM faculty member and 20.3% with a CCM fellow. The majority of these mentors were anesthesiology-trained intensivists (75.1%), followed by those trained in internal medicine (13.1%), surgery (8.7%), and pediatrics (2.9%). 59.1% of respondents indicated that they did not have a mentoring relationship to foster interest in CCM.

Regarding other possible factors influencing interest in CCM fellowship training, the median debt for residents was $100,000-150,000 but amount of debt did not correlate with fellowship interest. 47.1% of respondents perceived that the average income of critical care intensivists would be $200,000-250,000/yr compared to an overall median anticipated post-residency income of $250,000-300,000. Anticipated income, though, was also not associated with interest or disinterest in pursuing CCM (OR 1.05, 95% CI .84-1.31, p = .68).

The majority of respondents indicated that CCM was more stressful (61.6%), required longer working hours (66.9%), and required a greater intensity of work (63.6%) compared to other anesthesia subspecialties. The three most frequent suggestions to make CCM more appealing were a lighter and less difficult call schedule during fellowship, better income potential, and more resident exposure to CCM in a private practice setting.

Conclusion: Anesthesiology trainees maintain interest in CCM as a possible career throughout their residency experience, although perceptions of CCM as being more work and less income may be important to address to improve recruitment. Development of mentoring relationships between CCM faculty/fellows and residents is an underutilized strategy to improve sub-specialty interest and understanding.


No Interest
Low Interest
Neutral
Moderately Interested
Extremely Interested
0
5
10
15
20
25
Percent

Reduction in Healthcare Associated infections by a Novel Hand Hygiene System in a mixed patient ICU

Matthew D. Koff, M.D., MS; Howard Corwin, M.D.; Ingrid Mroz, R.N.; Stephen D. Surgenor, M.D.; Randall W. Loftus, M.D.; Kathleen M. Richard, M.D.
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Background: Hospital-acquired infections account for >90,000 patient deaths and $4.5 billion in additional health care costs annually in the United States. Hand hygiene compliance is considered a necessary part in achieving a reduction in the incidence of nosocomial infection.1 Recently, the intraoperative use of the GJ Sprixx alcohol based gel device was shown to reduce the incidence of nosocomial infections.2 We extended the application of this device utilizing a multimodal approach to our intensive care unit and assessed the impact on hospital-acquired infections.1,3

Objective: To evaluate the impact of a multimodal hand hygiene system on nosocomial infections in an intensive care unit (ICU).

Methods: This was a before and after time interrupted study (over a 3 year period) conducted in a 26 bed multidisciplinary ICU at Dartmouth-Hitchcock Medical Center, a tertiary care medical center. We introduced the GJ Sprixx alcohol based gel device as part of a multimodal program into the ICU. Participation by all providers was voluntary. The control period was from 12/06-12/07. Study period was from 12/07-12/08 and the time-interrupted period was from 12/08-12/09. During the time-interrupted study period, the availability of the device remained in the ICU, however the multimodal system was not supported. The incidence of catheter related blood stream infections (CRBSI) and ventilator associated pneumonias (VAP) were the primary outcome variables. Infections are reported as infection/1,000 line days or infections/1,000 ventilator days for CRBSI and VAP respectively.

Results: Ventilator pneumonias were significantly reduced during the study period (3.7/1000 vent days in the study period vs 7.0/1000 vent days during the control period, p=0.02) There was no significant reduction in CRBSI (1.3/1000 line days study period versus 2.63/1000 line days control period p=0.13). During the time interrupted period VAP significantly increased back towards the control rate (7.5/1000 vent days $p < 0.01$). There was no change in CRBSI during the time interrupted period (1.6/1000 line days $p = 0.75$) however by submission date of this abstract 4 months since study termination date the current CRBSI rate has risen to 1.9/1000.

Conclusions: The institution of a multimodal hand hygiene system in an ICU was associated with a significant reduction in the incidence of ventilator-associated pneumonia. This system if properly supported could be incorporated into the IHI ventilator bundle as an important means to reduce VAP's.4

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Pediatric Delirium: Validation of the Pediatric Confusion Assessment Method for the ICU

Heidi A.B. Smith, M.D., MSCI; D. Catherine Fuchs, M.D.; Pamela Berry, R.N.; Svetlana K. Eden, M.S.; Pratik P. Pandharipande, M.D., MSCI; E. Wesley Ely, M.D., M.P.H.
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Context: Delirium is a common complication of critical illness and an independent predictor of death in adults. Epidemiology and data on pediatric delirium occurring among critically ill children admitted to the pediatric intensive care unit (PICU) are limited due to the absence
of a valid and reliable diagnostic instrument for bedside delirium monitoring by non-psychiatrists on the PICU team.

Objective: To validate a diagnostic instrument for pediatric delirium in critically ill children, both ventilated and non-ventilated, using
standardized, developmentally appropriate measurements.

Design, Patients, and Setting: Prospective cohort study investigating the Pediatric Confusion Assessment Method for ICU patients
(pCAM-ICU) in the pediatric medical, surgical, and cardiac ICUs of a university-based medical center. A total of 437 patients admitted to the PICU from July 1, 2008 to March 30, 2009 were screened and of the 305 patients who were at least 5 years of age, 68 patients were consented and completed the study. Criterion validity including sensitivity and specificity, and inter-rater reliability were determined using daily delirium assessments with the pCAM-ICU by two critical care clinicians compared with delirium diagnosis by pediatric psychiatrists (Reference Standard) using Diagnostic and Statistical Manual (DSM) IV-TR criteria. The Reference Standard assessments for delirium were categorized as presence or absence of delirium. Subsyndromal delirium, a condition in which children possess more than one key DSM feature of delirium without demonstrating full delirium criteria, was also diagnosed when full-blown delirium was absent,

Results: A total of 146 blinded, paired assessments were completed between the Reference Standard and the pCAM-ICU raters. The Reference Standard identified delirium in 18 of the 146 (12.3%) patient assessments, or 9 of 68 (13.2%) patients, while the pCAM-ICU detected delirium in 16 of 146 (11%) patient assessments, or 8 of 68 (11.8%) patients. The nine patients with delirium during the study period demonstrated a mean age of 13.8 (1.9) years and 77.8% were male. The sensitivity of the pCAM-ICU was 83% (95% CI, 66%-93%) and the specificity was 99% (95% CI, 95%-100%). The pCAM-ICU thus demonstrated a positive predictive value of 93% (95% CI, 63%-99%) and a negative predictive value of 98% (95% CI 93%-99%). In addition, the pCAM-ICU was completed with extremely high inter-rater reliability of
κ= 0.96 (95% CI 0.74-1.0). There were 3 false negative and 1 false positive findings. These involved paired assessments greater than 2 hours apart with intervening clinical events (hypoxia or hypotension) that overtly altered the patients' status. 8 patient assessments (5.5%) met criteria for subsyndromal delirium, of which 7 (87.5%) had at least two positive pCAM-ICU features.

Conclusions: The pCAM-ICU is a highly reliable and valid instrument for the diagnosis of pediatric delirium in critically ill children, chronologically and developmentally at least 5 years of age. Use of the pCAM-ICU may facilitate earlier diagnosis of delirium, referral to psychiatric specialists, and monitoring for delirium in future epidemiological and interventional studies in critically ill children.

Criterion Validity of the pCAM-ICU Reported as Sensitivity, Specificity, PPV, and NPV[a]						
Group	Total Assessments	pCAM-ICU/ DSM Positive	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All	146	16/18[b]	83 (66-93)	99 (95-100)	93 (63-99)	98 (93-99)
Age (yrs)						
≤ 12	55	3/3	100	100	100	100
> 12	91	13/15[c]	80 (59-91)	99 (91-100)	92 (55-99)	96 (89-99)
Ventilation	17	4/4[d]	75 (67-100)	92 (67-100)	75 (0-100)	92 (50-100)

[a]Comparisons were made between ratings completed with the pCAM-ICU versus Reference Standard evaluations by pediatric psychiatrists using *Diagnostic and Statistical Manuel of Mental Disorders, Fourth Edition*, criteria. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are included. [bc]Three false negatives and one false positive. [d]One false negative and one false positive.

Group 4 – Hemodynamics and Monitoring

Moderator: Avery Tung, M.D.

#8 **Elevated PPV Predicts an Increased Length of Stay and Morbidity During High Risk Abdominal Surgery**
Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., M.B.A.; Thomas M. Dodds, M.D.; Maxime Cannesson, M.D., Ph.D.; Matthew D. Koff, M.D., M.S.

#17 **Local Fractal Analysis of Cardiac Interbeat Intervals During Hypovolemia in Healthy Volunteers**
Christopher C. Young, M.D.; Eugene W. Moretti, M.D.; Nicola Scafetta, Ph.D.; Stephanie McGuire, M.D.; Richard E. Moon, M.D.

#19 **TEE Monitoring With a Miniaturized Disposable Probe Influences Post-Operative Management of Cardiac Surgery Patients**
Chad E. Wagner, M.D.; John H. Selby, M.D., J.D.; Clifford L. Parmley, M.D.,J.D.

#23 **Central Venous Pressure Measurement Correlates with 3 Dimensional Assessment of Right Ventricular Volume and Function**
Daniel S. Rubin, M.D.; Avery Tung, M.D.

#27 **Non-Invasive Measurement of Oxygen Delivery Index: Is This the Future of Goal Directed Therapy?**
Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., MBA; Thomas M. Dodds, M.D.; Randall W. Loftus, M.D.; Matthew D. Koff, M.D., MS

#28 **Functional Hemodynamics During High Risk Abdominal Surgery: Are All Monitors Created Equal?**
Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., MBA; Timothy J. Quill, M.D.; Maxime Cannesson, M.D., Ph.D.; Matthew D. Koff, M.D., MS

Elevated PPV Predicts an Increased Length of Stay and Morbidity During High Risk Abdominal Surgery

Kathleen M. Richard, M.D.[1]; Matthew R. Novak, M.D., M.B.A.[1]; Thomas M. Dodds, M.D.[1]; Maxime Cannesson, M.D., Ph.D.[2]; Matthew D. Koff, M.D., M.S.[1]
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Background: High risk abdominal surgery has been reported to have morbidity between 20-40% and mortality of up to 10%.1 Intraoperative fluid resuscitation has been shown to reduce morbidity and hospital length of stay(LOS).2 Functional hemodynamic parameters are sensitive and specific for fluid responsiveness and could be effective to guide intraoperative goal directed therapy.3 We performed a prospective observational study to evaluate the effect on LOS in high risk abdominal surgery patients with adequate resuscitation based on the percent of intraoperative time that the patient spent below a PPV threshold of 13%.

Methods: After IRB approval and informed consent, 28 patients ASA class 2-4 scheduled for major elective intraabdominal surgery (with potential EBL of 500+cc) were enrolled in this prospective observational trial. Exclusion criteria were patients with arrhythmias, CHF, hemodynamically significant heart disease, and patients with intraoperative massive transfusion. Of the 28 patients enrolled, 3 were excluded due to ASA status, unrecorded data (equipment malfunction) and massive transfusion. After induction of GA, a radial arterial line was placed. Hemodynamic values were recorded using the LIDCO Rapid. At case termination, audit values of PPV threshold >13% were utilized for analysis as determined by LIDCO view Pro software. All patients were followed prospectively. Patients were divided into adequate resuscitation and inadequate resuscitation groups based on the percent of intraoperative time spent above or below a PPV threshold of 13%. Adequate resuscitation was defined as less than or equal to 25% of intraoperative time spent above a PPV threshold value of 13%. Inadequate resusciation was defined as >25% of intraoperative time spent above a PPV threshold of 13%. The primary analysis was to evaluate for difference in LOS between groups. Secondary anlaysis included a reduction of postoperative complication rates including PONV, cardiac, renal or bowel dysfunction, and mortality. Data was analyzed using an unpaired t-test, chi square or Fisher's exact test. A p-value of <0.05 was considered significant.

Results: Patients with adequate resuscitation had a significant decrease in LOS from 10.1 to 6.1 days respectively (p<.02 95% CI=-7.20 to -0.79). The adequate resuscitation group had a reduction in postoperative complication rates: 7 vs. 1 (P= 0.03). No significant difference was noted between groups with regard to case duration, EBL, crystalloid (5.7 vs. 5.6l) or colloid administration (0.917 vs. 1.0l), age, gender or ASA status. There was one patient mortality in the inadequate resuscitation group; this was not statistically significant.

Conclusions: A significant decrease in LOS was noted in the adequate resuscitation group based on PPV threshold audit analysis of 25% case duration. This group also had a reduction in post-operative complications. Further study utilizing this and other functional hemodynamic parameters to guide intraoperative fluid resuscitation should be performed and could improve the quality and safety of health care delivery to these patients.

1)Ghaferi A, Ann Surg. 2009;250(6):1029-1034
2)Giglio M, Br J Anaesth. Nov 2009;103(5):637-646
3)Lopes M, Crit Care. 2007;11(5):R100

Local Fractal Analysis of Cardiac Interbeat Intervals During Hypovolemia in Healthy Volunteers

Christopher C. Young, M.D.; Eugene W. Moretti, M.D.; Nicola Scafetta, Ph.D.; Stephanie McGuire, M.D.; Richard E. Moon, M.D.
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Introduction: The healthy human heart demonstrates beat-to-beat fluctuations of the R-R interval (RRI) which are irregular and complex. The pattern of fluctuation of the RRI has been shown to be multi-fractal in nature. Lower body negative pressure (LBNP) as a model of progressive hypovolemia produces an increase in multifractality of the RRI as measured by the Holder exponent (West BJ, Scafetta N, et al. Ann Biomed Eng 2004;32:1077). No studies have confirmed the correlation of the LBNP model compared with hypovolemia due to actual blood loss. Measurement of RRI variability during early stages of hemorrhagic shock may prove more sensitive than currently measured variables. This study was performed to test the hypothesis that frequency analysis and the Hurst exponent can provide early indicators of hypovolemia due to blood loss.

Methods: After IRB approval and informed consent 5 healthy volunteers were studied (mean age 25.4, F=1). Exclusions were cardiopulmonary, GI disease, abnormal Hb, anemia and pregnancy. In the supine position, 25% of estimated blood volume (EBV) was removed via a catheter in the basilic vein over an average of 45 min in 2-3 aliquots depending on patient weight. Blood pressure (BP) was measured from radial arterial pressure waveform. The RR interval time sequence was processed with a band pass wavelet filter centered in the low frequency (LF) range 0.005-0.035 Hz. This component was analyzed during 5 minute intervals using a moving window, during which the standard deviation of the signal (LF amplitude, LFA) was evaluated. The Hurst exponent (H) was calculated during 10 minute intervals using a moving window after processing using a high pass wavelet filter (>0.005 Hz) (Scafetta N, Grigolini P. Phys Rev E 2002;66, 036130).

Results: One of 5 subjects developed hypotension at the end of the blood draw; in the remainder BP remained relatively stable. Heart rate (HR) did not change significantly as seen in this subject. Early in the blood removal process average values for both LFA and H decreased from baseline.

Conclusions: In this small cohort of healthy volunteers, spectral and Hurst analysis of RR interval appear to be early indicators of hypovolemia despite stable hemodynamics.

Acknowledgment: The study was funded by the GVLT Division, Duke Dept. of Anesthesiology.

TEE Monitoring with a Miniaturized Disposable Probe Influences Post-Operative Management of Cardiac Surgery Patients

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Introduction: Post-operative management following cardiac surgery poses many challenges, including decisions about both re-operation and fluid management. Re-operation due to bleeding, a common complication, has been shown to increase morbidity, ventilation time, and mortality (14.2% vs 3.4%, p = 0.001); however, one should operate quickly when needed [1]. Goal-directed transesophageal echocardiography (TEE) by intensivists using a pediatric monoplane probe has been shown safe and effective [2], and urgent TEE in "patients with unexplained hemodynamic instability after cardiac surgery" led to medical management changes in 43.3% of patients; surgical intervention in 15.3% [3].

Purpose: Given the limitations of PAC and similar indirect methods, and the known benefits of direct visualization by TEE, we explore the effects of moving TEE out of the operating room, and beyond on-demand assessment to an episodic monitoring tool, using a miniaturized disposable probe (ImaCor ClariTEE). The ImaCor probe is a 5.5 mm detachable probe, cleared by the FDA to remain indwelling for up to 72 hours.

Methods: Retrospective quality improvement review of 17 cardiac surgery patients.

Results: Fluid and vasopressor management was adjusted in 8 of 17 patients (47%) based on echo data. Re-operation was avoided in two patients (12%). In one patient (see Fig. 1 below), the CVICU team and cardiac surgeon decided to monitor pericardial effusion and filling status rather than returning to the operating room for re-exploration. Over the next ten hours episodic assessment demonstrated continued resolution of pericardial fluid collection with increased LVEDA and improved hemodynamics. Multiple imaging sessions were performed in monitoring 53% of patients. In the case of one LVAD patient, multiple assessments were performed over 24 hours to optimize pulse index by adjusting LVAD flow rate.

Conclusions: Episodic TEE monitoring using a miniaturized disposable probe leads to significant changes in patient management (frequency similar to the meta-analysis of Hüttemann [4]; see also [5]), including both changes in fluid management and avoided re-operations. Thus TEE monitoring can be expected to reduce both mortality and cost. Further study is planned.

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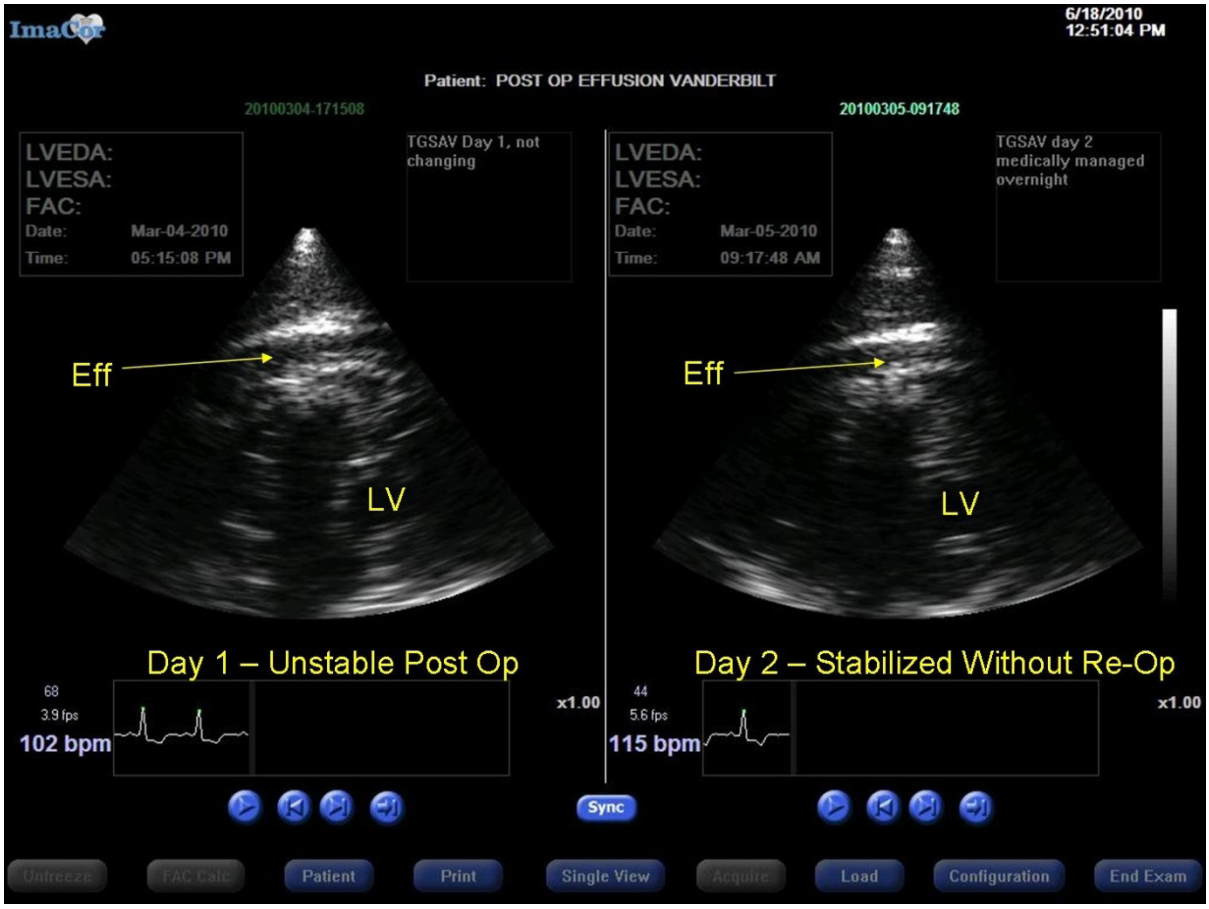
Fig. 1. TEE monitoring of pericardial effusion over 16 hours in a patient with postoperative hemodynamic instability.


ImaCor
6/18/2010
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20100304-171508
LVEDA:
LVESA:
FAC:
Date: Mar-04-2010
Time: 05:15:08 PM
TGSAV Day 1, not changing
Eff
LV
Day 1 – Unstable Post Op
68
3.9 fps
102 bpm
x1.00
20100305-091748
LVEDA:
LVESA:
FAC:
Date: Mar-05-2010
Time: 09:17:48 AM
TGSAV day 2 medically managed overnight
Eff
LV
Day 2 – Stabilized Without Re-Op
44
5.6 fps
115 bpm
x1.00
Sync
Unfreeze
FAC Calc
Patient
Print
Single View
Acquire
Load
Configuration
End Exam

Central Venous Pressure Measurement Correlates with 3 Dimensional Assessment of Right Ventricular Volume and Function

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Introduction: Recent research has suggested that central venous pressure (CVP) measurement may not to accurately assess intravascular volume and hemodynamic response to fluid administration. These data suggest that the right ventricle does not exhibit Starling behavior, and that contractility does not increase with increasing preload. We recently found that CVP did not correlate with a qualitative assessment of RV function using 2D transesophageal echocardiography2. One reason for these findings is the difficulty in assessing volume in the irregularly shaped RV with a two dimensional tool. Real-time three-dimensional echocardiography (RT3DE) clarify the relationship between CVP and RV function. We hypothesized that CVP would correlate with RT3DE assessment of RV function. To test our hypothesis, we correlated CVP measurements and RT3DE evaluation of the RV in patients undergoing cardiac surgery.

Methods: After IRB approval we retrospectively reviewed the 3D transesophageal echocardiograms of 13 patients undergoing cardiac surgery. We identified those patients with a 3D flow volume loop of the right ventricle after induction and before cardiopulmonary bypass. 3D images and flow volume loops of the RV were then evaluated for RV end diastolic volume (RVEDV), RV stroke volume (RVSV), and RV ejection fraction (RVEF) using 3D RV analysis software (TomTec, Munich, Germany). CVP measurements obtained at the time of the echo exam were then recorded for comparison. Statistical analysis was performed using Microsoft Excel.

Results: 13 patients were studied. 3 had CABG and valve repair or replacement and 10 underwent valve repair or replacement. 1 patient underwent left ventricular assist device placement. The mean CVP was 9.8 ± 4.1, mean RVEDV was 130 ± 54.8 cc and the mean SV was 54.2 ± 25.3 cc. Mean EF was 41 ± 6.4%. CVP correlated strongly with SV ($R=0.60$ $P<0.05$) and EF ($R=0.64$ $P<0.05$). Correlation was also significant with RVEDV ($R=0.35$ $P<0.01$).

Conclusions: We found that RT3DE assessment of RVSV, RVEF, and RVEDV correlated with simultaneous CVP measurement. Our findings suggest that 3D and 2D assessments of RV function may differ considerably, and that in some circumstances CVP may be used to assess some aspects of RV. Further research is needed to further understand the value of RT3DE with respect to RV functional assessment and the relationship between CVP and RV function.

Non-Invasive Measurement of Oxygen Delivery Index: Is This the Future of Goal Directed Therapy?

Kathleen M. Richard, M.D.; Matthew R. Novak, M.D., MBA; Thomas M. Dodds, M.D.; Randall W. Loftus, M.D.; Matthew D. Koff, M.D., MS
Dartmouth Hitchcock Medical Center

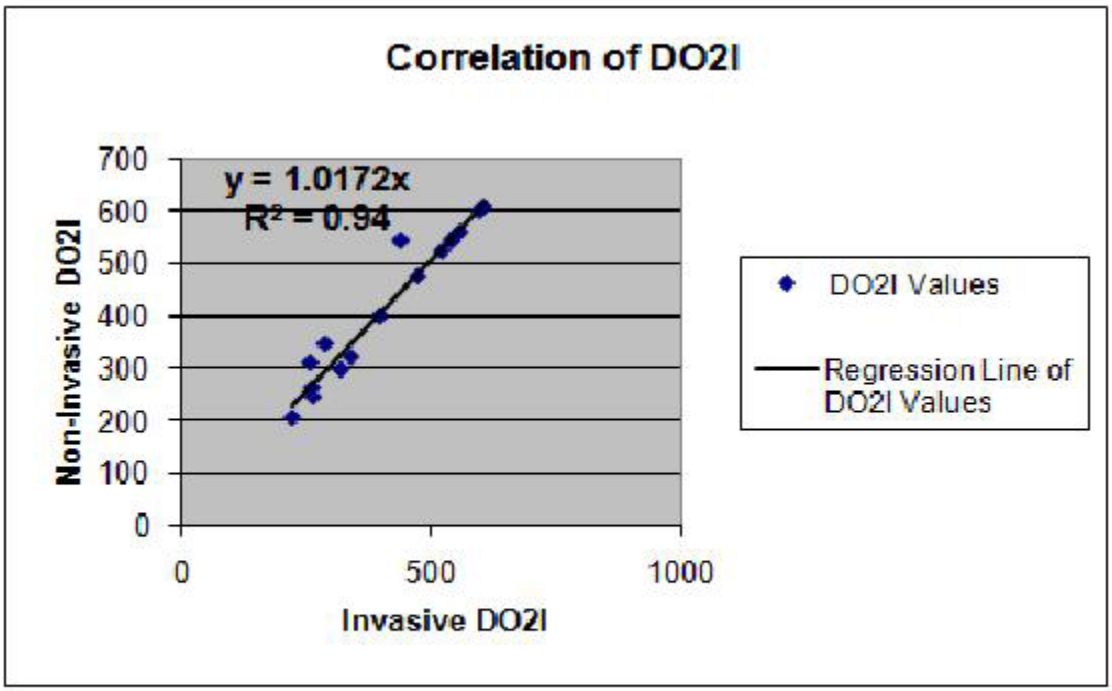
Background: Oxygen delivery index (DO2I) has been shown to be a useful parameter in guiding goal-directed fluid therapy.(1) Recent technology allows for a complete and non-invasive measurement of DO2I. We present a prospective case series investigating the ability to non-invasively measure oxygen content and cardiac output to allow for direct calculation of DO2I using Masimo Rainbow SET Radical 7 Co-oximeters (Irvine, CA) measuring total hemoglobin (SpHb) and oxygen content (CaO2) and the NICOM (Cheetah Medical, Portland, OR) non-invasive cardiac output monitor.

Clinical Features: After obtaining IRB approval and informed consent, patients were prospectively enrolled in an observational study to compare the accuracy of SpHb measurements obtained from Masimo Rainbow SET Radical 7 Co-oximeters against total hemoglobin (tHb) measurements obtained from traditional arterial blood gas (ABG) analyzers. All patients were ASA class 2-4 and were undergoing elective major abdominal surgery for which placement of an arterial line for blood pressure monitoring was indicated and part of the anesthetic plan. Standard ASA monitors were applied in all cases and anesthetic management was not altered by data obtained from study monitors. Continuous non-invasive SpHb levels and oxygen content (CaO2) were recorded from 2 Masimo Rainbow SET Co-oximeters with optically isolated sensor probes connected to the middle finger on the patients[apos] left and right hands. These readings were compared with tHb measurements obtained from ABG analysis intra-op. CaO2 measured by Masimo co-oximeters was compared to CaO2 calculated from ABG results using the formula: CaO2 = (1.34*Hbt*SaO2) + (0.003*PaO2). DO2I was calculated separately with data from each device using the formula: DO2I = cardiac index*CaO2* 10. Data were compared using Bland-Altman assessment for agreement. A range of agreement was defined as mean bias +/-2 SD.

Results: Interim analysis of 5 study patients showed a correlation (R^2) of 0.87 between Masimo SpHb and ABG tHb values. Bland-Altman analysis of the two methods of calculating total hemoglobin indicated that the 95% limits of agreement ranged from -1.2 to 1.3 with two data points lying outside these limits. Bias was 0.03. Correlation (R^2) between DO2I calculated from Masimo values vs ABG values was 0.94. Bland-Altman analysis of the two methods of calculating oxygen delivery indicated that the 95% limits of agreement between the two methods ranged from -76 to 64 with several data points lying outside these limits. Bias was -5.7. Precision was 0.19. [figure 1]

Conclusions: Though further study is necessary, preliminary analysis indicates that use of these 2 devices provides an accurate and completely non-invasive method for calculating oxygen delivery. This could be used to guide early goal directed therapy with an appropriate patient-centered algorithm in patient populations that may lack more invasive access for such monitoring.

References:
(1) Pearse R, Critical Care 2005; 9: R687-R693


Correlation of DO2I
y = 1.0172x
R² = 0.94
Non-Invasive DO2I
Invasive DO2I
0
100
200
300
400
500
600
700
0
500
1000
DO2I Values
Regression Line of DO2I Values

Functional Hemodynamics During High Risk Abdominal Surgery: Are All Monitors Created Equal?

Kathleen M. Richard, M.D. [1]; Matthew R. Novak, M.D., MBA [1]; Timothy J. Quill, M.D. [1]; Maxime Cannesson, M.D. [2], Ph.D.; Matthew D. Koff, M.D., MS [1]
Dartmouth Hitchcock Medical Center [1]; UC Irvine Medical Center, Orange[2]

Background: A growing body of evidence indicates that functional hemodynamic parameters derived from arterial pressure wave form analysis are superior predictors of preload and fluid responsiveness compared to static measures. Many new devices have been developed to continuously monitor these parameters. Few studies directly compare measurements from multiple devices capable of measuring functional hemodynamic parameters concurrently on the same patient. This study compared measurements of arterial pulse pressure variation (PPV) and stroke volume variation (SVV) from LiDCO Rapid, NICOM, and Philips MP50 monitors on patients during high-risk abdominal surgery.

Methods: After IRB approval and informed patient consent, 26 patients ASA class 2-4 scheduled for elective major intra-abdominal surgery (potential EBL of 500+cc) were enrolled in this prospective observational trial. Exclusion criteria were patients with arrhythmias, heart failure, or hemodynamically significant heart disease. Prior to induction of general anesthesia (GA), 4 NICOM non-invasive cardiac output monitor leads were applied to the thorax in addition to standard ASA monitors. After induction of GA, a radial arterial line was placed in each patient per standard of care. Hemodynamic values via arterial line were recorded using LIDCO Rapid and Philips MP50. Continuous PPV values were recorded by both Philips MP50 and LiDCO Rapid monitors. Continuous SVV values were recorded by both the NICOM and LiDCO Rapid monitors. Anesthesia providers were blinded to these results. Philips MP50 was used as the reference monitor for PPV values. LiDCO Rapid was used as the reference monitor for SVV values. PPV values from the LiDCO Rapid were plotted against those from the Philips MP50 to determine correlation. SVV values from the NICOM were plotted against those from the LiDCO Rapid to determine correlation. In both comparisons, Bland-Altman assessment for agreement was used to compare values from the various monitors. A range of agreement was defined as mean bias ±2 SD.

Results: A total of 121 PPV values from 26 patients were compared. The correlation between the Philips MP50 and LiDCO Rapid for PPV measurements (R^2) was 0.83. Bland-Altman analysis indicated that the 95% limits of agreement between the two PPV methods ranged from -3.8 to 4.3. Bias was 0.28. Precision was 0.19. A total of 152 SVV values from 26 patients were compared. The correlation between the LiDCO Rapid and NICOM for SVV measurements (R^2) was 0.004. Bland-Altman analysis indicated that the 95% limits of agreement between the two SVV methods ranged from -6.3 to 13 with several data points lying outside these limits. Bias was 3.4. Precision was 0.40.

Conclusions: The LiDCO Rapid PPV measurement demonstrated a high degree of correlation with the Philips MP50 PPV values. Use of either monitor should generate accurate measurements of continuous PPV to guide fluid resuscitation. There was a low degree of correlation between SVV values from NICOM versus LiDCO Rapid. Many devices are emerging that could serve to provide beat to beat measures of fluid responsiveness, however the accuracy & precision of these devices must be validated in the appropriate context to prevent inaccuracies and avoid patient harm.

Group 5 – Basic Science and Therapeutics

Moderator: Walter Boyle, M.D.

#2 **Intraoperative Glycemic Control with Intravenous GLP-1 in Cardiac Surgery**
Benjamin A. Kohl, M.D.; Mary S. Hammond, BSN; Stanley Schwartz, M.D.; Edward A. Ochroch, M.D.

#10 **Isoflurane Protects Against Renal Ischemia-Reperfusion Injury Induced Liver and Intestine Dysfunction via Intestinal Sphingosine Kinase Activation**
Minjae Kim, M.D.; Sang Won Park, Ph.D.; Jinu Kim, Ph.D.; Mihwa Kim, B.S.; Vivette D'Agati, M.D.; H. Thomas Lee, M.D., Ph.D.

#14 **Estrogen Renoprotection After Cardiac Arrest is Ablated by Novel Estrogen Receptor GPR30 Deletion**
Michael P. Hutchens, M.D., MA; Yasuhara Kosaka, M.D.; Paco S. Herson, Ph.D.; Halina Offner, M.D.; Patricia D. Hurn, Ph.D.

#15 ***Young Investigator Award***
iNOS Inhibition Prevents Muscle Wasting, Apoptosis and Decreased Akt Activity in Burned Rodents
Marina Yamada, Ph.D; Kazuhiro Ishimaru, M.D., Ph.D; Nobuo Yasuda, Ph.D; Masao Kaneki, M.D., Ph.D; J.A.Jeevendra Martyn M.D., F.R.C.A.

#21 **Increased IL-6 and NGAL with Transaminitis after Laparoscopic Donor Nephrectomy**
Steven C. Yap, M.D.; Sang Won Park, Ph.D.; H. Thomas Lee, M.D., Ph.D.

#24 **Effects of Denervation and Consecutive Reinnervation on the Expression of the Fetal and Adult Acetylcholine Receptor**
Christopher Kramer, M.D.; Manfred Blobner, M.D.; Saida Zoubaa, M.D.; Alexander Kretschmer, M.D.; Veronika Lehmeyer, M.D.; Heidrun Fink, M.D.

Intraoperative Glycemic Control with Intravenous GLP-1 in Cardiac Surgery

Benjamin A. Kohl, M.D.; Mary S. Hammond, BSN; Stanley Schwartz, M.D.; Edward A. Ochroch, M.D.
University of Pennsylvania

I. Introduction. Perioperative glycemic control in cardiac surgery remains a contentious issue (1,2). Whether extrapolation of data from the postoperative period to the intraoperative period is appropriate remains uncertain. It is unclear if the potential benefit of glycemic control is being offset by the deleterious effects of Insulin induced hypoglycemia. We therefore sought to evaluate the efficacy of the incretin GLP-1 to improve glycemic control intraoperatively while minimizing hypoglycemia. Preliminary data has suggested that this alternative may be a promising therapy (3). After Institutional Review Board approval, patients were consented to enroll in a randomized, double-blind, placebo controlled study with two arms, consisting of GLP-1 (7-36)-amide infusion and placebo. The primary outcome was defined as serum glucose 30 minutes after initiation of cardiopulmonary bypass.

II. Methods. Adult patients undergoing cardiac surgery with cardiopulmonary bypass were randomized to receive GLP-1 (7-36)-amide infusion (1.5 pmol/kg/min) or placebo (normal saline). Patients with insulin dependent diabetes mellitus (IDDM) were excluded. Infusion of study drug was initiated after endotracheal intubation and was stopped when bandages were placed on incision. Insulin was administered according to institutional protocol to maintain serum glucose < 200 mg/dL. A sample size was estimated to detect a 50% reduction in the incidence of hyperglycemia (defined as ≥ 160 mg/dL). With a proposed sample size of 80 the study will have a power of 83% to detect a statistically significant result. A decision was made a-priori to unblind the investigators to the first 30 patients for safety analysis. Glucose and GLP-1 mean values were compared by two-way analysis of covariance.

III. Results. The first 30 patients were analyzed. One patient had their surgery cancelled prior to incision and the study drug was terminated immediately. In the remaining patients, 17 received placebo and 12 received GLP-1. There were 5 diabetic patients in the placebo group and 1 in the GLP-1 group. Intraoperative data are presented in figure 1. No adverse events were reported in either subgroup.

IV. Conclusion. While there was no statistically significant difference in plasma glucose intraoperatively, this study was powered to detect a difference at 80 patients. There was a trend towards improved glycemic control in the GLP-1 group. GLP-1 represents a potential therapeutic modality to maintain glycemic control intraoperatively.

Illustrations: Figure 1. Intraoperative Glucose and GLP-1. Abbreviations: P- = Placebo group; G- = GLP-1 group, CPB= Cardiopulmonary bypass. * p< 0.05 by two-way ANOVA.
Consistency: All drugs are identified consistently by generic names

References:
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2.Gandhi GY, et al. Ann Intern Med 2007
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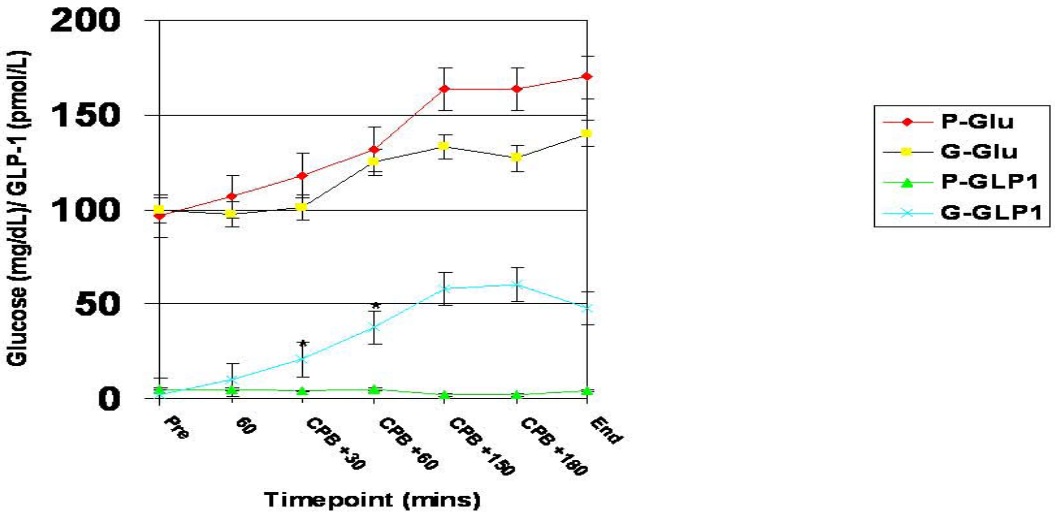
200
150
100
50
0
Glucose (mg/dL)/ GLP-1 (pmol/L)
Pre
60
CPB +30
CPB +60
CPB +150
CPB +180
End
Timepoint (mins)
P-Glu
G-Glu
P-GLP1
G-GLP1

Isoflurane Protects Against Renal Ischemia-Reperfusion Injury Induced Liver and Intestine Dysfunction via Intestinal Sphingosine Kinase Activation

Minjae Kim, M.D.; Sang Won Park, Ph.D.; Jinu Kim, Ph.D.; Mihwa Kim, B.S.; Vivette D'Agati, M.D.;
H. Thomas Lee, M.D., Ph.D.
Columbia University

Introduction: Acute kidney injury (AKI) is a major clinical problem and often leads to multi-organ dysfunction and systemic inflammation which contribute significantly to morbidity and mortality. We recently showed that AKI led to hepatic dysfunction mediated by cytokine release from the small intestine (SW Park et al., in revision, Lab Invest). We also previously showed that isoflurane (Iso) protects against renal ischemia-reperfusion injury (IRI) in mice via sphingosine kinase-1 (SK1) activation (1). Here, we aimed to determine whether 1) renal IRI produces hepatic dysfunction in mice, 2) Iso protects against renal IRI-induced liver injury, and 3) the mechanisms involved in Iso-mediated protection.

Methods: After IACUC approval, C57BL/6 mice were anesthetized with pentobarbital (PB) and subjected to 30 min left renal ischemia after right nephrectomy. Immediately after reperfusion, mice were further exposed to 4 h of equi-anesthetic doses of PB or Iso and then allowed to awaken from anesthesia. Twenty-four hours after reperfusion, plasma creatinine (Cr, mg/dL) and alanine aminotransferase (ALT, U/L) were measured. Liver and intestine tissues were analyzed for pro-inflammatory mRNAs (RT-PCR), histology (H&E), SK1 immunoblotting, SK1 activity, and sphingosine-1-phosphate (S1P) levels. The data were analyzed with t-tests or one-way ANOVA and are expressed as mean ± SEM.

Results: Mice exposed to PB after renal IRI developed severe AKI (Cr=2.39±0.05, N=10, $p<0.01$) and hepatic injury (ALT=238±18, N=10, $p<0.01$) compared with sham mice (Cr=0.47±0.03, N=6; ALT=61±8, N=4) 24 h after injury. The rise in ALT was associated with focused peri-portal hepatocyte necrosis, vacuolization, neutrophil infiltration, and pro-inflammatory mRNA upregulation. Iso exposure protected against AKI (Cr=1.61±0.17, N=8, $p<0.01$) and reduced hepatic injury (ALT=140±16, N=7, $p<0.05$) compared to PB exposure. Mechanistically, Iso induced liver protection via induction of small intestinal crypt SK1 as SK1 mRNA (Fig 1A), protein expression (Fig 1B), and enzymatic activity (Fig 1C) all increased in the small intestine. In addition, intestinal S1P levels also increased (Fig 1D) with Iso exposure. We confirmed the importance of SK1 as mice treated with an SK inhibitor (SKI-II) or mice deficient in SK1 enzyme were not protected against hepatic and intestinal dysfunction with Iso exposure.

Discussion: Our model of renal IRI caused rapid hepatic and intestinal injury in mice. We show that Iso protected against renal IRI induced hepatic and intestinal injury via upregulation of SK1/S1P in the small intestine. Activation of the SK/S1P pathway in the intestine by Iso reduced small intestinal injury induced liver necrosis. Modulation of the SK1/S1P pathway may have important therapeutic implications to reduce extra-renal complications arising from AKI.

1. Am J Physiol Renal Physiol 2007, 293(6):F1827-35.

Figure 1

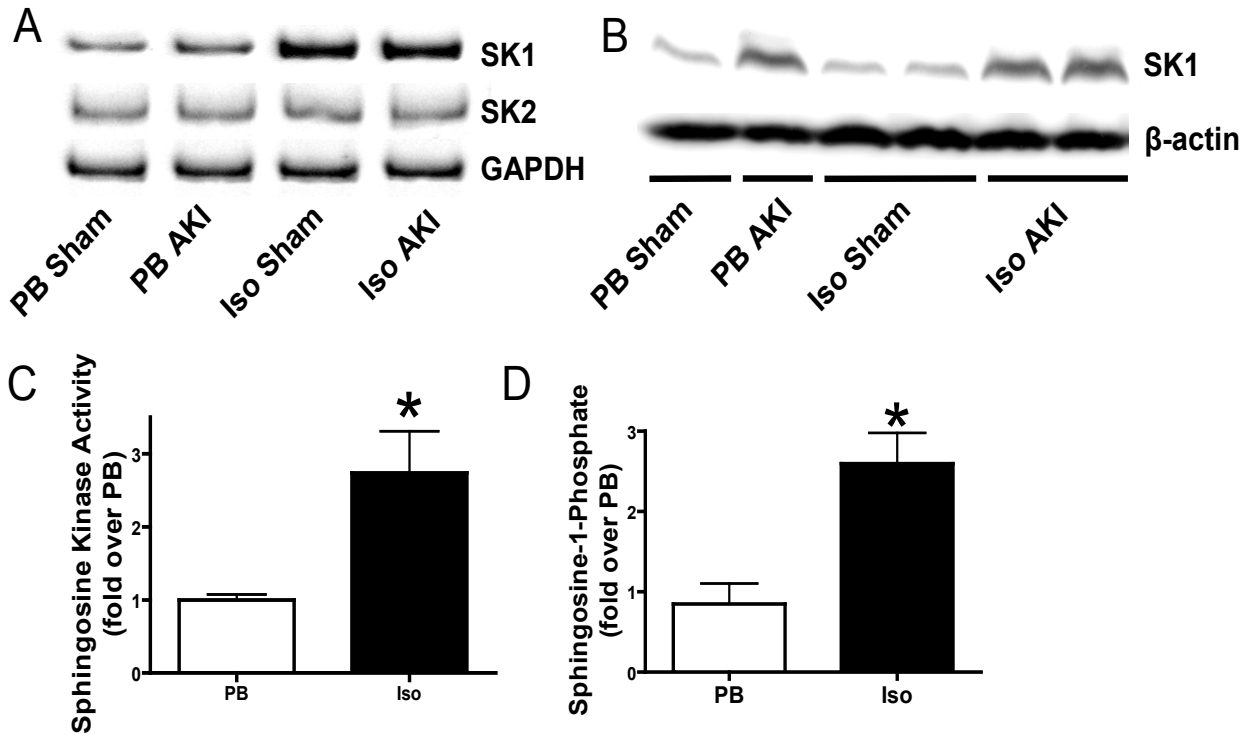

Figure 1

(A) Representative gel images of RT-PCR (of 4 experiments) of SK1, SK2, and GAPDH from intestines of C57BL/6 mice with exposure to 4 h of pentobarbital (PB) or isoflurane (Iso) after sham operation or acute kidney injury (AKI). (B) Representative immunoblot images of SK1 and β-actin from C57BL/6 mice exposed to 4 h of PB or Iso after sham operation or AKI. (C) Relative SK1 activity (fold over PB group) from intestines of C57BL/6 mice exposed to 4 h of PB or Iso (N=10 per group). * $p<0.05$ vs. PB group. (D) Relative formation of sphingosine-1-phosphate (S1P) (fold over PB) from the intestines of C57BL/6 mice exposed to 4 h of PB (N=4) or Iso (N=6). * $p<0.05$ vs. PB group.

Estrogen Renoprotection After Cardiac Arrest is Ablated by Novel Estrogen Receptor GPR30 Deletion

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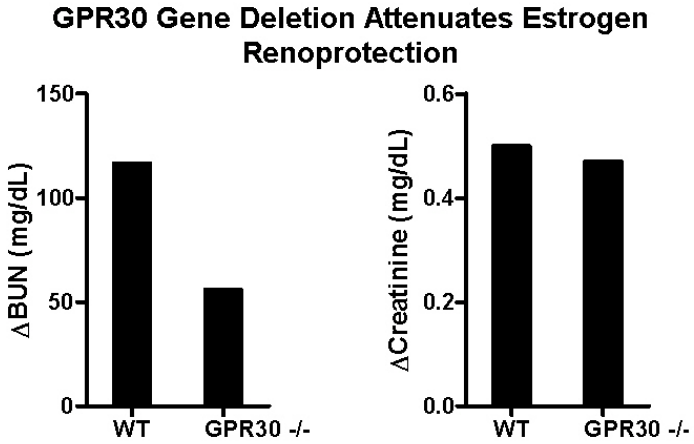
Introduction: Estrogen is renoprotective after cardiac arrest and cardiopulmonary resuscitation (CA/CPR). We have previously found that this protection is not lost with deletion of either estrogen receptor alpha or estrogen receptor beta, suggesting another mechanism is at work. Recent investigation into rapid effects of estrogen has focused on the G protein-coupled estrogen receptor GPR30. We hypothesized that GPR30 gene deletion would prevent the renoprotective effect of estrogen after CA/CPR.

Methods: Ovariectomized female C57BL/6 and GPR30 gene deleted (GPR30-/-) mice were treated with implanted silastic pellets containing either vehicle (VEH) or 17- estradiol (EST,6.3 mcg) for 7 days. They were then subjected to 10 min apneic CA/CPR, induced with potassium chloride. 24 h after resuscitation, mice were killed and blood drawn for blood urea nitrogen (BUN) and serum creatinine assays performed using an enzymatic analyzer (Abaxis, Union City CA). ΔBUN and Δcreatinine were calculated as the EST-treated mean BUN and creatinine subtracted from the VEH treated BUN and creatinine respectively. Statistical analysis was performed using Prism 5.0 software. Two-group, two-treatment analyses were carried out using 2-way ANOVA with Bonferroni post-testing.

Results: There were no significant differences in time to resuscitate, mortality or epinephrine dose between strains or
treatment groups. BUN was significantly higher in VEH compared with EST treated WT animals (VEH 166±28 mg/dL n=5, EST 50±14 mg/dL, n=8 $p<0.05$) but not significantly different in GPR30-/- animals (VEH 169±41 mg/dL n=5, EST 113±29 mg/dL, n=6 $p>0.05$). Creatinine was significantly reduced by EST treatment in the whole cohort (WT: VEH 0.7±0.3 mg/dL n=5, EST 0.2±0.03 mg/dL, n=8, GPR30-/-: VEH 0.9±0.3 mg/dL n=5, EST 0.5±0.1 mg/dL, n=6, overall p=0.01, Bonferroni posttest intra-group differences nonsignificant.).ΔBUN and Δcreatinine were reduced in GPR30-/- animals (figure 1).

Discussion: The mechanism of estrogen ischemic renoprotection is unclear, but important as specific manipulation of this mechanism might avoid the many disadvantages of perioperative estrogen administration. We found attenuation of estrogen renoprotection in GPR30-/- animals, suggesting that GPR30 may mediate this effect. The difference we have found thus far is small and further investigation is underway, however GPR30 is an attractive therapeutic target with available specific agonists.

Extra Files:



Poster 15

Young Investigator Award

iNOS Inhibition Prevents Muscle Wasting, Apoptosis and Decreased Akt Activity in Burned Rodents

Marina Yamada, Ph.D; Kazuhiro Ishimaru, M.D., Ph.D; Nobuo Yasuda, Ph.D; Masao Kaneki, M.D., Ph.D; J.A.Jeevendra Martyn M.D., F.R.C.A.

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Introduction: Muscle wasting leads to decreased mobilization, difficulties in weaning off respirators, prolonged rehabilitation and hospitalization. Insulin resistance is a major contributor to muscle wasting. Akt promotes hypertrophy and survival of muscle cells, while GSK-3β induces atrophy and apoptosis. Akt inhibits GSK-3β activity by phosphorylation. Inducible nitric oxide synthase (iNOS), a major mediator of inflammation, plays a pivotal role in obesity- and endotoxin-induced insulin resistance. We have previously shown that the inhibition of iNOS prevents burn-induced insulin resistance in skeletal muscle, and that muscle wasting by burn is associated with apoptosis. However, a role of iNOS in muscle wasting in critical illness (e.g., burn) has not yet been studied. Therefore, we examined the effects of iNOS inhibition on apoptosis, fiber size, and basal activities of Akt and GSK-3β in skeletal muscle of rodents.

Methods: Full-thickness third degree burn injury comprising 45% and 30% of total body surface area was produced under anesthesia in male Sprague-Dawley rats, and wild-type and iNOS knockout (-/-) C57BL/6 mice, respectively, by immersing the trunk in 80□ water. Burned and sham-burned rats were treated with a specific inhibitor of iNOS, L-NIL (60 mg/kgBW, b.i.d., IP) or PBS. Apoptosis was assessed by TUNEL assay and ELISA kit. The muscle was stained with hematoxylin eosin for measurement of fiber size. Activities of Akt and GSK-3β were evaluated by phosphorylation of Akt, GSK-3β , and glycogen synthase, an endogenous substrate of GSK-3β , and immune complex kinase assay.

Results: Burn injury induced iNOS expression, apoptosis, and decrease in fiber size in skeletal muscle of rats and mice. iNOS inhibitor, L-NIL, decreased apoptosis in skeletal muscle to 33% of the level in PBS-treated burned rats at 3 days after burn ($p<0.01$). In wild-type mice, muscle fiber size was decreased to 61% of that in sham-burned mice at 7 days after burn ($p<0.01$). Burn-induced decrease in muscle fiber size was significantly attenuated in iNOS-/- mice (80% of those in sham-burned wild-type and iNOS-/- mice, $p<0.05$), although fiber size did not differ between in sham-burned wild-type and iNOS-/- mice. Basal (exogenous insulin-nave) phosphorylation of Akt and GSK-3β was decreased in skeletal muscle after burn, indicating decreased Akt activity and activation of GSK-3β. Consistently, phosphorylation of glycogen synthase was increased after burn in rats. L-NIL reversed these alterations in the Akt/GSK-3β pathway in burned rats, although neither burn nor L-NIL altered the protein expression of Akt and GSK-3β . Similarly, phosphorylation of glycogen synthase was increased in muscle of wild-type, but not iNOS-/-, mice after burn.

Conclusions: Our data demonstrate that: (1) the inhibition of iNOS by L-NIL or gene disruption significantly prevented burn-induced muscle apoptosis and atrophy in rodents; and (2) burn resulted in decreased Akt activity and activation of GSK-3β in muscle, which were reverted by iNOS inhibition. Our results clearly indicate that iNOS plays an important role in muscle apoptosis and wasting following burn. These findings suggest that altered activities of Akt and GSK-3β may be involved in iNOS-mediated myopathy in burn injury.

Increased IL-6 and NGAL with Transaminitis After Laparoscopic Donor Nephrectomy

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Background: Acute kidney injury (AKI) is a major clinical problem during the perioperative period (1). Patients in ICU with AKI frequently develop extra-renal organ dysfunction which contributes to increased mortality (2). In particular, hepatic dysfunction associated with AKI is a major complication in patients receiving ICU care. We showed previously that murine models of AKI led to increased levels of pro-inflammatory cytokines including TNF-α and IL-6 that directly contributed to hepatic dysfunction (3). Despite the large number of nephrectomies performed in the United States for either kidney donation or for treatment of renal cancer, the impact of these findings in humans is unclear. In this study, we examined whether patients undergoing laparoscopic donor nephrectomy showed increased postoperative IL-6 and TNF-α levels with injury to the liver and whether the remaining kidney sustains injury.

Methods: Serum and urine were collected for 25 patients undergoing laparoscopic donor nephrectomy and 14 patients undergoing non-renal laparoscopic surgery after induction of anesthesia, and again at 5 and 24 hours after surgery. TNF-α, IL-6 (eBioscience, San Diego) and Neutrophil Gelatinase Associated Lipocalin (NGAL) (R&D, Minneapolis) were quantified using human-specific ELISA kits. Serum was also analyzed by Quest Laboratories (Teterboro, NJ) for creatinine (Cr), aspartate transaminase (AST) and alanine transaminase (ALT).

Results: Our results show that patients who undergo nephrectomy not only demonstrate increased creatinine (Figure 1A), but also had significant increases in IL-6 (Figure 1B) compared to patients who undergo other types of laparoscopic surgery. Increases in serum TNF-α did not reach significance most likely due to variance and small sample size. Urinary elimination of IL-6 and TNF-α were significantly increased after nephrectomy. AST (Figure 1C) and ALT (not shown) were significantly increased and correlated with transaminitis (IL-6 vs. ALT, Pearson $r=0.42$, $P=0.02$). Increased urinary NGAL after donor nephrectomy (0.22 ± 0.05, $N=19$) directly correlated with age (Figure 1D) whereas urinary NGAL remained stable after control laparoscopy (0.10 ± 2.2, $N=7$).

Discussion: Our results show that patients subjected to laparoscopic nephrectomy had increased levels of serum IL-6, as well as increased urinary elimination of IL-6 and TNF-α. These findings correlated with transaminitis and suggest that donor nephrectomy results in increased production of cytokines that directly contribute to transaminitis, possibly explaining the relationship between AKI in the broader ICU population and hepatic dysfunction. In addition, elevated urine NGAL that directly correlated with age suggests that older patients may sustain additional injury to the remaining kidney after donor nephrectomy. This may be the result of increased renal blood flow in the setting of decreased renal reserve, resulting in tubular stress in the remaining kidney.

References

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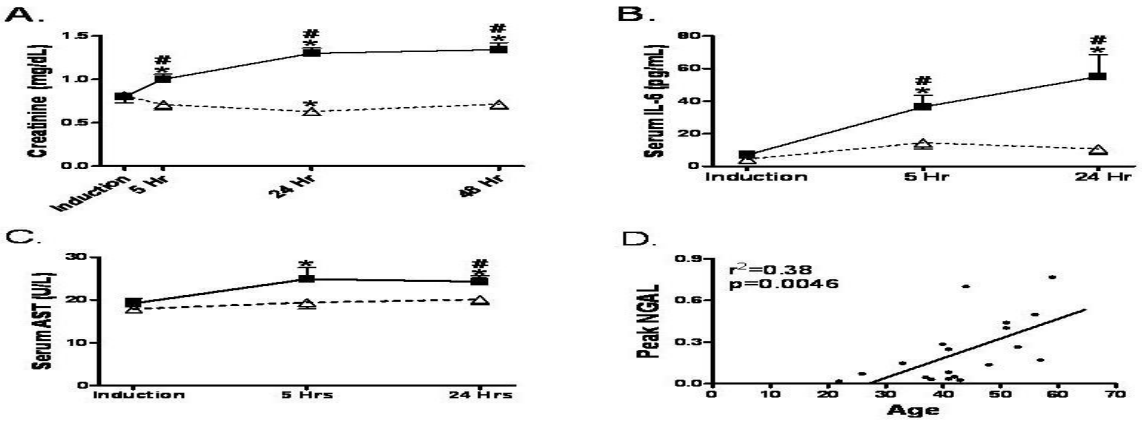

Figure 1: Serum levels of creatinine (A), IL-6 (B) and AST (C) in patients subjected to laparoscopic donor nephrectomy (N=25, ■) and control laparoscopic non-renal surgery (N=13, Δ). Peak urine NGAL corrected for urine creatinine after laparoscopic donor nephrectomy (N=19, ●) correlated with patient age (D). *P<0.05 vs. Control, #P<0.05 vs. Induction. Error bars represent SEM.

Effects of Denervation and Consecutive Reinnervation on the Expression of the Fetal and Adult Acetylcholine Receptor

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Background: Diaphragmatic synaptic plasticity of the neuromuscular junction with expression of adult acetylcholine receptors is maintained by neural input of the phrenic nerve. However, parts of the dorsal regions are innervated by the accessory phrenic nerve. This accessory nerve could also initiate reinnervation of the diaphragm should the main phrenic nerve be damaged. Aim of this study was therefore to investigate the effects of denervation and consecutive recovery on the expression pattern of acetylcholine receptor isoforms and Muscle-specific kinase (MuSK) on the functional protein level and electromyographic activity.

Methods: After approval, 91 Sprague-Dawley rats were unilaterally phrenicotomized by transection of 20mm of the main phrenic nerve. After 1, 3, 9, 27 or 81 days, respectively, electromyographic activity from the ventral, central and dorsal parts of the denervated and the non-denervated hemidiaphragms was analyzed. Consecutive weighted spectral median frequency (WSMF) and permutation entropy (PeEn; 34-70Hz) were calculated. Adult and fetal acetylcholine receptor isoforms were determined by Western Blot. Isoform and MuSK expression was localized by immunohistochemistry (IHC). Fiber type composition, cross-sectional area and histological changes were evaluated. Effects of denervation and recovery were indicated using Mann-Whitney-U and chi-square test.

Results: After denervation, WSMF and entropy were diminished, particularly in the central and ventral parts (Figure 1; * = $p<0.05$ compared to adjacent group; + = $p<0.05$ overall effects between day 1 and 81). During recovery a shift towards higher median frequencies and higher entropy values was observed, clearly indicative of reinnervation. Moreover, clinical and histological signs proved reinnervation. Adult acetylcholine receptor expression remained unchanged during denervation and recovery (Figure 2). Fetal acetylcholine receptors were significantly upregulated both junctionally and extrajunctionally with a maximum at day 9 after denervation, but returned to baseline values by day 81 upon reinnervation (Figure 2: * = $p<0.05$ compared to adjacent group). Peak upregulation of MuSK was observed on day 3 after denervation and decreased during recovery.

Conclusion: Denervation selectively upregulates junctional and extrajunctional fetal acetylcholine receptors as well as receptor tyrosine kinase MuSK. In contrast, the expression of the adult acetylcholine receptors remains unaffected upon disruption of neurotrophic influence and reinnervation. Moreover, reinnervation and functional recovery have antagonistic effects on the denervation-induced overexpression of fetal acetylcholine receptors and MuSK.

Figure 1

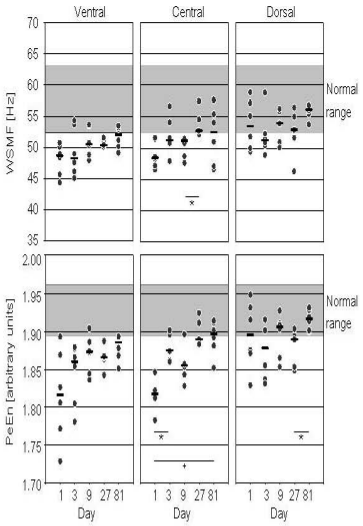
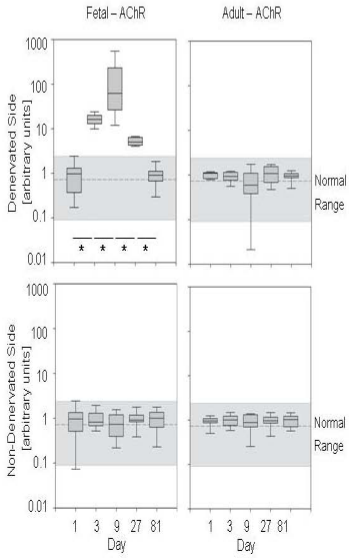


Figure 2



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Chicago, Illinois

ASCCA 25th Annual Meeting

Friday, October 12, 2012
Washington, D.C.