TRAVMA KONUSUNDA DENEYSEL ÇALIŞMALAR

AMERİKA DENEYİMİ

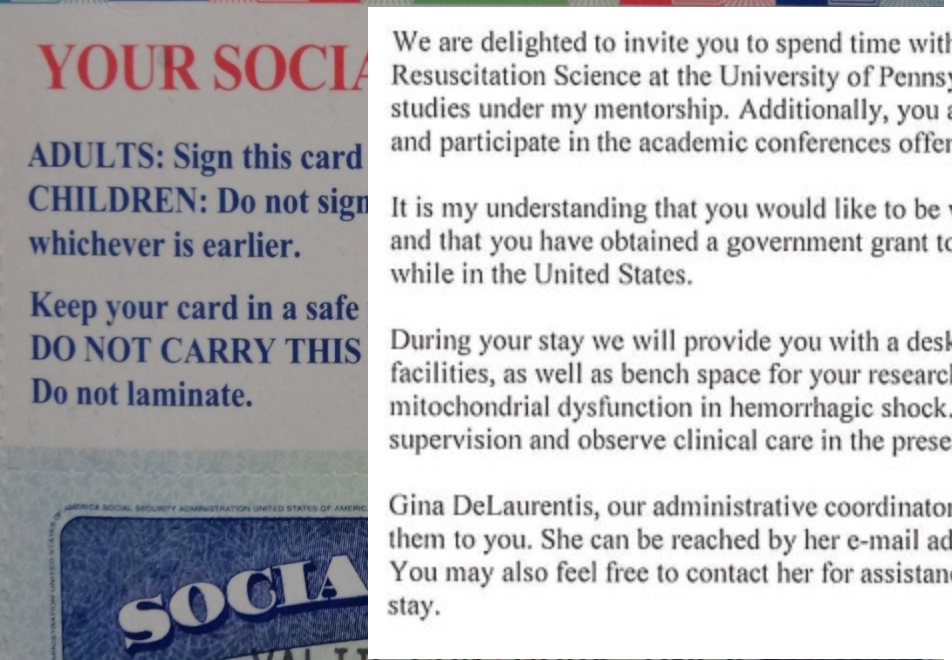
Yrd. Doç. Dr. Mehmet Akif KARAMERCAN
G.Ü.T.F Acil Tıp AD

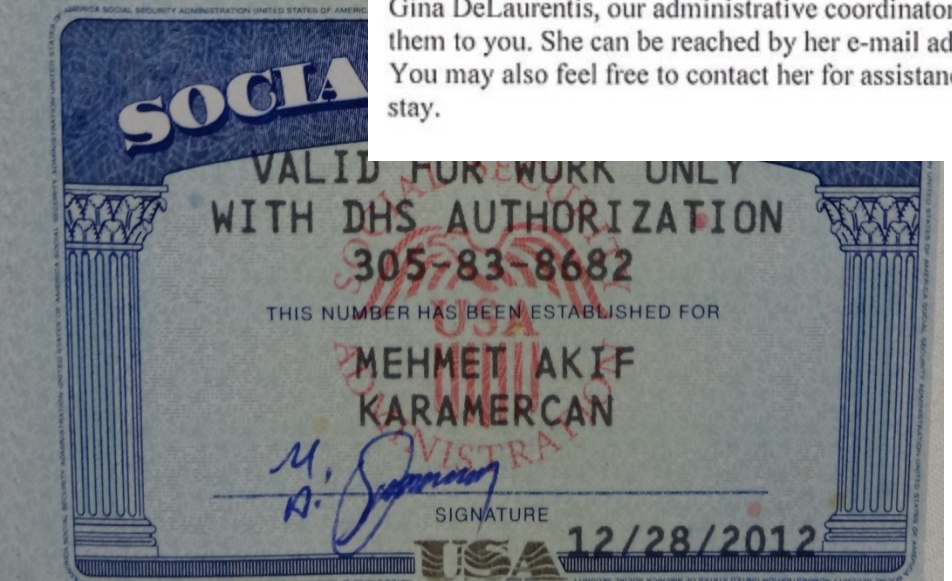
SUNUM PLANI

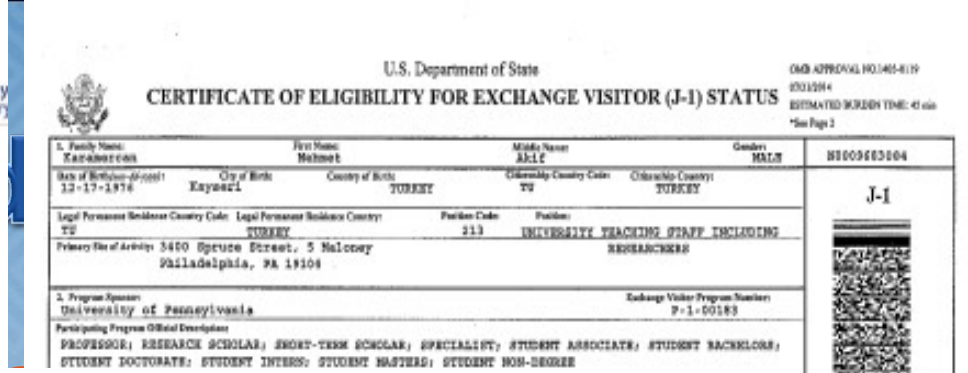
- Amerika'ya Gidiş…?
- Nerede / Nasıl Çalışırsınız?
- Acilleri Nasıl?
- Travma Konusunda Neler Yapıyorlar?
- Deneysel Çalışmalar?
- Sonuçlar

Amerika'ya Gidiş

- CV'nizi mutlaka önceden hazırlayın
- Ne için gideceğinize karar vermiş olun?
- Kendinizi açık ve net olarak ifade edin
- Amacınız öncelikli olarak kabul mektubu almak
  - Bununla uygun vizeye başvurmak
    - B1/B2 (1 aydan az) veya J1 (2 aydan fazla)







We are delighted to invite you to spend time with the Trauma Center at Penn and Center for Resuscitation Science at the University of Pennsylvania, carrying out independent laboratory studies under my mentorship. Additionally, you are invited to observe our clinical trauma team and participate in the academic conferences offered by our division.

It is my understanding that you would like to be with us for 4 months, starting October 1, 2012 and that you have obtained a government grant to provide your salary and pay for health benefits while in the United States.

During your stay we will provide you with a desk, access to our computer and other core facilities, as well as bench space for your research. Your research work will focus on mitochondrial dysfunction in hemorrhagic shock. You will conduct laboratory studies under my supervision and observe clinical care in the presence of our credentialed physicians.

Gina DeLaurentis, our administrative coordinator, will process your visa documents and forward them to you. She can be reached by her e-mail address: gina.delaurentis@uphs.upenn.edu. You may also feel free to contact her for assistance securing living accommodations during your stay.

Amerika'ya Gidiş

- Hastane ve özellikle acilde observer (gözlemci)
- Acilde nöbetler
- Travma timi
- Bilimsel toplantılar
- Deneysel çalışmalarda researcher (araştırmacı) (Hemorajik şokta mitokondrial biogenesis ve mitokondrial dysfunctions)

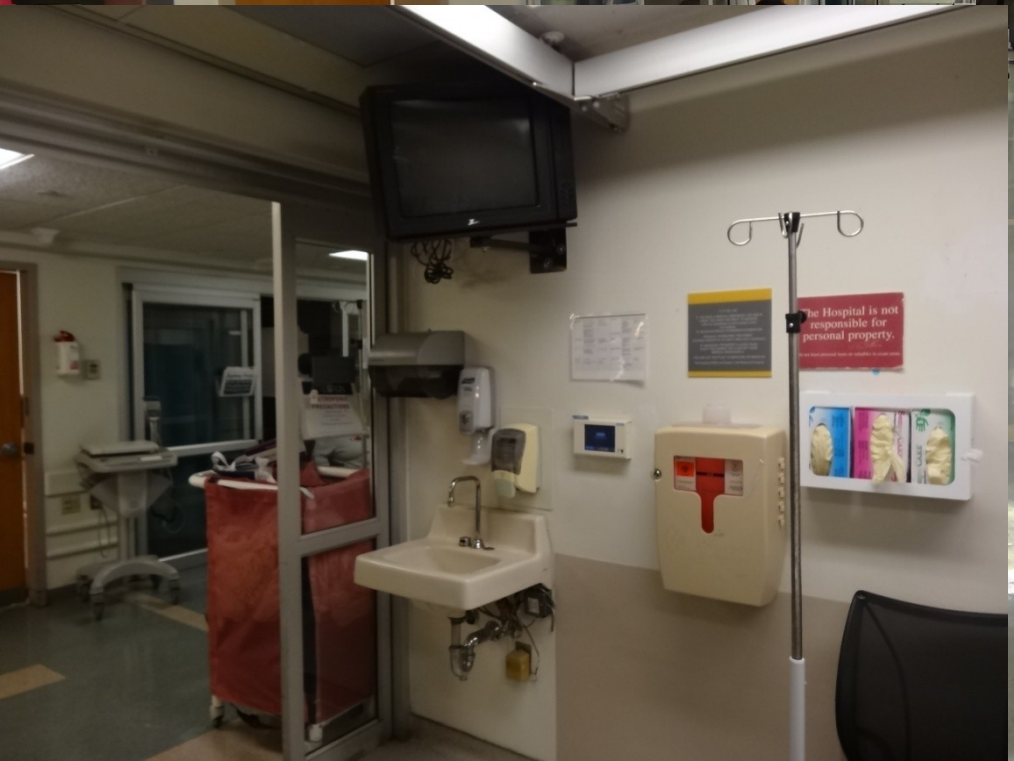
Nerede, Nasıl Çalışırsınız?


HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
Penn Medicine

Acilleri Nasıl?


Penn Medicine
Metal Detector


RESTROOM


he Hospital is not
responsible for
personal property.


Continental
DO NOT
REFRIGERATE


EXIT


lenovo


lenovo


TRAUMA

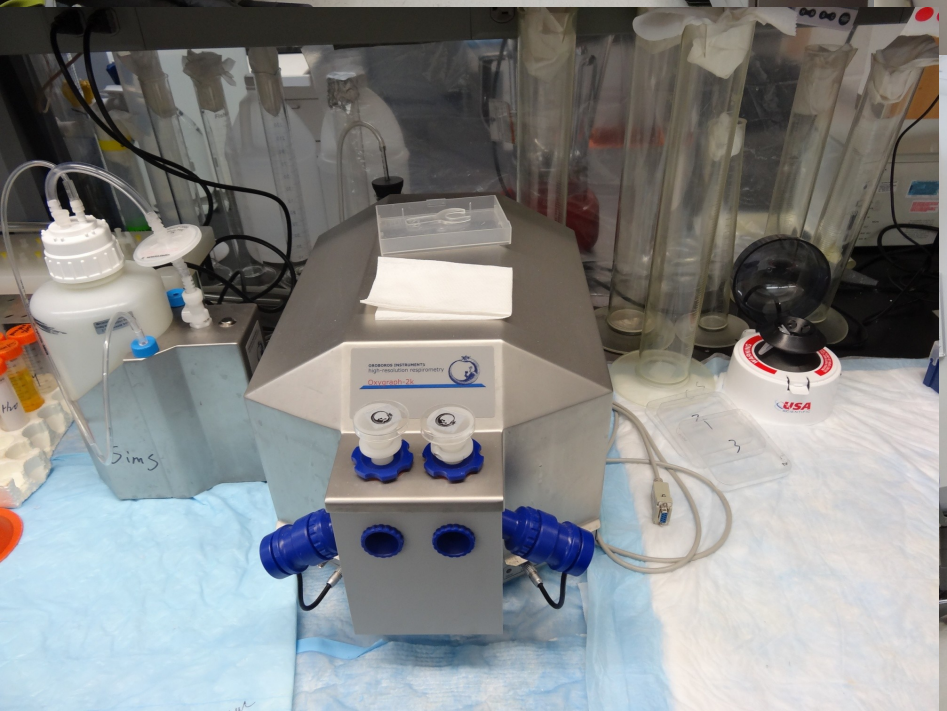
Travma Konusunda Neler Yapıyorlar?

- Kılavuzlarda yazılanları yapmaya ÇALIŞMIYORLAR…
- Çünkü ‘Yaptıklarını Yazıyorlar’

- Deneysel Çalışmalar
  - Translational Labarotories (Çeviriyle İlgili)
    - Hayvan Çalışmaları ---- İnsan Çalışmaları


125


VORTEX GENIE 2


OROBOROS INSTRUMENTS
high-resolution respirometry
Oxygraph-2k


NITROGEN NIT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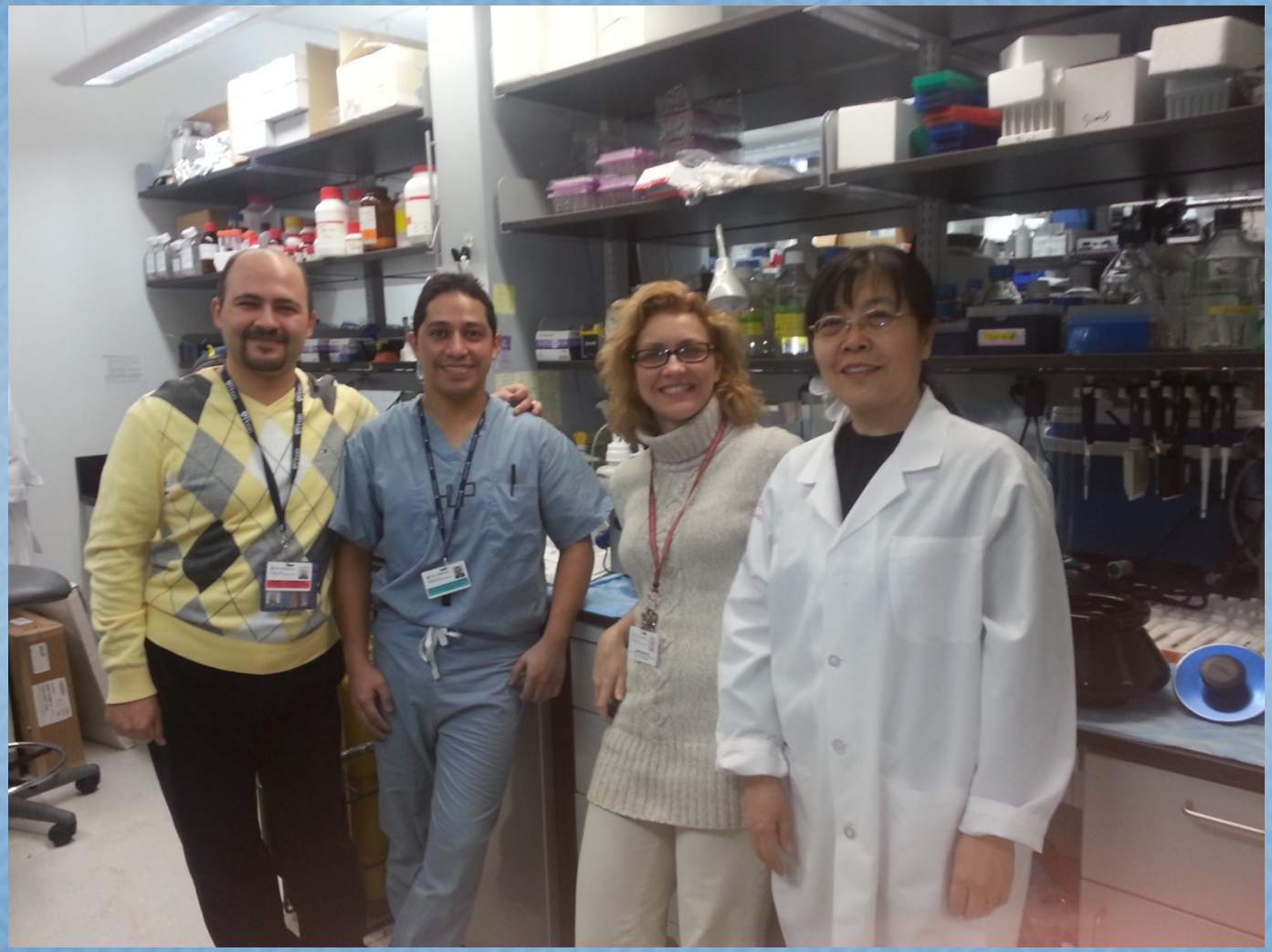


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170
169
168
167
NALGENE

Neler Yaşadım?

- İlk 10 gün tanışma ortama alışma (kimlikler,ev arama, etrafı tanıma, ulaşımı çözme)
- İkinci-Üçüncü on gün (hastane-laborat tanıma, toplantı-vizitlere katılma, acil-travma nöbetleri, travma timinde görev …. ameliyat izleme… katılma)
- İlk aydan sonra laboratuvarda çalışma,
- Sertifikalar-Hayvan deneyleri
- PCR-Western Blot öğrenme ….
- Shock Society Üyeliği, Toplantılar …

Bu Laboratuvarlarda Ne Yaptım?

- Hemorojik Şok Oluşturulan Ratlarda
- Karaciğer-Kalp-Böbreklerde
  - Mitokondriyal Disfonksiyonlar
  - Motokondriyal Biyogenesis
    - Hidrasyonun etkisi
    - Vazopressinin etkisi (düşük doz, yüksek doz, çok yüksek doz)
- Kan hücrelerinde (PMNL ve Trombositlerde)
  - Mitokondriyal Disfonksiyonlar

Bu Laboratuvarlarda Ne Yaptım?

Hemorajik şok oluşturulan ratlarda

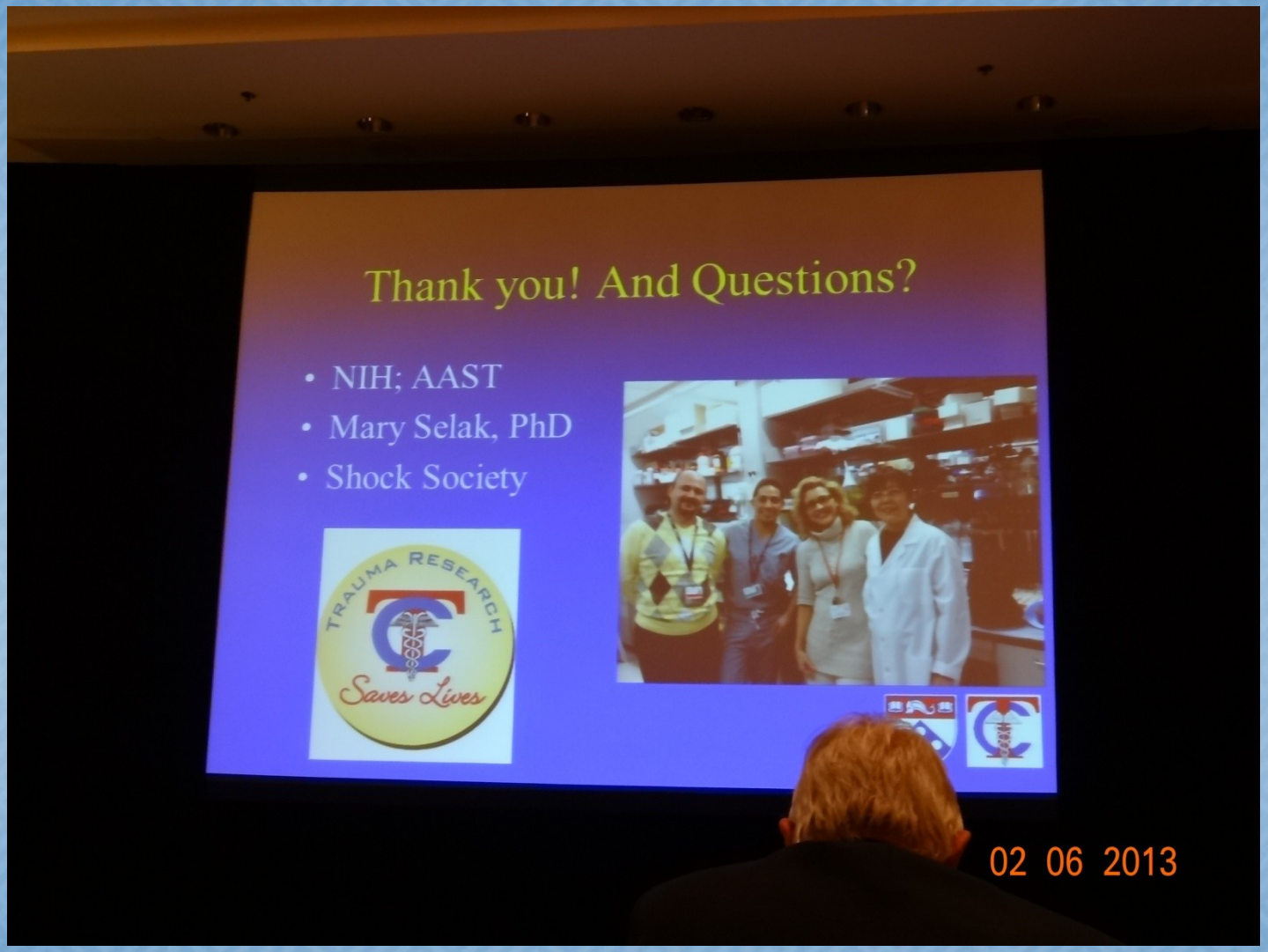
- Karaciğer-Kalp-Böbrek mitokondriyal disfonksiyonlar ile PMNL mitokondriyal disfonksiyonlar

ARASINDA KORELASYON ???

- 2013 San Diago Shock Society Kongresine
  - **Oral Abstract Sunumu**

ANA SALONDA ÇALIŞMANIN SUNUMU


CAN PERIPHERAL BLOOD MONONUCLEAR CELLS BE USED AS A PROXY FOR MITOCHONDRIAL DYSFUNCTION IN VITAL ORGANS DURING HEMORRHAGIC SHOCK AND RESUSCITATION?
Mehmet A. Karamercan, MD;
Scott Weiss, MD; José Paul Perales Villarroel, MD; Yuxia Guan, BS;
Evan Werlin, BS; Ronald Figueredo, MD; Lance B. Becker, MD;
Carrie A. Sims, MD, MS.
Gazi University
School of Medicine
Department of Emergency Medicine
Division of Traumatology, Surgical Critical Care, & Emergency Surgery
Hospital of the University of Pennsylvania
02 06 2013

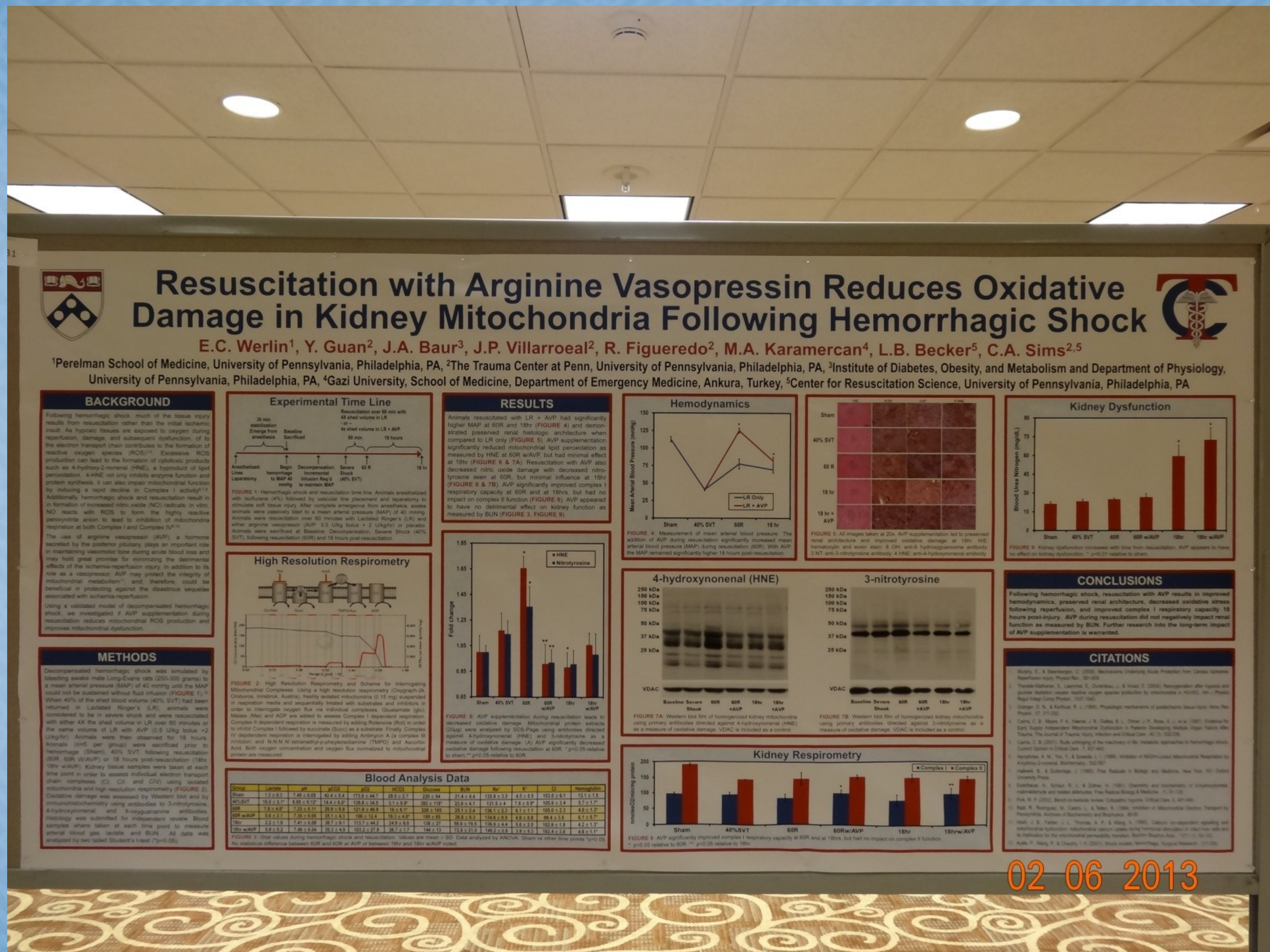

Thank you! And Questions?
• NIH; AAST
• Mary Selak, PhD
• Shock Society
TRAUMA RESEARCH
Saves Lives
02 06 2013

Mitochondrial Function During Hemorrhagic Shock: Where You Come From Counts.

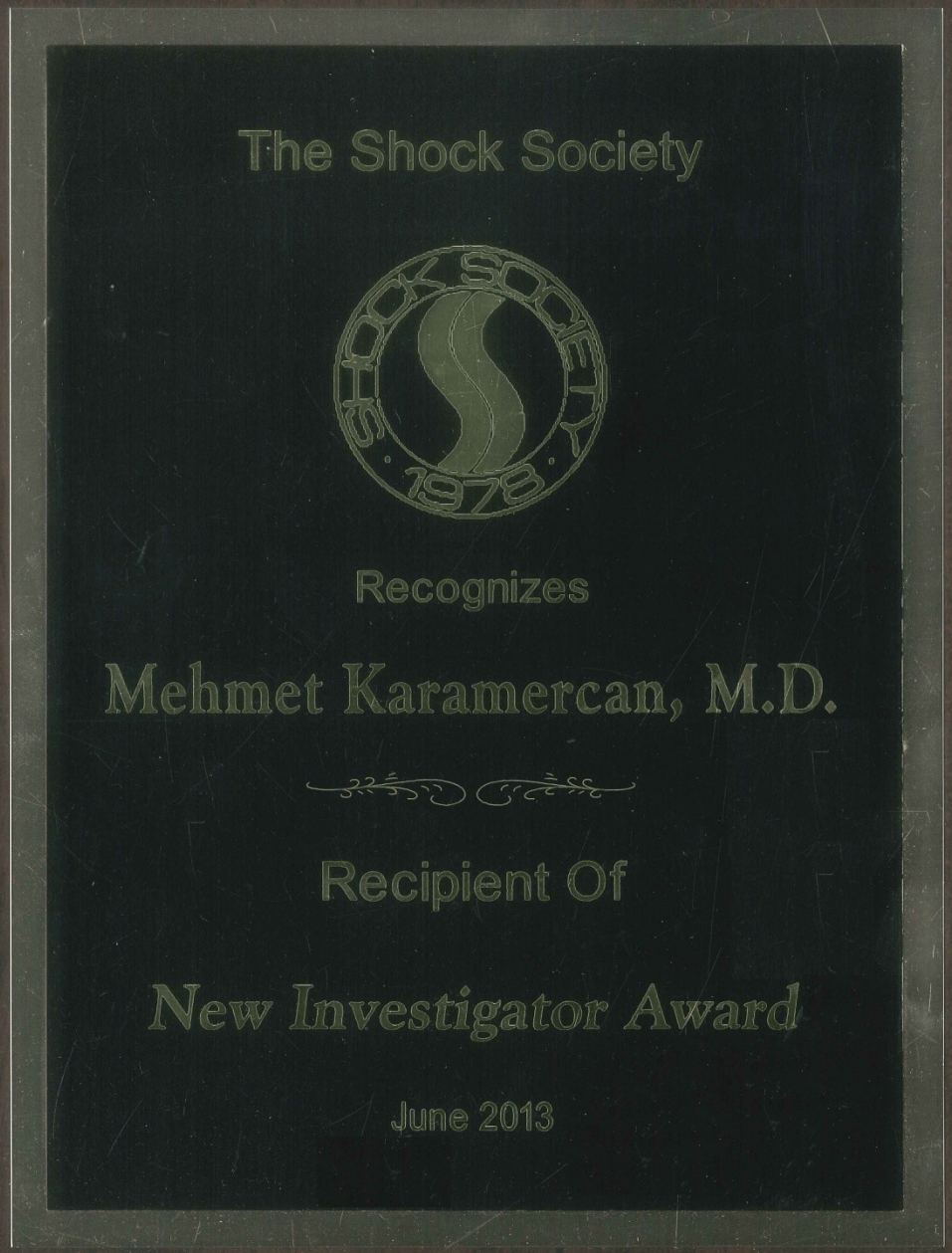
CA Sims, Y Guan, MA Karamercan, M Selak,
JA Baur, LB Becker

Trauma Center at Penn
Center for Resuscitation Science
University of Pennsylvania

02 06 2013


Resuscitation with Arginine Vasopressin Reduces Oxidative Damage in Kidney Mitochondria Following Hemorrhagic Shock
E.C. Werlin1, Y. Guan2, J.A. Baur3, J.P. Villarroeal2, R. Figueredo2, M.A. Karamercan4, L.B. Becker5, C.A. Sims2,5
1Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 2The Trauma Center at Penn, University of Pennsylvania, Philadelphia, PA, 3Institute of Diabetes, Obesity, and Metabolism and Department of Physiology, University of Pennsylvania, Philadelphia, PA, 4Gazi University, School of Medicine, Department of Emergency Medicine, Ankura, Turkey, 5Center for Resuscitation Science, University of Pennsylvania, Philadelphia, PA
BACKGROUND
Experimental Time Line
RESULTS
Hemodynamics
Kidney Dysfunction
High Resolution Respirometry
4-hydroxynonenal (HNE)
3-nitrotyrosine
CONCLUSIONS
METHODS
CITATIONS
Kidney Respirometry
Blood Analysis Data
02 06 2013


OCCUPANCY
02 06 2013


The Shock Society
SHOCK SOCIETY
U.S. 1978
Recognizes
Mehmet Karamercan, M.D.
Recipient Of
New Investigator Award
June 2013


EXIT
02 06 2013


02 06 2013


03 06 2013


PSAV
02 06 2013

THE
SHOCK SOCIETY

Presented to

Mehmet Karamercan

In Recognition and
Certification of
Being Elected
Member

2013

Sanna Goyert, Ph.D.
Secretary

Shock. 2013 Jul 17. [Epub ahead of print]

Can Peripheral Blood Mononuclear Cells be Used as a Proxy for Mitochondrial Dysfunction in Vital Organs During Hemorrhagic Shock and Resuscitation?

Karamercan MA, Weiss SL, Villarroel JP, Guan Y, Werlin E, Figueredo R, Becker LB, Sims C.

1 Gazi University School of Medicine, Department of Emergency Medicine. Ankara/TURKEY (makaramercan@gazi.edu.tr) 2 Children's Hospital of Philadelphia, Anesthesiology, Critical Care and Pediatrics, Perelman School of Medicine at the University of Pennsylvania (weisss@email.chop.edu) 3 Division of Traumatology, Critical Care and Acute Care Surgery. University of Pennsylvania, Philadelphia/USA (jose.peralesvillarroel@uphs.upenn.edu); (Yuxia.Guan@uphs.upenn.edu); (Ronald.Figueredo@uphs.upenn.edu); (Carrie.Sims@uphs.upenn.edu) 4 University of Pennsylvania, Perelman School of Medicine. Philadelphia/USA (evan.werlin@gmail.com) 5 Center for Resuscitation Science. University of Pennsylvania, Philadelphia/USA (Lance.Becker@uphs.upenn.edu).

Abstract

INTRODUCTION: Although mitochondrial dysfunction is thought to contribute to the development of post-traumatic organ failure, current techniques to assess mitochondrial function in tissues are invasive and clinically impractical. We hypothesized that mitochondrial function in peripheral blood mononuclear cells (PBMCs) would reflect cellular respiration in other organs during hemorrhagic shock and resuscitation (HS&R).

METHODS: Using a fixed pressure HS model, Long Evan's rats were bled to a mean arterial pressure (MAP) of 40 mmHg. When blood pressure could no longer be sustained without intermittent fluid infusion (Decompensated HS), Lactated Ringer's (LR) was incrementally infused to maintain the MAP at 40 mmHg until 40% of the shed blood volume was returned (Severe HS). Animals were then resuscitated with 4X total shed volume in LR over 60 minutes (Resuscitation). Control animals underwent the same surgical procedures, but were not hemorrhaged. Animals were randomized to Control (n=6), Decompensated HS (n=6), Severe HS (n=6) or Resuscitation (n=6) groups. Kidney, liver, and heart tissues as well as PBMC's were harvested from animals in each group to measure mitochondrial oxygen consumption using high resolution respirometry. Flow cytometry was used to assess mitochondrial membrane potential (Ψm) in PBMCs. One-way ANOVA and Pearson correlations were performed.

RESULTS: Mitochondrial oxygen consumption decreased in all tissues, including PBMC's, following Decompensated HS, Severe HS, and Resuscitation. However, the degree of impairment varied significantly across tissues during HS&R. Of the tissues investigated, PBMC mitochondrial oxygen consumption and Ψm provided the closest correlation to kidney mitochondrial function during HS (complex I: $r = 0.65$; complex II: $r = 0.65$; complex IV: $r = 0.52$; $p < 0.05$). This association, however, disappeared with resuscitation. A weaker association between PBMC and heart mitochondrial function was observed but no association was noted between PBMC and liver mitochondrial function.

CONCLUSION: All tissues including PBMC's demonstrated significant mitochondrial dysfunction following HS&R. Although PBMC and kidney mitochondrial function correlated well during hemorrhagic shock, the variability in mitochondrial response across tissues over the spectrum of hemorrhagic shock and resuscitation limits the usefulness of using PBMC's as a proxy for tissue-specific cellular respiration.

PMID: 23867522 [PubMed - as supplied by publisher]


Mitochondrial Pathways

J Surg Res. 2013 Sep;184(1):422-9. doi: 10.1016/j.jss.2013.05.097. Epub 2013 Jun 19.

Increased platelet storage time is associated with mitochondrial dysfunction and impaired platelet function.

Perales Villarroel JP, Figueredo R, Guan Y, Tomaiuolo M, Karamercan MA, Welsh J, Selak MA, Becker LB, Sims C.

Division of Traumatology, Department of Surgery, Critical Care and Acute Care Surgery, University of Pennsylvania, Philadelphia, Pennsylvania.

Abstract

BACKGROUND: Hemorrhagic shock is a leading cause of death following severe trauma, and platelet transfusions are frequently necessary to achieve hemostasis. Platelets, however, require special storage conditions, and storage time has been associated with loss of platelet quality. We hypothesized that standard storage conditions have a deleterious effect on platelet mitochondrial function and platelet activation.

MATERIALS AND METHODS: Platelet donations were collected from healthy donors (n = 5) and stored in gas-permeable collection bags according to American Association of Blood Bank recommendations. Platelet units were sampled from day of collection (day 0) until day 7. High-resolution respirometry was used to assess baseline mitochondrial respiration, maximal oxygen utilization, and individual mitochondrial complex-dependent respiration. Fluorescence-activated cell sorting was performed to analyze mitochondrial content, mitochondrial reactive oxygen species, the expression of P-selectin (both before and after challenge with thrombin receptor-activating peptide), and apoptosis. Data were analyzed using analysis of variance and Pearson correlation ($P < 0.05$ significant).

RESULTS: Mitochondrial respiration decreased significantly in platelets stored longer than 2 d ($P < 0.05$). Platelets also demonstrated a persistent decrease in response to stimulation with thrombin receptor-activating peptide by the third day of storage ($P < 0.05$) as well as an increase in mitochondrial reactive oxygen species and apoptosis ($P < 0.05$). Mitochondrial respiration significantly correlated with platelet capacity to activate ($r = 0.8$, $P < 0.05$).

CONCLUSIONS: Platelet mitochondrial respiratory function and activation response decrease significantly in platelets stored for 3 d or more. Because platelet transfusions almost universally occur between the third and fifth day of storage, our findings may have significant clinical importance and warrant further in vivo analysis.

J Trauma Acute Care Surg. 2013 Jul;75(1):24-31. doi: 10.1097/TA.0b013e3182988b1f.

Hemorrhagic shock and resuscitation are associated with peripheral blood mononuclear cell mitochondrial dysfunction and immunosuppression.

Villarroel JP, Guan Y, Werlin E, Selak MA, Becker LB, Sims CA.

Division of Traumatology, Critical Care and Acute Care Surgery, Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

Abstract

BACKGROUND: Trauma and hypovolemic shock are associated with mitochondrial dysfunction and septic complications. We hypothesize that hypovolemic shock and resuscitation results in peripheral blood mononuclear cell (PBMC) mitochondrial dysfunction that is linked to immunosuppression.

METHODS: With the use of a decompensated shock model, Long-Evans rats were bled to a mean arterial pressure of 40 mm Hg until the blood pressure could no longer be maintained without fluid infusion. Shock was sustained by incremental infusion of lactated Ringer's solution until 40% of the shed volume had been returned (severe shock). Animals were resuscitated with four times the shed volume in lactated Ringer's solution over 60 minutes (resuscitation). Control animals underwent line placement but were not hemorrhaged. Animals were randomized to control (n = 5), severe shock (n = 5), or resuscitation (n = 6) groups. At each time point, PBMC were isolated for mitochondrial function analysis using flow cytometry and high-resolution respirometry. Immune function was evaluated by quantifying serum interleukin 6 (IL-6) and tumor necrosis factor (TNF-α) after PBMC stimulation with lipopolysaccharide. The impact of plasma on mitochondrial function was evaluated by incubating PBMCs harvested following severe shock with control plasma. PBMCs from control animals were likewise mixed with plasma collected following resuscitation. Student's t test and Pearson correlations were performed (significance, $p < 0.05$).

RESULTS: Following resuscitation, PBMCs demonstrated significant bioenergetic failure with a marked decrease in basal, maximal, and adenosine triphosphate-linked respiration. Mitochondrial membrane potential also decreased significantly by 50% following resuscitation. Serum IL-6 increased, while lipopolysaccharide stimulated TNF-α production decreased dramatically following shock and resuscitation. Observed mitochondrial dysfunction correlated significantly with IL-6 and TNF-α levels. PBMCs demonstrated significant mitochondrial recovery when incubated in control serum, whereas control PBMCs developed depressed function when incubated with serum collected following severe shock.

CONCLUSION: Mitochondrial dysfunction following hemorrhagic shock and resuscitation was associated with the inhibition of PBMC response to endotoxin that may lead to an immunosuppressed state.

DİNLEDİĞİNİZ İÇİN TEŞEKKÜRLER

Sorular?

Katkılar?

Yrd. Doç. Dr. Mehmet Akif KARAMERCAN

G.Ü.T.F Acil Tıp AD