The 12th International Conference on Complex Acute Illness

August 8-11, 2013, Budapest, Hungary

iccai
International Conference on Complexity in Acute Illness

Welcome to ICCAI 2013 in Budapest!

Dear long time attendees and first-timers,

On behalf of the Organizing Committee of the 12-th International Conference on Complexity in Acute Illness (ICCAI) 2013, it is my pleasure to welcome attendees and our fantastic sponsors in Budapest, Hungary and wish everyone a scientifically productive and culturally rich experience in the heart of Europe.

ICCAI unites medical providers and scientists representing all areas from physiology, through physics, modeling and mathematics to translational clinical research with the overarching aim to bring modern technology and medical informatics to the bedside and improve outcomes in critically ill patients.

Previous ICCAI meetings were held predominantly in USA and Germany with the exception of 2012 when we convened in Canada with great success.

ICCAI 2013 will be the first organized in Eastern Europe and is anticipated to be attended by participants from all different countries representing cutting edge clinically applicable transdisciplinary science serving the patient. The Budapest meeting has an overarching topic of “Complexity of Single and Multiorgan Support in the Critically Ill“. We have World class speakers on the agenda and would be delighted if you could join us at the meeting.

We are looking forward to seeing you in Budapest in August.

Sincerely, Andriy Batchinsky MD, ICCAI 2013 Scientific Program Chair.

On behalf of the Society for Complexity in Acute Illness (SCAI), I would like to extend my warm welcome to all of the attendees of the 12th International Conference on Complexity in Acute Illness (ICCAI).

We thank all of our sponsors as well as the *Journal of Critical Care* for their support; we could not put on the ICCAI or expand our reach as we have in the past decade without you.

Our Society is the only one dedicated to the application of complex systems methods to the direct, urgent needs of critical care while also fostering novel basic and pre-clinical studies.

This year’s meeting continues our tradition of presenting cutting-edge interdisciplinary research from both academia and industry, and furthermore expands our interactions with new colleagues from more countries than ever. This meeting promises to be wide-ranging in both scope of material and methods of presentation, including ample opportunities for networking.

In this spirit of interaction, I welcome both old friends and new attendees to Budapest, Hungary

Sincerely, Yoram Vodovotz PhD, President, SCAI

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Table of Contents

2013 Conference Logistics Information

HOTEL RESERVATION INSTRUCTIONS

Conference location: Marriott Hotel Budapest overlooking the Danube river. Address: Apaczai Csere Janos u. 4. · Budapest, 1052 Hungary Phone: + 36-1-486-5000; Fax: + 36-1-486-5005

Find a list of toll free reservation phone numbers using the following web address: http://www.marriott.com/reservation/worldwide-hotel-reservation-numbers.mi

WEB: **http://www.marriott.com/hotels/travel/budhu-budapest-marriott-hotel/**

Single rooms each cost 105 EU per night; double rooms cost 120 EU each per night with additional upgrade options at discounted rates. Room rates include breakfast and reservations are open until July 08, 2013 using the following link: http://www.marriott.com/hotels/travel/budhu?groupCode=strstra&app=resvlink&fromDate=8/7/13&toDate=8/11/13&stop_mobi=yes

For special arrangements (i.e. family booking or early arrival or extended stay) please phone: + 011 36 1 235 4888 or e-mail: budapest.reservations@marriotthotels.com

If you encounter any difficulties please contact Eszter Peti, Event Coordinator for assistance. Budapest Marriott Hotel | Apáczai Csere János u.4. 1052 Budapest, T: +36 1 235 4845; F: +36 1 266 4295 | Email: eszter.peti@marriott.com

Airport transfers: Taxi transfer from the airport: 7.900- Hungarian Forints (HUF) and to the airport: 6.900- HUF. For personalized reservations and pick-up and drop-off at the hotel please send your flight details in advance (after room reservations) to the hotel concierge (budapest.concierge@marriott.com) or call the hotel directly and request a taxi pick-up when you arrive at the airport. Taxi cost can be added to your hotel bill upon request.

Exchange rate 1 USD= 219 HUF (as of 6/19/2013 according to www.x-rates.com).

IMPORTANT NOTICES

Abstract submission deadline has passed. Acceptance decisions regarding abstract submission and acceptance for Posters have been e-mailed. If you have not heard back regarding a submitted abstract or if you want to submit a late breaking abstract with the possibility of invitation for a poster presentation only, please e-mail the conference Chair Andriy Batchinsky MD via e-mail (andriy.i.batchinsky.ctr@mail.mil)

Poster dimensions:

All posters are 1 meter high and 1 meter wide. Poster boards will be available on site and are 1 m high and 2 meters wide. Thus each poster board will fit 1 poster next to each other on both sides. Poster presentation times will be e-mailed in the final program with the possibility of further time adjustments (if necessary on site). Please check with the conference coordinator regarding your poster presentation time and day when you pick up your badge and conference materials (Elizabeth Hall entrance).

Speaker and exhibitor information:

Speakers are personally responsible for uploading their presentations from memory sticks or CD/DVDs before each respective conference session. Official format is Microsoft Windows PowerPoint.

Duration of invited plenary talks is 20 minutes total. Duration of talks selected from abstracts or via wild cards is 10 minutes. Discussion is scheduled to follow at the end of each session—time permitting.

NOTE: all time limits for talks will be strictly followed, please expect to be cut-off if you exceed your time limit. We appreciate your understanding and compliance with this rule.

Sponsors and exhibitors will have a dedicated room with a standard 1.8 m long table per exhibitor area equipped with access to electricity.

Sign-up sheets will be available on site for structured training sessions at sponsor booths.

For customizable cultural program, tours and sightseeing please see the end of this document.
Official conference language is English.

Conference registration is $400(US dollars) for regular attendees and $200 for students, residents/trainees and post doctoral fellows if submitted before Jul 1, 2013. After Jul 1, 2013 or on-site conference registration will be $500 for regular attendees and $250 for students, residents/trainees and post doctoral fellows. Optional single day registration is $100 (payable on-site in cash).

Conference registration fee includes:

1. **1-year membership in the Society for Complex Acute illness**
2. **Access to the meeting and conference registration materials: badge, program, souvenir**
3. **Accepted abstracts (submitted before May 20, 2013) will be published in the Journal of Critical Care**
4. **Attendance of coffee breaks, lunches and gala dinner is complimentary with paid registration**
5. **Attendance of gala dinner for guests is $60 (payable on-site in cash)**

Please note: attendees not staying at the conference hotel (Marriot Budapest) do not have their breakfast included in the conference package. If you are not staying in the hotel and decide to enjoy the breakfast at the Marriot, please remember to settle the bill/cost with the hotel.

Coffee breaks, lunches and gala dinner are included with all paid registrations (except for the single day registration option, which does not cover the gala dinner) regardless if the attendee does or does not stay at the conference hotel.

Scientific Program/Conference Schedule

All sessions are held at Elizabeth Hall, Danube View

Thursday, Aug 8, 2013

11:00-12:00	**SCAI business meeting, election of officers**
12:00-13:00	**Business Lunch (for business meeting attendees)**
13:00-17:00	**Pre-meeting sessions**
	Location: Elizabeth Hall, Danube view
13:00-13:45	**Workshop/tutorial 1.** Presenter/moderator: Vitaly Herasevich MD, PhD, Mayo Clinic, Rochester Minnesota, USA Topic: How to evaluate technologies in healthcare? 13:45- 14:00 Open microphone discussion
14:00-14:45	**Workshop/tutorial 2.** Presenter/moderator: James Blum MD, Assistant Professor Department of Anesthesiology, Ann Arbor, Michigan, USA Topic: How to measure outcome and process of care using custom designed reporting databases? 14:45- 15:00 Open microphone discussion
15:00-17:00	**Meeting session 1** **Title: Modeling inflammation and Immunity** **Iin collaboration with "SepsEast":** Moderators: Corey O'Hearn Yale University, USA and Zsolt Molnar Hungary, Szeged University, Hungary
15:00- 15:20	Lajos Bogar, Department of Anesthesia and Intensive Therapy, University of Pécs: Sepsis audit in Hungary - where we stand?
15:20 – 15:40	Michael Kirby, Departments of Mathematics and Computer Science, Colorado State University, Early warning algorithms for infectious disease
15:40 – 16:00	Corey O'Hern, Graduate Program in Computational Biology & Bioinformatics, Yale University, Predicting and controlling the onset and progression of infectious disease
16:00- 16:20	Mark Shattuck, Department of Physics, CCNY Dynamical systems modeling of tuberculosis
16:20 – 16:40	Vineet Bhandari, Department of Pediatrics, Yale University: The identification of biomarkers for neonatal sepsis
16:40- 17:00	Open microphone discussion. Adjourn
19:00 -21:00	Informal reception at hotel lobby (pay your own way) or free evening

Friday, August 9, 2013

7:00 – 7:45	Continental breakfast, Peppers Restaurant, main floor Marriott (free for all registered attendees residing at the conference hotel (Marriott)
7:45 – 8:00	Official Opening of the Meeting. Welcome and Introductory Remarks (Andriy Batchinsky, USA, meeting Chair and Yoram Vodovotz, USA, outgoing president SCAI)
	Meeting Session 2 **Title: Transdisciplinary complexity** Moderators: Philip Lumb MD, BS, MCCM, USA and Eddy Neugebauer, Germany
8:00 – 8:20	Philip D. Lumb, M.D., B.S., MCCM, Professor and Chairman, Department of Anesthesiology Keck School of Medicine of the University of Southern California, USA. Editor in Chief, Journal of Critical Care: Ethics in Research and Publication; what's in a name?
8:20-8:40	Peter Csermely, Hungary: Structure and dynamics of molecular Networks
8:40– 9:00	Tim Buchman, Emory, Atlanta, USA: Social norms and group dynamics: an empiric approach to manipulating behaviors in critical care
9:00 – 9:20	Zsolt Molnar, Department of Anesthesiology and Intensive Therapy, University of Szeged, SzepsEast and SepsWest: What do we not know about sepsis?
9:20- 9:40	Yoram Vodovotz, Pittsburgh, USA: A decade of measurement, modeling and modulation in sepsis and trauma
9:40 –10:00	**Break, refreshments**
10:00 – 10:20	Randall Moorman, USA: Multidimensional time series entrainment in acute complex illness
10:20 – 10:40	Vicsek Tamas, Hungary: Spontaneous formation of hierarchical networks
10:40 – 11:00	Andriy Batchinsky, San Antonio, USA: Single and multi-organ support for critical illness: new dimensions of complexity at the bedside
11:00 – 12:00	**Keynote of the day: Michael Pinsky, Pittsburgh USA: "Redefining Health and Disease"**
12:00 – 15:00	Boxed lunch and Guided Bus tour of Budapest (in English). Buses will depart from the hotel main entrance. This service is not included in registration fees. An additional charge of 25 EUR per person will apply per all participants of bus tour: attendee, family and guests. Family and guests may order Boxed lunch (if lunch is desired) for an additional nominal fee as determined on site. Signup sheets will be available on site.
	Meeting Session 3. Title: Engineering Principles in Modeling Inflammation, Immunity and Organ Function Moderators: Mitchell Cohen, USA and Gilles Clermont, USA
15:00-15:20	Ioannis Androulakis, USA: The relationship between autonomic function and heart rate variability in human endntoxemia
15:20- 15:40	Gary An, Chicago, USA: Augmenting dynamic computational modeling with a computational modeling assistant (CMA)

15:40 – 16:00	Giuseppe Baselli, Italy: Autonomic control in a rat shock model prior to fatal drop in blood pressure
16:00 – 16:20	Sven Zenker, Germany: Applying mechanistic mathematical models to biological data: the role of uncertainty
16:20- 16:40	Niels Wessel, Germany: Model-based Synchronization and Coupling Analysis During Sleep
16:40 – 17:00	Thomas Dick, Cleveland, USA: Development of Brainstem Inflammation correlates with uncoupling of the cardiorespiratory system in an Endotoxemic Rodent Model
17:0- 17:20	Open microphone discussion
17:30-18:30	**Poster session #1 with formal reviews and 5 min presentations.** First 20 abstracts selected for poster. (Check on site for final updated poster numbers and display times). Abstract review committee: Yoram Vodovotz, Andrew Seely, Sven Zenker, Behnood Gholami, Bela Suki
	Free Evening. Enjoy the heart of Budapest and the Vaci Utca!

Saturday, August 10, 2013

7:00 – 7:45	Continental breakfast, Peppers Restaurant, main floor Marriott (free for all registered attendees residing at the conference hotel (Marriott)
	Meeting Session 4. Title: Complexity of Critical Illness and Multi Organ Support Technology Moderators: Andriy Batchinsky MD, San Antonio, Texas, USA and Balazs Szamosfalvi, Michigan, USA/Hungary
8:00 - 8:20	Stefan Kreyer MD, Bonn, Germany: Physiological benefits of preserving spontaneous breathing during treatment of an injured lung
8:20- 8:40	Alberto Zanella MD, Italy: Ultra low-flow extracorporeal CO_2 removal: enhancing CO_2 elimination with acidification of blood
8:40 - 9:00	Marie Csete, USA: Current generation liver support
9:00 - 9:20	Balazs Szamosfalvi Henry Ford, USA/Hungary: Regional Citrate Anticoagulation Automated Renal Support
9:20 – 9:40	Thomas Langer MD, Milan, Italy: Extracorporeal gas exchange as an alternative to mechanical ventilation for the treatment of ARDS
9:40—10:00	Marian Walter, Germany: Closed loop control of O_2 and CO_2 for management of patients with ARDS
10:00 -10:20	**Coffee break, refreshments**
10:20 – 10:40	Philippe Morimont, Liege, Belgium: Ventriculo-arterial coupling in ARDS and expected benefits of low flow CO_2 removal therapy

10:40 -11:00	Dan Karbing, Aachen, Germany: Model-based optimization of mechanical ventilation - from control to support modes
11:00 – 11:20	Christian Putensen, Germany: Short and Mid-range Transport of Patients in ARDS
11:20- 11:40	Jeremy Cannon MD, San Antonio, Texas, USA. The ECMO TAXI
11:40- 12:00	Open microphone discussion.
12:00- 13:00	**Working lunch in the Elizabeth Hall.** Questions and Answers session. Meet the Editor of Journal of Critical Care: Philip D. Lumb, M.B., B.S., MCCM Professor and Chairman, Department of Anesthesiology Keck School of Medicine, University of Southern California, USA. Editor in Chief, Journal of Critical Care
	Meeting Session 5. Title: Modeling Coagulation Function and Dysfunction Moderators: Sven Zenker, Bonn, Germany; Yoram Vodovotz, Pittsburgh, USA
13:00 – 13:20	Janos Fazakas, Semmelweis University, Budapest: Coagulation disturbances in trauma
13:20 – 13:40	Nithiananthan Mayooran, S. Fong, Ajayi Olushola, Patrick O'Keefe, Sinead O'Gorman, Doneagal, Ireland: Head injury on warfarinized patients, can we predict the bleed?
13:40 – 14:00	Mitch Cohen, UCSF, San Francisco, USA: Modeling Acute Traumatic Coagulopathy
14:00 – 14:20	Linda Petzold, San Francisco, USA: Toward a data driven model of trauma dynamics
14:20 – 14:50	Open microphone discussion
14:50 – 15:00	Break, refreshments.
	Meeting Session 6. Title: Best of the Best talks from Poster sessions and Industry. Moderators: Tilmann Schwab, Maquet; Marcus Osypka, Germany, Laura Lund, USA and Sophia Zhou, Phillips, USA
15:00 – 15:10	James Biondi, Cardiopulmonary Corporation, USA: Real-time data extraction: the missing piece of modern critical care
15:10 - 15:20	Best of the Best Abstracts: Mary Mohr, Manisha Patel, Hoshik Lee, Matthew Clark, Douglas Lake, Brooke Vergales, John Kattwinkel, Randall Moorman, Karen Fairchild, John Delos: Automated Detection and Characterization of periodic Breathing in Preterm Infants
15:20 - 15:30	Industry talk/ Maquet: Tilmann Schwab MD, Clinical Director Advanced Therapies MAQUET Cardiovascular
15:30 - 15:40	Best of the Best Abstracts: Alistair Ew Johnson; Andrew Kramer; Gari Clifford: Measures of RR Interval Complexity are Predictive of Mortality in a General ICU population
15:40 – 15:50	Industry talk/Alung Inc. Laura Lund PhD, Pittsburgh, Philadelphia, USA: Hemolung as therapy for CO_2 retention syndromes
15:50 – 16:00	Best of the Best Abstracts: Best of the Best Abstracts: Mehmet Suzen, Andreas Hoeft, Sven Zenker: Can Arterial Pressure Serve as a Surrogate for Cardiac Output when Evaluationg Patient Response to Hemodynamic Interventions? A Simulation Study.

16:00 – 16:10	Industry talk/Osypka medical, Germany/USA: Aesculon in Critical Care Monitoring
16:10 – 16:20	**Coffee break**
16:20 - 16:30	Best of the Best Abstracts: Ruben Zamora, Cordelia Ziraldo, Rami Namas, Khalid Almahmoud, Victor Tapias, Qi Mi, Derek Barclay, Bahiyyah Jefferson, Guoqiang Chen, Timothy Billiar, Yoram Vodovotz: Central Role for MCP-1/CCL2 in Injury-Induced Inflammation Revealed by In Vitro, In Silico, and Clinical Studies
16:30 – 16:40	Industry talk/Bellco: Combination therapy using minimally invasive CO_2 removal and continuous renal replacement therapy
16:40 – 16:50	Best of the Best Abstracts: Sabrina Camargo, Maik Riedl, Celia Anteneodo, Jurgen Kurths, Niels Wessel: Nonparametric Segmentation of Hear Beat Intervals
16:50 – 17:00	Abstract Wild Card: Hari Radhakrishnan, John Harvin, Matthew Pommering, Charles Wade, John Holcomb, Houston, USA: An advanced algorithm for predicting mortality using simple parameters obtained early in the hospitalization of a trauma patient
17:00 – 18:00	**Poster session #2 with formal reviews and 5 min presentations.** Second half of Abstracts selected for posters (check on site for final updated poster numbers and display times). Abstract review committee: Gary An, Randall Moorman, Wassim Haddad, Sophia Zhou, Marie Csete
18:30 – 18:45	**Departure by bus to Gala dinner. Meet at Marriott front desk**
19:00-22:00	**Tour of the Hospital in the Rock Museum (World War II underground hospital) followed by Hungarian style entertainment and dinner at "Szeker Csarda" folklore center**

Sunday, August 11

7:00 – 7:45	Continental breakfast, Peppers Restaurant, main floor Marriott (free for all registered attendees residing at the conference hotel (Marriott)
	Meeting Session 7. Clinical applications of Complexity Science. **Moderators: Timothy Buchman, Emory, Atlanta, USA and Wassim Haddad, Atlanta, USA**
8:00 – 8:10	Abstract Wild Card: Edward Pugh, Anirudh Thommandram, Carolyn McGregor, Mikael Eklund, Andrew James, University of Toronto, Canada: Classifying neonatal spells using real-time temporal analysis of physiological data streams-verification tests
8:10 - 8:30	Andrew Seely, Ottawa, Canada: Making WAVE's in Critical Care or predicting extubation outcomes with heart and respiratory rate variability
8:30 – 8:40	Abstract Wild Card: Andrea Bravi, Christophe Herry, Andrew Seely, Andre Longtin: What is the meaning of heart rate variability?
8:40 – 9:00	John Doyle, Caltech, USA: What Complexity in Critical Illness Means for a Mathematician
9:00-9:20	SepsEast Speaker – Béla Fülesdi, Department of Anesthesiology and Intensive Therapy, University of Debrecen, Monitoring septic encephalopathy

9:20-9:40	Soojin Park. Philadelphia, USA: Smart Alarms and Decision Caddies: Clinical Decision Support in Critical Care
9:40 – 10:00	**Break, refreshments**
10:00 – 10:20	Nicolas Chbat, Principal Scientist, Clinical Decision Support Solutions Dept., Philips Research North America, Briarcliff Manor, New York The title of the talk: Critical Care Forecasting - Acute Respiratory Distress Syndrome
10:20- 10:40	Bela Suki, USA/Hungary: Externally applied variability improves lung function during mechanical ventilation
10:40 – 11:00	Break, refreshments
11:00- 11:20	Joydeep Sarkar PhD, Pittsburgh, USA: Application of Clinical Decision Support Technology in Fluid Management of Burn Patients
11:20- 11:40	Gilles Claremont MD, Pittsburgh, USA: Predicting cardiopulmonary decompensation in step-down unit patients
11:40- 12:00	Wassim Haddad, Atlanta, USA: Clinical Decision Support and Closed-Loop Control for Cardiopulmonary Management and Intensive Care Unit Sedation Using Expert Systems
12:00-13:00	**Lunch. Adjourn of SCAI 2013. Closing remarks Andriy Batchinsky, USA**
13:00-15:00	*International workgroup meeting on minimally invasive extracorporeal life support.* *Moderator: Andriy Batchinsky, USA. Title: Toward clinical practice guidelines for minimally invasive ECLS.* *Participants: Phillip Lumb M. D.,* B.S., MCCM, (USA); *Jeremy Cannon MD (San Antonio, Texas); Christian Putensen (Bonn, Germany); Thomas Langer (Milan, Italy); Alberto Zanella (Monza, Italy); Balazs Szamosfalvi, (Detroit, USA); Philippe Morimont (Liege, Belgium); Gilles Clermont (Pittsburgh, USA); Marian Walther PhD, (Germany); George Pantalos, (Louisville, KY, USA.* *Industry: Representative Alung (Pittsburgh, USA); Represenatitve (Bellco, Italy); Representative Maquet (Germany-USA).*
15:00-16:00	***International workgroup coordination meeting***

1 (Selected for poster)

QUANTITATIVE INVESTIGATION OF THE IMPACT OF NOISE ON HEART-RATE VARIABILITY AND COMPLEXITY ANALYSIS IN TRAUMA PATIENTS

NEHEMIAH LIU 1, ANDRIY BATCHINSKY 1, LEOPLODO CANCIO 1, JOSE SALINAS 1

1. U.S. Army Institute of Surgical Research

Objectives: Despite extensive studies in the past few decades on the significance and meaning of the many different measures of heart-rate variability and complexity (HRV, HRC), few studies exist to assess the influence of noise on these measures. The aims of this study were to review selected measures of HRV and HRC and investigate how noise affects metric calculations, particularly, relationships between mean values corresponding to trauma patients who received at least one life-saving intervention (LSI) and those who received none. **Methods:** 108 pre-hospital trauma patients with blunt or penetrating injuries admitted to a Level I trauma center in Houston, TX were selected based upon availability of electrocardiogram (ECG) waveform data and manual verification of all R-R interval (RRI) sequences. 82 patients received at least one LSI, while the remaining 26 patients received none. ECGs were approximately 15 to 20 minutes long and acquired at a sampling frequency of 375 Hz. Noise was defined to be any source that alters the true RRI sequence of an ECG, and consequently, modifies calculation of an ECG-derived metric. Noise was both simulated and naturally obtained. Artificial modifications of RRI sequences corresponding to patient records were carried out by dropping every Mth multiple of the true RRI sequence for M = 10, 9, ., 1. Furthermore, ECGs of patient records were loaded into an in-house-developed R-wave detection algorithm in order to produce detected RRI sequences. Selected metrics were calculated afterwards and means between LSI and non-LSI patient groups were then compared using Wilcoxon tests. The gold standard for obtaining true means was manual verification of R waves and subsequent metric calculations. **Results:** There were no significant differences between LSI and non-LSI patients in age, gender and transport time, and 82 patients underwent 142 LSIs. Mean age was 37±14, 76% were male, 86% suffered blunt injury, and injury severity score was 17±11. Furthermore, numerical relationships between mean values of patient groups were preserved, regardless of noise derivation (LSI versus non-LSI; sample entropy: 0.8±0.3, 1.1±0.4, p=0.002; quadratic sample entropy: 3.0±0.9, 3.5±0.7, p=0.004; multiscale entropy: 0.5±0.4, 1.0±0.6, p=0.001; Poincaré variability ratio: 0.5±0.2, 0.4±0.2, p=0.370; fractal scaling exponent: 1.0±0.2, 0.9±0.2, p=0.101; autocorrelation coefficient: 0.1±0.1, 0.1±0.0, p=0.004; degree of nonstationarity: 0.7±0.2, 0.6±0.2, p=0.039; standard deviation: 45.8±60.6, 40.4±25.7, p=0.309; successive differences: 44.5±70.3, 35.7±31.3, p=0.454). However, for detection-derived measures, there were only statistical differences ($p<0.01$) between groups for entropy measures and autocorrelation. Importantly, p-values for sample and multiscale entropy were the lowest of all measures. **Conclusions:** This study demonstrated that under some noisy environments, selected measures of HRV and HRC can still discriminate between patient groups. In particular, sample and multiscale entropy have predictive power and promising clinical use for the trauma patient cohort.

2 (Selected for poster)

THE PROGNOSTIC VALUE OF MULTISCALE ENTROPY IN MOUSE MODELS OF SEPSIS AND A NOVEL SCORING METHODOLOGY

BENJAMIN VANDENDRIESSCHE 1, ELKE ROGGE 1, OLIVER STIEDL 2, PETER BROUCKAERT 1, ANJE CAUWELS 1

1. VIB - Ghent University 2. CNC - VU Amsterdam

Objectives: Sepsis is associated with high mortality despite decades of research. It has been well established that the sympathetic/parasympathetic balance is altered in critically ill patients, and that assessment of autonomic function has prognostic value that can be used to direct treatment. However, due to a lack of validated intermediary endpoints and biomarkers predictive for the outcome in the frequently used animal models of septic shock, a problematic disconnect in “bench-to-bedside” translation exists. The extrapolation of experimental data is far from straightforward, indicating the need for proper markers that have a similar profile in both groups. **Methods:** Implantable telemetry devices (Data Sciences International) were used to monitor blood pressure (BP) and heart rate in conscious mice, continuously after a shock-inducing challenge. From this data, linear (time domain and frequency domain) and nonlinear indices (detrended fluctuation analysis and multi-scale entropy) of BP variability (BPV) were derived. In addition, we developed a scoring methodology that captures the information embedded in an MSE profile in a single value, allowing more straightforward follow-up of disease progression as a function of time. **Results:** As proof of principle, we first determined these indices on BP measurements from mice that were injected intravenously with varying doses of tumor necrosis factor (TNF). In retrospect, the animals were grouped according to outcome. Challenge with TNF causes morbidity, hypotension, bradycardia, organ failure and finally death, similar to other shock-inducing stimuli. As such, the TNF model is a useful tool for the reproducible study of a simpler subset of the complex septic shock phenomenon. We found that only multiscale entropy (MSE) has early prognostic value in the TNF model, predicting outcome already in the first 2 hours post-

challenge, independent of the administered dose. Preliminary data indicates that this observation can be expanded to other –more complex– models of sepsis (i.e. endotoxemia and cecal ligation and puncture). To deal with the fact that a single MSE profile contains a lot of information, we developed the MSE Scoring (MSES) methodology which summarizes an MSE profile in a single value, and allows easy monitoring of loss of complexity behavior over time in the different animal models. **Conclusions:** MSE and MSES capture changes in complexity behavior very early after challenge with a shock-inducing stimulus that can predict outcome before this is possible with any other (absolute or derived) parameters. Similar methods will be applied to data obtained from septic ICU patients (Ghent University hospital) in order to test the translational possibilities of this approach.

3 (Selected for podium)

CENTRAL ROLE FOR MCP-1/CCL2 IN INJURY-INDUCED INFLAMMATION REVEALED BY IN VITRO, IN SILICO, AND CLINICAL STUDIES

RUBEN ZAMORA 1, CORDELIA ZIRALDO 1, RAMI NAMAS 1, KHALID ALMAHMOUD 1, VICTOR TAPIAS 1, QI MI 1, DEREK BARCLAY 1, BAHIYYAH JEFFERSON 1, GUOQIANG CHEN 1, TIMOTHY BILLIAR 1, YORAM VODOVOTZ 1

1. University of Pittsburgh

Objectives: The translation of in vitro findings to clinical outcomes is often elusive. Trauma/hemorrhagic shock (T/HS) results in hepatic hypoxia that drives inflammation. We hypothesize that in silico methods would help bridge in vitro hepatocyte data and clinical T/HS, in which the liver is a primary site of inflammation. **Methods:** Primary mouse hepatocytes were cultured under hypoxia (1% O2) or normoxia (21% O2) for 1-72 h, and both the cell supernatants and protein lysates were assayed for 18 inflammatory mediators by Luminex™ technology. Statistical analysis and data-driven modeling were employed to characterize the main components of the cellular response. **Results:** Statistical analyses, hierarchical and k-means clustering, Principal Component Analysis, and Dynamic Network Analysis suggested MCP-1/CCL2 and IL-1 -mediated inflammation in C57BL/6 mouse hepatocytes. Hepatocytes from MCP-1-null mice had altered dynamic inflammatory networks. Circulating MCP-1 levels segregated human T/HS survivors from non-survivors. Furthermore, T/HS survivors with elevated early levels of plasma MCP-1 post-injury had longer total lengths of stay, longer intensive care unit lengths of stay, and prolonged requirement for mechanical ventilation vs. those with low plasma MCP-1. **Conclusions:** This study identifies MCP-1 as a main driver of the response of hepatocytes in vitro and as a biomarker for clinical outcomes in T/HS, and suggests an experimental and computational framework for discovery of novel clinical biomarkers in inflammatory diseases.

4 (Selected for poster)

COAGULATION MODELING FOR IMPROVED THROMBOSIS RISK PREDICTION

BART BAKKER 1, RENE VAN DEN HAM 1, HENK VAN OOIJEN 1

1. Philips Research

Objectives: Deep venous thrombosis is the most common preventable cause of death in the hospital, claiming between 100,000 and 200,000 lives per year in the US alone. A large number of cases can be prevented by the proper use of anti-coagulants. Such treatment has a strong side effect however: the risk of serious bleeding events. Optimal treatment therefore requires the accurate identification of those patients that are at strong risk of thrombosis, so that anti-coagulants are administered only to those who really need it. Our objective is to identify new and better ways to identify such high risk patients. **Methods:** At Philips Research we implement and improve existing methods for thrombosis risk estimation. We base our methods on insights in the biology that underlies the coagulation process, which we express in a large, quantitative computer model. This model so far describes the protein dynamics of the coagulation cascade in terms of ordinary differential equations (ODEs). The model is initially based on qualitative knowledge and quantitative constraints that are gathered from literature and has been further optimized based on laboratory experiments. The model takes the measured protein concentrations of a particular patient as inputs, and simulates the dynamics of each protein that is involved in the coagulation process under any circumstances that we may choose. **Results:** We show that the optimized model can be used to take the measured protein concentrations and translate them into more telling model outputs that much more strongly indicate patient specific thrombosis risk. We combine the distilled model features with classical, non-molecular features like recent surgery and patient immobility by use of a neural network, and show that we can significantly improve on existing risk estimation methods in terms of sensitivity and specificity. **Conclusions:** Classical thrombosis risk estimation methods can be strongly improved through the use of a quantitative model that simulates the biology underlying the coagulation process.

5 (Selected for poster)

ECG PREDICTS RESPONSE TO CARDIAC RESYNCHRONIZATION THERAPY ASSESSMENT BY MEANS OF COMPLEXITY INDEX

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Objectives: Cardiac resynchronization therapy (CRT) is effective in patients with HF with wide QRS. However CRT is only successful in about 70% of patients after implant; checking post-implant results is usually obtained by mean of clinic (NYHA class improvement) and instrumental (EF and LV volumes by mean of Echocardiogram) evaluation. Objective of the present study was to evaluate the association between the novel nonlinear index, calculated from ECG pre and post procedure, compared with traditional linear indices to assess the reliability and effectiveness in evaluating results of resynchronization therapy. **Methods:** We have used OntoCare System (OntoMed LLC, USA) to measure Cardiac resynchronization therapy (CRT) impact among patients (pts) who received (CRT) via pacemaker (CRT-P) or defibrillator (CRT-D) in combination with optimal pharmacological therapy, according to guidelines. Particularly, we measured the impact of stimulation analyzing the ECG performed before and after implant. ECG Complexity values have been considered significant (the difference between basal and stimulated ECG) when â‰¥25%. The OntoCare system measures complexity analyzing the structure of information, in particular the multi-dimensional structure of the ECG, taking into account the interactions between ECG channels and establishing an innovative means of characterizing generic dynamical systems and biologic signals. **Results:** We retrospectively analyzed 87 pts ECG implanted with CRT in our Centre. NYHA class, LV ECHO measurements and EF pre and post implant have been analyzed and compared with Complexity values. The OntoCare system found that 69/87 pts (79%) had a significant impact of therapy (Complexity value threshold 25%), while in the remaining 18/87 pts (21%) there is no variation in the Complexity. We then compared the two groups, called Responder (R) and Non Responder (NR), respectively, with clinical and instrumental data in our possession. If we compare the values before and after the implant, we find that LVEDV changes from 190 ml to 159 ml (-31 ml; p=0,039) in R group, and from 214 ml to 201 ml (-13 ml; p=0,62) in NR group. The Ejection Fraction (EF) increases from 28.1 % to 37.2 % (+ 9.1%; p=0,0001) in R group and from 27.3% to 33.6% (+ 6.3%; p=0.0005) in NR group; NYHA Class changes from 2.84 to 1.69 (- 1.15; p=0.01) in R group and from 2.55 to 2.65 (+0.1; p=0.5) in NR group. **Conclusions:** Even if results are drawn from a small sample of patients with retrospective analysis, this study shows that the Complexity index is reliable and effective in providing prognostic data in patients implanted with CRT. In addition Complexity index shows a strong association with other parameters (EF, ECHO measurements, NYHA class) traditionally used to evaluate efficacy of CRT.

6 (Selected for poster)

AUTOMATIC HEART-RATE COMPLEXITY MONITORING IN A SWINE MODEL OF CARDIAC ARREST DUE TO MASSIVE EXSANGUINATION

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Objectives: Carry out automated real-time calculation of heart rate complexity as measured by sample entropy during lethal hemorrhagic shock. **Methods:** Under midazolam sedation (320.5 ± 85.6 mL dose over the experiment), 4 female Yorkshire pigs were subjected to computer-controlled exponential withdrawal of up to 73.2 ± 16.4 % of the estimated blood volume (EBV) via femoral and carotid arterial catheters. Continuous real-time unsupervised measurements of heart rate complexity, as assessed by the method of Sample entropy (HRC), were carried out using an FDA-approved monitor (Aesculon, Osypka medical/Cardiotronics, La Jolla, CA). The following parameters were recorded: heart rate (HR, bpm), mean arterial pressure (MAP, mm Hg), mean pulmonary artery pressure (Mean PAP, mm Hg), central venous pressure (CVP, mm Hg), pH, partial arterial pressure of carbon dioxide (PaCO¬2, mm Hg), Lactate, mmol/L, base excess (BE, mmol/L) and heart rate complexity (HRC). Measurements were recorded at each level of hemorrhage to include cardiac arrest (CA) defined as sustained mean aortic pressure of 20mm Hg. ECG data was not reviewed manually, cleaned or modified. Data were compared during timepoints with one-way ANOVA with post-hoc Dunnett's test. Data are presented as means ± SD.

Results:

Variable	Baseline	25% TBVH	44% TBVH	62% TBVH	CA (~67% TBVH)	*p*-value
HRC	0.7 ± 0.3	0.7 ± 0.2	0.4 ± 0.3	0.5 ± 0.1	0.4 ± 0.3	0.15
HR, bpm	98.3± 27.0	167.3± 93.75	162.0 ± 51.9	167.5 ± 69.5	125.7 ± 74.0	0.37
MAP, mm Hg	100.0 ± 11.4	82.0 ± 19.03	59.5 ± 22.5*	34.3 ± 3.5*	16.7 ± 3.8*	<0.001
Mean PAP, mm Hg	26.5 ± 2.6	23.8 ± 9.6	19.5 ± 4.2	11.3 ± 2.1*	11.5± 2.4*	0.007
CVP, mm Hg	7.8 ± 2.2	4.8 ± 1.9	4.8 ± 2.5*	2.7 ± 2.5*	6.0 ± 3.3*	0.013
pH	7.3 ± 0.04	7.3 ± 0.08	7.3 ± 0.05	7.4 ± 0.05	6.9 ± 0.5	0.15
$PaCO_2$, mm Hg	52.3 ± 4.9	49.8 ± 6.2	42.1 ± 9.5	39.7 ± 3.9	81.9 ± 54.7	0.24
Lactate, mmol/L	4.6 ± 2.0	5.7 ± 2.7	6.5 ± 2.8	7.1 ± 2.9	6.9 ± 2.3	0.72
BE, mmol/L	2.0 ± 3.6	-2.3 ± 3.1	-3.0 ± 3.7	-2.7 ± 3.2	-12.0 ± 14.0	0.06

* indicates Dunnett's post-hoc test p value <0.05 when compared to baseline measurements

Conclusions: This preliminary data from an ongoing study shows that absolute changes in HRC trend toward reduction with loss of volume although did not reach statistical significance in this small dataset due to sample size. Real-time automatic calculation of HRC is viable for monitoring of profound exsanguination.

7 (Invited podium)

EXTERNALLY APPLIED VARIABILITY IMPROVES LUNG FUNCTION DURING MECHANICAL VENTILATION

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Objectives: The accepted protocol to ventilate patients with acute lung injury is to use low tidal volume (VT) in combination with recruitment maneuvers or positive end-expiratory pressure (PEEP). However, an important aspect of mechanical ventilation has not been considered: the combined effects of PEEP and ventilation modes on the integrity of the epithelium. Additionally, it is implicitly assumed that the best PEEP-VT combination also protects the epithelium. We aimed to investigate the effects of ventilation mode and PEEP on respiratory mechanics, peak airway pressures and gas exchange as well as on lung surfactant and epithelial cell integrity in mice with acute lung injury. We also hypothesized that adding external variability to VT will improve lung biology and function. **Methods:** HCl-injured mice were ventilated at PEEPs of 3 and 6 cmH2O with conventional ventilation (CV), CV with intermittent large breaths (CVLB) to promote recruitment, and a new mode, variable ventilation, optimized for mice (VVN). Mechanics and gas exchange were measured during ventilation and surfactant protein (SP)-B, proSP-B and E-cadherin levels were determined from lavage and lung homogenate. **Results:** PEEP had a significant effect on mechanics, gas exchange and the epithelium. The higher PEEP reduced lung collapse and improved mechanics and gas exchange but it also down regulated surfactant release and production and increased epithelial cell injury. While CVLB was better than CV, VVN outperformed CVLB in recruitment, reduced epithelial injury and, via a dynamic mechanotransduction, it also triggered increased release and production of surfactant. **Conclusions:** For long-term outcome, selection of optimal PEEP and ventilation mode may be based on balancing lung physiology with epithelial injury.

8 (Invited podium)

RIGHT VENTRICULO-ARTERIAL COUPLING IN ARDS AND EXPECTED BENEFITS OF CO2 REMOVAL THERAPY

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Objectives: The cardiovascular system works better when the heart and the arterial system are coupled. Protective ventilation is a beneficial adjunct to the strategies of mechanical ventilation in ARDS. However, hypercapnia and acidosis due to lower tidal volume may lead to right ventricular (RV)-arterial uncoupling. As a result, the effects of CO2 removal on RV-arterial coupling and cardiovascular performance could be beneficial. **Methods:** RV-arterial coupling and cardiovascular performance can be assessed by the ratio of two elastances: Ees/Ea, where Ees is the RV elastance characterizing the RV system and Ea is the arterial elastance characterizing the pulmonary vascular system. When Ees/Ea is > 1, the system is coupled. However, when Ees/Ea is < 1, the system is uncoupled. This ratio is related to mechano-energetic aspects of heart-arterial coupling. It can be demonstrated that efficiency of energy transfer from the RV to the pulmonary circulatory system is optimal when Ees/Ea = 2 while mechanical RV work is maximal when Ees/Ea = 1. Ea is defined as a steady-state arterial parameter that incorporates the 4-element windkessel model of the pulmonary vascular bed. Ea is computed by combining the pulmonary vascular compliance, the characteristic impedance, and the resistance of the main pulmonary vessels, as well as the pulmonary peripheral resistance. Ea can also be simply assessed by the steady-state ratio of end-systolic pressure to stroke volume. This ratio can be easily obtained from steady-state ventricular pressure-volume measurements. Ees is the slope of the RV end-systolic pressure-volume relationship. Ees is a load independent index of RV contractility. Calculation of Ees requires preload variation. In experimental settings, preload reduction is obtained by inflating a balloon in the inferior vena cava. In clinical practice, variation of preload resulting from respiratory pressure changes (or PEEP levels) can be used to determine end-systolic points. **Results:** There is strong evidence that pulmonary vessels constrict during hypoxia, hypercapnia, and acidemia. High CO2 tension with elevated hydrogen ion concentration in the blood increases the extracellular Ca++ influx, which is thought to be the main cause of vasoconstriction in the pulmonary circulation. CO2 usually causes weak vasoconstriction under normal vascular tone. Addition of acid also causes vasoconstriction, whereas alkali administration causes vasodilation. As vasoconstriction induces an increase in Ea, RV contractility (Ees) should increase in order to maintain coupling. However, hypercapnic acidosis leads to decreased RV contractility. As a result, hypercapnia and acidosis are responsible for uncoupling. CO2 removal therapy could restore RV-arterial coupling by reducing deleterious effects of hypercapnia and acidosis on vascular tone and RV contractility. **Conclusions:** RV-arterial coupling and cardiovascular performance during ARDS can be severely compromised because hypercapnia and acidosis increase pulmonary arterial elastance while decreasing RV elastance. Continuous low flow CO2 removal therapy could help to restore optimal RV-arterial coupling and improve prognosis.

9 (Selected for poster)

CARDIORESPIRATORY PHYSIOLOGICAL DATA AS AN INDICATOR OF FENTANYL PHARMACOKINETICS AND PHARMACODYNAMICS IN CRITICALLY ILL NEWBORN INFANTS: A CASE REPORT

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Objectives: Critically ill premature infants are subjected to multiple interventions while in the Neonatal Intensive Care Unit (NICU) that range from routine handling to invasive, potentially painful, procedures such as endotracheal intubation, the insertion of chest drains, and surgery. The effects of continuous and prolonged intravenous infusion of opioid analgesics range from heart rate variability fluctuation1 to an increase of sensitivity to noxious stimuli that may evolve to a painful response to non-noxious stimuli known as opioid-induced hyperalgesia2. The provision of optimal analgesia, without pharmacologically induced side or adverse effects, during these procedures is a major challenge for neonatologists. The objective of this report is to describe our preliminary experience with the use of cardiorespiratory physiological data streams and drug infusion data from the Artemis Project3 to analyse fentanyl pharmacokinetic and pharmacodynamic (PKPD) behavior in a population of premature babies in the NICU. The Artemis platform is a framework for concurrent multi-patient and multi-stream temporal analysis in real-time for clinical decision support and retrospective clinical research. The relationship between estimated drug concentration and both heart rate variability (HRV) and respiratory rate variability (RRV) should provide insights about fentanyl's pharmacodynamics in the population of premature infants. **Methods:** A critically ill female preterm infant, gestational age 27 weeks, birth weight 997 grams, enrolled in the Artemis

project is the subject of this case report. The infant presented with severe respiratory distress due to maturational surfactant deficiency that was managed with surfactant replacement therapy and high frequency jet ventilation at 240 breaths/minute. Cardiorespiratory physiological data (heart rate, respiratory rate, blood pressure), drug infusion data (drug infusion rate [ml/h]), drug dose and drug concentration), and the infant's Premature Infant Pain Profile score (PIPP)4 were captured using the Artemis platform. HRV and RRV were calculated using CRISP-TDMn5 and STDMn06. Plasma and effect site concentrations (Cp/Ce) were simulated by the PKPD modeling module of the Artemis platform7. Encinas' PKPD8 model for fentanyl was used in this retrospective analysis. HRV and RRV were analysed using the estimated Cp/Ce at the specific point in time. Data from the periods of the infant's NICU hospital course were used for the analysis of the relationship between drug concentration, HRV, RRV and PIPP score. **Results**: A fentanyl Ce=0.02µg/ml was correlated with a low HRV, statistical significance p=0.01 ($p<0.05$) and a PIPP score of 6. The infant's PIPP score was 9 before the increased fentanyl drug dose. There was no detectable effect on RRV for this infant whose respiratory failure was managed with high frequency jet ventilation at 240 breaths/min. **Conclusions:** This case study demonstrates that a high concentration of fentanyl in this critically ill premature infant is associated with a reduction in PIPP score and correlates with decreased HRV. The estimated effect-site concentration correlations with low HRV suggests that high fidelity cardiorespiratory physiological data could serve as an indicator for fentanyl`s pharma codynamics as well as controller variable for a novel Pain Profile index.

10 (Selected for poster)

CONTRASTING PAIRED SIGNALS ARISING FROM THE SAME PHYSIOLOGICAL PROCESS

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Objectives: Consider a setting where three signals, X, Y, and S, are simultaneously measured on each of n subjects over T equally spaced time points t, where X, Y, and S are alternative measures of the same physiological process, S is considered a gold standard, and the degree of closeness of X and Y to S is of interest. X and Y may for example arise from two competing devices where one device may be considered better than the other if its signal is closer to S than its competitor. **Methods:** The null hypothesis, Ho, is that X and Y are equally close to S. We sought a statistical procedure to test Ho while addressing the paired and repeated measures nature of the data. A solution is to conduct a paired t-test on within-subject squared differences summed over time. Specifically, compute the within-subject squared difference between the ordinates at each time point t for X and S and sum over the T time points to obtain $\sum(Xt - St)2$, do the same for Y and S and to get $\sum(Yt - St)2$ and then, for each of the n subjects, compute the within-subject difference $D = \sum(Xt - St)2 - \sum(Yt - St)2$ between these sums and test the null hypothesis that the mean of D is zero using a paired t-test. A similar approach can be used by first fitting a wavelet model to each signal and computing within subject squared differences of wavelet coefficients. Finally, a Fourier model can be used in place of a wavelet model. **Results:** We applied these methods to 3 measurements of stroke volume, where X and Y were signals produced by competing devices and S was a gold standard signal. All three approaches, original units, wavelet coefficients, and Fourier coefficients, gave consistent results. **Conclusions:** This approach provides a readily programmable method to test the null hypothesis in the sometimes difficult design with a small number of subjects, a large number of measurements per subject, and paired measurements.

11 (Invited podium)

RETHINKING PARACRINE EFFECTS OF STEM CELL THERAPIES

MARIE CSETE

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Objectives: Almost 4500 stem cell-related clinical trials are registered with clinicaltrials.gov. Most are designed around using stem cell therapies for paracrine trophic effects rather than for true regeneration. Although mechanism of action is not required for early clinical trials, the assumption of positive trophic activity of stem cells underlies most study design to date. Our work and that of others suggest that this assumption requires fundamental re-examination, especially in light of anticipated stem cell trials for sepsis. Objectives: (i) Review of published an unpublished data showing specific therapeutic mechanisms of action of stem cells independent of secreted trophic factors. **Methods:** With Emory IRB approval, unilateral chronic constriction injury of (male, S-D) rat sciatic nerve was used as an ischemic nerve injury model (n=24). Ischemic injuries are common clinical trials targets for stem cell therapies (MI, stroke, trauma, CLI, etc.) At end of surgery with rats still anesthetized, freshly isolated syngeneic bone marrow mononuclear cells were injected via tail vein in half the rats, PBS in the controls. At ten days, pain behavior was quantified, animals euthanized, and protein isolated from sciatic nerves. Standard western blots were used to examine candidate regulators (heat shock proteins, endothelin axis) of the analgesic response as a function of BMMC injection. **Results:** BMMCs mediated a potent anti-analgesic effect for both temperature and mechanical sensitivity. Westerns for heat shock protein abundance showed that HSP32 was specifically upregulated in both injured and uninjured sciatic nerve as a function of BMMCs. Endothelin A receptor was

downregulated in injured nerve as a function of BMMCs. Endothelin B receptor levels were unchanged. In principle, upregulation of HSP32 results in increased CO production; CO is a potent vasodilator. Downregulation of endothelin A signaling results in reduced vasoconstriction. Together these results suggest that local control over vascular tone at the site of ischemic injuries may mediate some of the SC therapeutic response in ischemic injuries. Other mechanisms emerging in the literature include exosome secretion, mitochondrial transfer, and anti-bacterial effects, providing a new view of the mechanism of action of stem cell mediated cytoprotection. **Conclusions:** These 'new' potential therapeutic mechanisms of stem cells suggest that modification of the environment (vasodilation, anti-bacterial effects), and changes in energy metabolism, redox potential and secondary effects of redox on transcription play important roles in 'paracrine' effects of stem cells, independent of secreted classical growth factors. These mechanisms have important implication for the choice of particular cell subpopulations for therapy and the optimal target patient populations in clinical trials design. Further evaluation of these mechanisms may make it possible to design potency assays that predict clinical efficacy.

12 (Selected for poster)

MODELING NON-UNIFORMITY OF LEFT VENTRICULAR RELAXATION IN ACUTE MYOCARDIAL ISCHEMIA

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Objectives: The time constant of left ventricular (LV) relaxation derived from a monoexponential model is widely used as an index of LV relaxation rate, although this model does not reflect the non-uniformity of LV pressure fall during isovolumic relaxation. In the present study, we investigated in anaesthetized pigs whether the relaxation curve can be better fitted with a "quadratic" model than with the "conventional" monoexponential model and if changes in LV relaxation waveform due to acute myocardial ischemia could be better detected with the quadratic model. **Methods:** Isovolumic relaxation was assessed with quadratic and conventional models during acute myocardial ischemia performed in 6 anesthetized pigs. Phase plane analysis of LV pressure fall derived from combined conductance-micromanometer catheter was achieved. Mathematical development indicates that one parameter (Tq) of the quadratic model reflects the rate of LV relaxation, while the second parameter (K) modifies the shape of the relaxation curve in the time space. **Results:** Analysis of experimental data obtained in pigs showed that the shape of LV relaxation consistently deviates from the conventional monoexponential decay. During early phase of acute myocardial ischemia, the rate and the non-uniformity of LV relaxation, assessed with the quadratic function were significantly enhanced. Tq increased by 16% ($p<0.001$) and K increased by 12% ($p<0.001$) within 60 minutes after left anterior descending (LAD) coronary artery occlusion. However, no significant changes were observed with the conventional monoexponential decay within 60 minutes of ischemia onset. **Conclusions:** The quadratic model better fits LV isovolumic relaxation than the monoexponential model and can detect early changes in relaxation due to acute myocardial ischemia undetectable with the conventional method.

13 (Invited podium)

THE RELATIONSHIP BETWEEN AUTONOMIC FUNCTION AND HEART RATE VARIABILITY IN HUMAN ENDOTOXEMIA

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Objectives: Analysis of heart rate variability (HRV) is a promising diagnostic technique due to the noninvasive nature of the measurements involved and established correlations with disease severity, particularly in inflammation-linked disorders. However, complexities underlying the interpretation of HRV complicate understanding the underlying mechanisms driving changes in HRV. Despite this, such interpretations are often found in the literature. We explored mathematical modeling of the relationship between the autonomic nervous system and the heart to illustrate the inherent challenges in straightforward interpretation of HRV data. Specifically, we focused on human endotoxemia, a well-established, controlled experimental model of systemic inflammation that provokes changes in HRV representative of acute stress. **Methods:** We studied two models linking the autonomic nervous system to the output of the heart. Both models consist of oscillating neurotransmitter concentrations (norepinephrine in the low frequency (LF) range, acetylcholine in the high frequency (HF) range) and an integral pulse frequency modulation (IPFM) model that combines sympathetic and parasympathetic influences, modeling the physiological function of the sinoatrial (SA) node. In one model (the linear model), autonomic oscillations are linearly combined at the SA node. In the other model (the nonlinear model), autonomic oscillations pass through a saturation function to mimic ligand-receptor kinetics before they reach the SA node. Based on these two models, we evaluated the relationship between changes in autonomic activity and HR/HRV by perturbing the mean levels of autonomic outputs and assessing changes in HR, low frequency (LF, 0.04-0.15 Hz) spectral

power, and high frequency (HF, 0.15-0.4 Hz) spectral power. Additionally, we explored how changes in HR/HRV observed in human endotoxemia (namely increased HR, decreased LF and HF, and decreased coupling between the autonomic nervous system and the heart) can arise from this general model structure. **Results:** Two features of our models contribute to a relationship between mean levels of autonomic activity and HRV. First, there is an effect related to the magnitude of the inputs to an IPFM model. As the mean value of the input to the IPFM model increases and thus heart beats become faster, variability decreases because successive intervals are more similar due to their closeness relative to the frequency of oscillations. Second, the inclusion of saturation, which only appears in the nonlinear model, results in oscillatory amplitude is blunted by saturation as the mean value of sympathetic or parasympathetic activity increases, thus leading to lower HRV. Under different regimes of autonomic signaling, these two effects can be either cooperative or competitive. For example, in the nonlinear model, HF power can either increase or decrease as parasympathetic activity increases, depending on which effect predominates due to the particular parametrization of the model. In the case of human endotoxemia, three hypothetical scenarios for autonomic function giving rise to these observed patterns of HR, HRV, and uncoupling in human endotoxemia were analyzed. These scenarios represent different types of autonomic modulation, receptor-level regulation, and uncoupling between the heart and autonomic nervous system that all produce similar outputs: (1) sympathetic and parasympathetic activities increase but sympathetic activity predominates and receptors are highly saturated; (2) sympathetic activity increases, parasympathetic activity decreases (or increases), and the heart experiences diminished sensitivity towards autonomic stimuli; and (3) the heart is uncoupled from the autonomic nervous system and changes in HR are driven by non-autonomic factors. **Conclusions:** By contrasting modeling results with published experimental data and analyses, we hypothesize that there exists significant uncertainty in the mechanistic implications of HRV changes in human endotoxemia. Multiple plausible alternative hypotheses, even in a relatively simple model-based framework, equally reconciled experimental results. This underscores the need for further experimental work towards unraveling the underlying mechanisms of autonomic dysfunction and HRV changes in systemic inflammation. Understanding the extent of information encoded in HRV signals is critical in appropriately analyzing prior and planning future studies.

14 (Invited podium)

MODEL-BASED SYNCHRONIZATION AND COUPLING ANALYSIS DURING SLEEP

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Objectives: The number of patients suffering from cardiovascular diseases increases unproportionally with the increase of the human population and aging, leading to very high expenses in the public health system. Therefore, the challenge of cardiovascular physics is to develop highly-sophisticated methods which are able to, on the one hand, supplement and replace ex-pensive medical devices and, on the other hand, improve the medical diagnostics with decreasing the patient's risk. **Methods**: Methods of cardiovascular physics are used to analyze heart rate, blood pressure and respiration to detect changes of the autonomous nervous system in different diseases. Data driven modeling analysis, synchronization and coupling analysis and their applications to biosignals in healthy subjects and patients with different diseases are presented. The symbolic coupling traces, defined as the symmetric and diametric traces of the bivariate word distribution, allow for a more reliable quantification of coupling and are compared with established methods like mutual information and cross recurrence analysis. **Results**: It is shown that the use of nonlinear approaches brings a significant improvement of fitting compared to linear models. Several transformations are highly similar within the individual groups, but significant different among the groups. The method of symbolic coupling traces is used to analyze and quantify time-delayed coupling of cardiovascular measurements during different sleep stages. Significant different regulatory mechanisms are detected not only between the deep sleep and the other sleep stages but also between healthy subjects and patients. **Conclusions**: The proposed coupling method may help to indicate pathological changes in cardiovascular regulation and also effects of continuous positive airway pressure therapy on the cardiovascular system. Moreover, newly derived synchronization methods of cardiovascular physics may help to find indicators for different health risks.

15 (Selected for podium)

NONPARAMETRIC SEGMENTATION OF HEART BEAT INTERVALS

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2. Humboldt-Universität zu Berlin

Objectives: The idea of the segmentation applied to time series is to provide patches of the signal where stationarity is verified. Instead of testing only the difference for the mean [Bernaola-Galvan 2001], we perform a nonparametric segmentation, taking into account the whole distribution, with all moments, especially mean and variance. We aim at characterize the nonstationarities present in three groups consisting of 15 young (YH; 11 females, 4 males, age 31±6 years)

and 18 elderly subjects (EH; 11 males, 7 females, age 50±7 years), and 15 patients suffering from congestive heart failure (CHF; 11 males, 4 females, age 56±11 years). **Methods**: For analysis, we consider the beat-to-beat intervals from 24 hours measurements of the electrocardiogram. The time series are segmented as follows: given a segment of a time series, a sliding pointer is moved in order to compare the two fragments, on the left (L) and the right (R) side of the pointer i. Then one selects the position imax that maximizes the normalized Kolmogorov-Smirnov (KS) statistics, D=DKS(1/nL+1/nR)^(-1/2), where DKS is the distance between the cumulative distributions of the samples in the left and the right fragment, and nL (nR) is the number of points to the left (right) of the pointer. After determining the position, imax, of the maximum value of D, Dmax, one checks the statistical significance (at a chosen significance level α=0.05) of a potentially relevant cut at imax by comparison with the result that would be obtained for a random sequence. If each resulting segment is greater than a defined minimum L0, then the pointer is set and the procedure is recursively applied, until no patch is segmented. **Results**: To quantify the nonstationarity, we obtain statistical values of the segmentation, which include not only segment length and jump size but also more sophisticated ones like the number of segments greater than 300, L>300, and %μ50. L>300 corresponds to approximately 5 min, the shortest required segment length of HRV analysis and %μ50 reflects the percentage of differences of the mean of two consecutive segments $|\mu i+1 - \mu i|$>50ms in an analogy to the standard HRV measure pNN50, the percentage of consecutive RR intervals differing by more than 50ms. We found high positive correlations of about 0.9 between %μ50 and the overall standard deviation as well as a negative correlation around 0.8 between L>300 and the normalized very low frequency power, VLF/P, linking the segmentation outcomes to standard measures. **Conclusions**: In this work we present the analysis of nonstationarities in heart rate by means of a nonparametric segmentation algorithm, being able to display differences between CHF and age-matched EH, as well as CHF and YH. Also, differences between YH and EH can be detected, showing the aging effect in the loss of complexity of the heart rate ($p < 0.05$). Through the outcomes of segmentation we have access to time characteristics of the signal that were no longer available, making possible a different approach to quantify nonstationarities in HRV analysis. Results are in agreement with previous knowledge and do not require arbitrary thresholds or excludes fragments of the time series.

16 (Selected for poster)

ESTIMATION OF ECG DERIVED RESPIRATORY POWER FOR APNEA DETECTION AND CONTINUOUS MONITORING

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Objectives: An important side effect of sleep apnea is the tiredness during the day, resulting from the lack of continuous sleep. This can lead to episodes of micro-sleep with possibly fatal consequences in cases where heavy machinery is being operated. Multiple government bodies are now considering mandatory sleep diagnostics for long-haul truck drivers. Since the diagnostics of sleep apnea involves up to two nights in a sleep laboratory, an effective screening methodology is needed to avoid overexerting existing infrastructure. **Methods**: We propose the use of the ECG, where established means for ambulatory long-term recordings exist. We use the existence of multiple independent embeddings of respiratory activity in the ECG. These have physical, the rotation of the electrical axis due to respiratory movement, as well as neural sources as in the case of respiratory sinus arrhythmia. Since each of these embeddings is noisy and infrequently sampled a means to integrate the information of all embeddings is needed. Our approach combines the signals on the basis of their estimated spectral power densities, while an estimation of the instantaneous respiratory rate allows us to exclude noise in bands not relevant to respiration. The resulting integrated spectrum can be used to estimate respiratory power from which the Respiratory Power Index can be calculated, a surrogate for the widely used apnea-hypopnea-index. **Results**: When applying our algorithms blinded to a test data set, we achieved a Pearson correlation coefficient of 0.833 comparing our index to an index based on apneas as scored by qualified technicians. **Conclusions**: While developed for apnea-detection we believe this method can be applied to a clinical context where ECG monitoring is standard and could thus be easily extended to provide continuous respiratory monitoring.

17 (Selected for podium)

CAN ARTERIAL PRESSURE SERVE AS A SURROGATE FOR CARDIAC OUTPUT WHEN EVALUATING PATIENT RESPONSE TO HEMODYNAMIC INTERVENTIONS? A SIMULATION STUDY

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Objectives: Clinically, arterial pressure (AP) response is often used as a surrogate for the physiologically potentially more relevant cardiac output (CO) response when titrating hemodynamic therapy. The determinants of such agreement or disagreement under therapeutic interventions (TI) are not fully understood. We therefore investigate the agreement of CO and AP trends under volume resuscitation (VR), changes in pure pressor (PT) and pure inotrope therapy (IT), and simultaneous PT/IT (PIT) with computer simulations using a simple mathematical model of the cardiovascular system for diverse simulated patient conditions. **Methods**: The mathematical model (Zenker et al., PLoS Computational Biology 2007, 3(11): e204) consists of five nonlinear ordinary differential equations with a total of 22 initial conditions (IC) and parameters. Pure TIs are modeled as alterations of intravenous volume (VR), myocardial contractility (IT), and arteriole resistance (PT), respectively. We locally determined AP and CO responses to infinitesimal perturbations as derivatives with respect to the relevant ICs/parameters using forward sensitivity analysis with automated differentiation. In the case of PIT, the directional derivative along unit norm linear combinations of IT and PT basis elements were considered in 15 directions. Computations were implemented in MATLAB™ and C using SUNDIALS and ADOL-H libraries. We simultaneously varied pairs of model parameters/ICs combinatorially in the range of one tenth to four times the reference values to simulate diverse patient conditions, resulting in a total of 231 two-dimensional slices of parameter/IC space per TI. **Results**: AP and CO responses to VR, PT, and IT agreed in 79.00, 0.00, and 33.66%, were negligible in 13.52, 13.60, and 66.34%, and disagreed in 7.48, 86.40, and 0.00% of the investigated patient conditions, respectively. The regions of negligible intervention effects were found to be robust to the choice of numerical threshold and integrator tolerances. For PIT, we observed consistent alterations of response patterns when transitioning from pure IT towards pure PT: as the pressor component of the intervention grows, regions of negligible inotrope effects in simulated patient condition space exhibit disagreement first, followed by gradual and eventually total displacement of the agreement regions, with boundaries and their evolution showing non-trivial dependency on simulated patient condition. **Conclusions**: Disagreement of AP/CO trends under VR appeared to be largely driven by the dominance of baroreflex-mediated decrease of heart rate over the increase in stroke volume and will thus depend on the specific shape of the baroreflex response curve. The observed, rather homogeneous responses to pure IT (agreement or negligible effect) and pure PT (disagreement) are consistent with physiological expectations. The more realistic simulations of PIT revealed that even in this massively simplified simulation scenario, which, e.g., completely ignores chronotropic effects of hemodynamic interventions, agreement of AP and CO response to an intervention depends on patient condition in a non-trivial way. These results emphasize that using AP responses as a surrogate for CO responses may be misleading when evaluating effects of realistically available hemodynamic interventions in critically ill patients, who can be expected to suffer from severe and temporally varying perturbations of their physiological condition.

18 (Invited podium)

DEVELOPMENT OF BRAINSTEM INFLAMMATION CORRELATES WITH UNCOUPLING OF THE CARDIORESPIRATORY SYSTEM IN AN ENDOTOXEMIC RODENT MODEL

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Objectives: Disordered systemic inflammatory response to septicemia leads to multiple organ dysfunction syndrome (MODS), the major cause of death in intensive care units. Early detection is critical for survival, as mortality increases 5 fold in the first 2h with deterioration to septic shock (Kumar et al., Crit Care Med, 2006). Developing biomarkers would facilitate identifying deteriorating septic patients. We are applying novel and established analytical tools to assess heart rate (HRV) and ventilatory pattern (VPV) variabilities. In addition, we analyze the reciprocal interaction between the cardiac and respiratory systems using power spectral density of heart rate (HR) and respiration, as well as measuring cardio-ventilatory coupling (CVC) (Friedman et al., J Appl. Physiol, 2011.), the tendency for inspiration to begin at a preferred latency after the last heart beat in expiration. **Methods**: We theorize that expression of pro-inflammatory cytokines in the nucleus tractus solitarius (nTS) decreases the efficacy of sensory input and leads to the loss of cardiorespiratory coupling. First, we tested the hypothesis that cytokine expression in the nTS is associated with loss of HRV and CVC in adult male Sprague Dawley rats anesthetized with isoflurane; diaphragmatic EMG and ECG were recorded. After recording 'baseline' patterns, lipopolysaccharide (LPS) (24 mg/kg, n=7) or saline (n=3) was injected intraperitoneally. **Results**: After LPS injections (6h), HR and breathing frequency increased compared to baseline. CVC, which was significant (χ^2 analysis) in

frequency component of HRV remained. In subsequent experiments, we microinjected IL-1 ☐ (n=3) or
nTS bilaterally and mimicked the finding that CVC but not RSA disappears with LPS. Finally, we addressed the hypothesis that downstream products in the inflammatory cascade reduced synaptic efficacy in the nTS. Using an in situ horizontal medullary slice preparation that preserves the solitary tract, we performed patch-clamp recordings from putative second-order nTS neurons before and after application of PGE2 receptor agonists. Even though spontaneous excitatory postsynaptic currents (EPSCs) changed variably, evoked EPSCs decreased consistently after the agonist. **Conclusions**: In our endotoxemic model, brainstem inflammation occurs quickly and is associated with 'uncoupling' of the cardiorespiratory systems, reflected by the loss of CVC but not necessarily HRV. Our preliminary data indicate that early in sepsis, downstream IL-1 receptor signaling in the nTS decreases the efficacy of sensory input. This may be a mechanism attenuating the influence of the blood pressure on ventilation. We speculate that the additional loss of HRV that we observed in chronically instrumented rats depends on inflammation developing in other cardiorespiratory control nuclei downstream of the nTS. These data support the concept that CVC, which depends on the integration of baroreceptor afferent input, could serve as a sensitive biomarker for the inflammation in sepsis and, thus complement HRV.

19 (Selected for podium)

AUTOMATED DETECTION AND CHARACTERIZATION OF PERIODIC BREATHING IN PRETERM INFANTS

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Objectives: Periodic breathing (PB – also called periodic apnea) is a normal developmental phenomenon in preterm neonates that, if exaggerated, might be pathologic. From our point of view, it represents a common and easily detected oscillation of normal physiology that has unexplored clinical consequences. Characterization of PB has previously been limited to short monitoring times in small numbers of infants. We developed two new algorithms to quantify PB in Neonatal Intensive Care Unit (NICU) patients and sought clinical correlations. **Methods**: Waveform (EKG, chest impedance, pulseOx) and vital sign (heart rate, respiration rate, oxygen saturation) data were collected continuously on University of Virginia NICU patients from 2009-2012. There are 1438 patients in this dataset. 170 are extremely low birth weight (<1000 kg at birth) and 340 are very low birth weight (between 1000kg and 1500 kg at birth). Fourier transform and wavelet methods were developed for detecting PB. A previously developed apnea-recognition algorithm gives the probability of apnea as a function of time. The Fourier transformation of this signal was taken and PB was identified as epochs in which the power in the frequency band of 0.025 – 0.1 Hz (10 to 40 second cycles) exceeded five standard deviations above the mean found for a randomly selected set of apnea events. In the wavelet method, PB is identified using a continuous wavelet transform of the apnea signal with a periodic mother wavelet. The absolute values of the wavelet coefficients are a function of time and have a range from zero to one. PB is marked at times when the coefficient exceeds 3/8. These methods were applied to our large dataset, and the percentage of time spent in PB was calculated. **Results**: The amount of time that infants spend in PB is typically small, 1-10%, depending on their postmenstrual age. We were surprised by the extent of PB in some and the poor outcomes that were associated. The infant who had the most PB in a 48 hour period (66%) was an apparently healthy late preterm infant who was released from the NICU, but later died unexpectedly at home – a case of sudden infant death syndrome (SIDS). Application of our PB detection methods revealed PB almost continuously throughout the course of this infant's stay in the NICU. A second infant who had PB for 58% of a 12 hour period also died unexpectedly a few hours later in the NICU with what appeared to be fulminant sepsis. **Conclusions**: Although PB has been thought to be benign, two cases of extreme PB occurred in infants who later died unexpectedly. Excessive PB may be a sign of poor development of respiratory control or impending pathology, underscoring the potential benefits of real-time monitoring of physiological oscillations.

20 (Selected for poster)

EARLY DETECTION OF INFECTION IN PIGS BASED ON IL-6 DYNAMICS

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Objectives: At present, infection is still one of the major death causes on ICU. To decrease infection-and sepsis-associated mortality of ICU patients, the search for early infection detectors is crucial. In this study, we used pigs as animal model to analyze dynamic changes of interleukin-6 (IL-6) time series in response to infection. **Methods**: Time series of

IL-6 responses (n=5 pigs) were analyzed before and after infection by Actinobacillus pleuropneumoniae (endobronchial inoculation with 1 x 107 CFU). Eight blood samples were collected starting from the moment of catheterization at a sample frequency of 1 sample/2hours (before infection). In addition, a second series of blood samples was taken with the same sampling frequency starting from eight hours before the moment of infection until maximally 24 hours after infection for the surviving pigs. For every blood sample the IL-6 value was determined resulting in one IL-6 time series for every pig. In addition, all pigs were clinically scored by a veterinarian. The experiments were approved by the ethical commission of Ghent University. Dynamics of the IL-6 responses to infection were quantified by first order autoregression models applied to IL-6 data before and after the moment of infection. **Results**: The estimated autocorrelation values were for all pigs close to zero in the pre-infection state. After infection, the autocorrelation values of the pigs were significantly different from the pre-infection state ($p < 0.0001$) and all parameter estimates where significantly different from zero (i.e. for all autocorrelation values (a1): $a1 – 2.SE(a1) > 0$). These results indicate that the infection causes a downwards shift of the autocorrelation value. **Conclusions**: These results might be a further step towards the development of an objective individualized method for monitoring of sepsis and inflammation processes and early prediction of disease outcome in pigs. In future, a similar approach should be investigated in the ICU setting.

21 (Invited podium)

A TWO YEAR AUDIT OF PROTHOMBIN COMPLEX CONCENTRATE USE IN THE ACUTE HOSPITAL SETTING

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Objectives: 1. To determine the indications, appropriateness, dosage and administration of Prothrombin Complex Concentrate (PCC) in a general hospital in the UK. 2. To monitor protocol violations, wastage and costs associated with the use of this product. **Methods**: Retrospective analysis of prospectively collected data, chart review and economic evaluation. **Results**: Between 1st April 2011 and 31st March 2013 the product was prescribed for 75 adult in-patients (74% males, median age 78). The commonest indication was intracranial bleeding, followed by gastrointestinal hemorrhage, over-anticoagulation and prior to operative procedures. All except one patient were receiving warfarin therapy, the exception was an 86 year old female with an acquired hemophilia. The clinical setting was most commonly the general ward, followed by the emergency department, coronary and critical care units and the operating theatre. Forty seven patients were alive at 30 days. Three hundred and ninty seven units of PCC were issued from the laboratory to the clinical areas during the period under study. Thirty seven units were returned unused and at least and 39 units were wasted. The cost of wasted product was 2,535 GBP (2991 Euro). Protocol violations were common, principally delays to administration and failure to give Vitamin K. The doses were often inadequiate and documentation was generally poor. **Conclusions**: PCC is commonly prescribed for the emergency reversal of warfarin therapy. Institutional protocols guide the use of the product, however protocol violations are common. Delays to treatment and inadequate dosing can lead to adverse outcomes and wastage is expensive. Extrapolated to the entire UK acute hospital setting, this would amount to 507,000 GBP (598,260 Euro). Regular audit of the use of the product, and training of physicians involved in its prescription and administration are recommended.

22 (Selected for poster)

CARBOHYDRATE PRE-FEEDING AFFECTS THE METABOLIC RESPONSE TO POLYTRAUMA, HEMORRHAGIC SHOCK, AND RESUSCITATION IN SERUM METABOLIC NETWORKS

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3. University of Minnesota Department of Electrical and Computer Engineering

Objectives: Pre-treatments with oral carbohydrate feeding prior to experimental hemorrhage are known to confer a survival benefit in small animal models. However, the impact of such fed states on the outcomes in traumatically injured humans is unknown. Our objective is to examine the effect of carbohydrate pre-feeding on metabolic response in a clinically-relevant large animal model of polytrauma and hemorrhagic shock by identifying potential metabolic networks. **Methods**: All animals were fasted overnight (n=64). Those animals that were randomized to pre-fed (n=32) received an oral bolus of 7 cc/kg of Karo® syrup diluted with 5 cc/kg of sterile water one hour prior to sedation. A pulmonary contusion, a 35% hemorrhage, and a liver crush injury were administered to simulate polytrauma and hemorrhage. Resuscitation measures were limited to maintaining blood pressure at 80 mmHg with lactated Ringers for the first hour post-injury, followed by full resuscitation (shed blood and lactated Ringers to 90 mmHg) for 20 hours. Serum samples

were obtained at set timepoints throughout. Metabolic profiles were constructed from analysis of separate NMR spectra of serum samples with Chenomx software. Relationships between metabolites were extracted by assuming a linear relationship between absolute metabolic concentration and the rate of change of concentration, and fitting parameters to minimize a weighted combination of sum of squared prediction error and sum of absolute parameter value. Central nodes were identified when the error in sum of squared predicted metabolic rate of change that was less than half of the nominal sum of squared rate of change. **Results**: Pre-treatment with oral carbohydrate was not associated with survival benefit in our porcine model of traumatic injury and hemorrhagic shock. The serum metabolic network in the fed subjects is noticeably different from the one in the fasted subjects. Seven metabolites were identified as central nodes in both feeding groups: adenosine, cytidine, glycerol, hypoxanthine, lactate, succinate, and uridine. Distinct groups of metabolites are observed to be repeatedly associated with these nodes; however, the composition of these groups depends on whether the subject is fed or fasted. O-phosphocholine, glutamate, leucine, isoleucine and valine are observed to be part of the networks associated with adenosine, cytidine, lactate, and uridine in fasted subjects, whereas phenylalanine and tyrosine are observed to be part of the networks associated with the nodes adenosine, cytidine, succinate, and uridine in fed subjects. **Conclusions**: We conclude that the response to trauma, hemorrhage, and resuscitation in serum metabolic networks depends on whether the subject is fasted or pre-fed carbohydrate. The association of branched chain amino acids with fasted subjects is likely associated with a reliance on amino acids and protein catabolism for fuel. Phenylalanine and tyrosine are known to be involved in catecholamine synthesis; however, it is unclear why these would be associated with fed animals and not animals who fasted. Further analysis must be done to confirm the mechanisms and metabolic pathways responsible for the observed differences in networks.

23 (Selected for podium)

MEASURES OF RR INTERVAL COMPLEXITY ARE PREDICTIVE OF MORTALITY IN A GENERAL ICU POPULATION

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Objectives: While many studies exists demonstrating added value of complexity metrics in intensive care unit (ICU) patient subpopulations, few analyses exist for the general ICU population. Here we aim to assess the added predictive value of complexity metrics extracted from high-resolution waveforms over static measurements of patient physiology. **Methods**: 3,851 patients from the MIMIC II clinical database were studied. Features were extracted across the first patient day in the ICU, and included static physiologically derived parameters (e.g. highest and lowest heart rate). Regularized regression models were developed and used as the baseline for comparison. The 3,851 clinical patient records were then matched to corresponding waveform records present in the MIMIC II v3 waveform database. If available, the first continuous 6 hour ECG trace was used to derive RR intervals. Various measures of complexity previously shown to be predictive of mortality were then used to extract features from the RR traces, including multiscale entropy, detrended fluctuation analysis, and various power related metrics (including power within established LF/HF bands, HF/LF ratio, and total power). Regression models were developed using these features independently and with the earlier extracted clinical parameters. Data was split into training and testing sets, and predictive utility was measured by the area under the receiver operator characteristic curve (AUROC) of the resultant predictions on the previously unseen test set. **Results**: Most measures of complexity were predictive of mortality (AUROC of various models: 0.65 for MSE, 0.66 for DFA, 0.58 for power metrics, and 0.67 for all complexity metrics). The model using only clinical covariates achieved an AUROC of 0.78. The addition of the complexity metrics to the clinical covariates improve the performance of the models as measured by the AUROC: 0.82 for MSE+clinical, 0.81 for DFA+clinical, 0.78 for power+clinical, and 0.816 for all complexity metrics+clinical. The differences were statistically significantly different from using only clinical data for all augmented models except power+clinical. **Conclusions**: Measures of RR trace complexity are predictive of in-hospital mortality for a general ICU patient base. Various methods of assessing this complexity seem to contain similar discriminatory information resulting in little added benefit from multiple approaches. However, the inclusion of complexity metrics in clinical models could benefit their clinical performance.

24 (Selected for podium)

HEAD INJURY ON WARFARINISED PATIENTS, CAN WE PREDICT THE BLEED?

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Objectives: Introduction Head injury is a common presenting complaint at the emergency department; particularly the patients on Warfarin have a low threshold for immediate CT scan regardless of their clinical status. The predictors of ICH are less understood in this cohort of patients. Our aim is to identify the possible clinical and biochemical predictive factors of intra cranial hemorrhage on warfarinaized patients by using the correlation between the CT brain report with their mechanism of injury, clinical status (GCS), INR level and other injuries. **Methods**: Retrospective analysis of CT brain scans performed on head injury patients (n=478) in the last 18 months (2012 January to March 2013), patients on Warfarin were identified (n=53). Their clinical status, GCS score on arrival, indication for CT scan, time for CT scan, results of CT scan, INR level and follow up management of patient were reviewed. **Results**: 53 (male n=31, Female n=22) warfarinized patients were identified out of 458 head injury patients between Jan2012- March 2013. Age range was 36-92 years, Median Age was 79. GCS on arrival was 15/15 in 39 patients 2 out of these patients had ICH on CT brain, GCS<8 was only on 4/56 only 2 out these patients had ICH on CT brain and one was diseased. About 96% had INR checked prior to CT brain (sub therapeutic30%, Therapeutic45% and supra therapeutic20%). 6 /53 had evidence of ICH on CT scan, 3/53 infarction without bleeding, 1/53 showed intracranial oedema no bleeding. 2 patients (INR was 2.9, 12 respectively) had reversal of warfarin in ED (vit K, Octaplex). Almost 55% (29/53) of scans performed within in 8 hours of ED admission, 4 patients in this cohort showed acute abnormalities in CT scan. 3/53of patients had re peat CT without any changes. Almost all (51/53) patients were admitted for neuro-observation and one deceased due to extensive ICH. **Conclusions**: This study concludes that ICH does not depend on INR level or neurological signs of the patients, but also suggests, that an individual case by case assessment is warranted to manage these patients.

25 (Selected for podium)

AN ADVANCED ALGORITHM FOR PREDICTING MORTALITY USING SIMPLE PARAMETERS OBTAINED EARLY IN THE HOSPITALIZATION OF A TRAUMA PATIENT

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Objectives: The identification of injury severity in the acute setting presents a complex challenge for the trauma surgeon. Triaging patients according to injury severity allows for the proper distribution of resources to manage patients. Important in the identification of injury severity is the ability to identify these patients quickly. We hypothesize that a Rotation Forest algorithm can be used to identify the likelihood of mortality in the acutely injured. **Methods**: A registry query was performed on all patients admitted to a busy level I trauma center for 2010-2011. 5235 patients met inclusion criteria. Average ISS was 14.5 with a 6.8% mortality rate. The mean age was 42.4 with 72.1% male. The following parameters were exposed to a Rotation Forest algorithm to determine mortality: age, prehospital and emergency department systolic blood pressure, pulse pressure, motor Glasgow Coma Scale (GCS) and total GCS. 66% (n=3455) of the data were used for training, 33% (n=1780) for testing. **Results**: The sensitivity for the model was 36.1%, specificity 99.7%, positive predictive value 89.6%, negative predictive value 95.6% and area under the receiver operating curve 0.922 **Conclusions**: A Rotation Forest algorithm can be used to quickly and accurately identify patients with high risk for mortality. An algorithm such as this can help identify patients for triage and aid in deployment of scarce resources.

26 (Invited podium)

TOWARD A DATA-DRIVEN MODEL OF TRAUMA DYNAMICS

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2. Cottage Hospital, Santa Barbara
3. University of California San Francisco

Objectives: In a clinical environment the ability to provide assessments of a trauma patient's disease state, as well as guidance on the potential impacts of interventions, could inform decision-making. We investigate the use of clinical data to explore models of disease progression, interventions and outcomes. **Methods**: Time point measurements, including "clinically relevant data points", such as temperature, heart rate, respiratory rate, pH value, PaCO2, PaO2, HCO3, and "coagulation factor data points", such as levels of fII, fV, fVII, fIX, fX, antithrombin, tissue factor pathway inhibitor, protein C, and activated protein C, of 859 patients were taken at intervals starting immediately after they entered the emergency department until, at most, 120hr. Interventions (blood units, FFP units, PLT units, crystalloids, cryo units, colloid) provided to patients were recorded during non-overlapping time intervals. Using these data we have developed a linear model capable of estimating the combination of interventions that will be most effective in shifting a trauma patient to a desired phenotypic state (clinically relevant observables). In addition, we have developed a second model for estimating a patient's phenotypic state in the form of a frequently occurring combination of discrete measurements. **Results**: Our first model suggests that each unit of fresh frozen plasma provided will decrease active protein C by 2.28

(ng/mL) and increase pH value by 0.02068 (p= 0.000485). In addition, each unit of blood will increase fVII by 4.443 (% activity) (p= 0.005) and each unit of platelet will increase PaCO2 by 5.246 (mmHg) (p= 0.006). The model makes additional statistically significant predictions and can also accommodate other information such as demographics, or category and severity of injuries. Using this methodology we can predict the effects of manipulation of relative factor concentration on coagulation profiles and translate the optimal combinations into transfusion paradigms (for example, plasma to blood ratio). Identification of subgroups of patients and interventions will enable targeted therapies. Using our second model, we have discovered the two most frequent phenotypic states to be: low fII, fIX, fX, fVII, protein C and high prothrombin time, which frequently occurs in patients before death, and high fII, fX, fVII, and high protein C, which frequently occurs in patients with a good prognosis. Understanding major states and how they transfer from one to another can reveal how trauma patients progress with medical treatments over time. **Conclusions**: We have developed a methodology to predict the effects of interventions on a trauma patient's phenotypic state. In addition, we have demonstrated how understanding of phenotypic states and their time evolution can reveal how trauma patients progress with medical treatments over time. Future work will focus on using models to (1) identify patient subgroups in order to design targeted interventions/therapies, and (2) predict prognoses of newly admitted patients.

27 (Selected for poster)

PREDICTIVE POWER OF HEART RATE COMPLEXITY TO ESTIMATE SEVERITY IN SEVERE SEPSIS PATIENTS

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2. Medical Intensive Care Unit, Raymond Poincaré hospital, AP-HP, Garches, France

Objectives: Prediction of adverse outcome is the intensive care unit (ICU) such as in-hospital mortality can be used to rationalize treatment options (Teres CCM 15.3 (1987): 208-213). Prediction techniques usually exploit scores derived from 'worst' physiological measurement during the first 24 hours after admission (Knaus CHEST 100.6 (1991): 1619-1636). Unfortunately, such approaches fail for physiologically homogeneous sub-populations such as severe sepsis patients. There is much literature covering the relation between complexity of heart rate time series (RR) and severity in sepsis patients (Goldstein CCM 26.2 (1998): 352-357). This work estimates the added predictive power of complexity measure extracted from heart rate time series. **Methods**: The MIMIC-II database is a multi-parameter ICU database of approximately 32,000 patients (v2.5) collected from 2001 to 2006 at a tertiary care hospital (Saeed CCM 39.5 (2011): 952). Severe sepsis patients were identified using the Angus criteria (Angus CCM 29.7 (2001): 1303-1310). Minute-by-minute heart rate, provided by bedside monitors, was extracted from the database when more than 5 hours of continuous data was available during the first 24 hours after admission. Multiscale entropy (MSE) coefficients (Costa Phy. rev. let. 89.6 (2002): 068102, r=0.15, n=20, m=2, a=2) were computed and used as predictors in a logistic regression model to estimate the probability of dying in the hospital. Ten independent 4-fold cross-validation procedures were used to estimate the out-of-sample discriminatory information with area under the receiver operating curve (AUROC) (Hanley Radiology 743 (1982): 29-36). MSE coefficients were then used in addition to APS score (Knaus CHEST 100.6 (1991): 1619-1636) to estimate the added predictive value using the Integrated Discrimination Improvement (IDI, Pencina Stat. in med. 31.2 (2012): 101-113.). **Results**: 2,155 patients were identified with the Angus criteria of which 238 patients had enough minute-by-minute heart rate time series provided by bedside monitor over the first 24 hours after admission. In-hospital mortality for these patients was 36.5%. MSE coefficients extracted from bedside monitors could predict in-hospital mortality with an AUROC of 63.3±9.8%. The APS score with its original coefficients (AUROC=67.6±9.9%), was then used in combination to MSE coefficients offering an IDI of 2.1% (p=0.12) with an AUROC of 69.7±10.5%. **Conclusions**: Our results suggest that MSE coefficients provide additional predictive power even though no statistically significant difference could be observed when used in addition to a standard physiological score. The population size possibly accounts for the lack of statistical power; considering a larger population could provide more data points. However, the relation between complexity measure and severity previously reported in sepsis patients may not replicate on a less specific population. Complexity measures from RR intervals extracted from ECG waveforms could possibly provide more accurate information, which is currently under investigation.

28 (Selected for poster)

IS THERE AN INFORMATION HIERARCHY AMONG HEMODYNAMIC VARIABLES FOR EARLY IDENTIFICATION OF OCCULT HEMORRHAGE?

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Objectives: There is an ever-expanding array of metrics to attempt hypovolemia detection. In the setting of ongoing occult bleeding, it would most useful to have an understanding of trade-off between how early bleeding can be detected and how many parameters physicians have at their disposal to pose a correct diagnosis. We hypothesize that there exists a hierarchy of physiological metrics, accessed through specific monitoring entities, expressing this trade-off. **Methods**: Eleven female Yorkshire pigs were anesthetized and intubated, then after a 30 minute baseline stabilization period they were bled at a rate of 20 cc/min to a mean arterial pressure (MAP) of 30 mmHg. The pigs were maintained at a MAP between 30 and 40 mm Hg for 90 minutes, then resuscitated using Hextend at a 1:1 ratio to blood lost. We collect continuous waveform data on arterial pressure (AP), pulse oximetry plethysmograph (SpO2) and right atrial pressure (CVP) at a frequency of 250 Hz as well as beat-to-beat measures of heart rate (HR), stroke volume (SV), and mixed venous saturation (SvO2). The dimensionality of the waveform signal was reduced sequentially by a moving window, a Harmonic analysis using Fourier transformation, and a principal component analysis (PCA). (Figure 1) Once all metrics were computed, we created a hierarchy based on the incremental availability of HR and SpO2 tracings (Gr1), AP tracings (Gr2), beat-to-beat derived variables (cardiac output, stroke volume variation, pulse pressure variation) computed from the AP signal (Gr3), CVP (Gr4), and SvO2 (Gr5). (Table 2) For each set of metrics in the hierarchy, we learned a mapping between those signals and the amount of blood lost using regressive random forest. This regressive model was used to identify the binary "bleeding state" of the pig. The quality of the methodology was evaluated with a 10-folds-leave-one-out cross validation where each fold was attached to one testing pig. Sets in the hierarchy were compared by their activity monitoring operating characteristic (AMOC) profiles. **Results**: At a fixed number of false positive alerts of bleeding (per 100 min), a model including Gr2 variables was able to detect bleeding earlier than a model with Gr1 variables, but did not achieve statistical significance (p=0.09; median difference=149.9 mL, or 7.5 minutes). There was no difference between Gr2 and Gr3 variables in their ability to identify ongoing bleeding (p=0.97; median difference=2.72mL, or 0.14 minutes) Gr4 improved bleeding detection time over Gr3 (p=0.02; median difference=123.6 mL, or 6.18 minutes). Gr5 did not improve performance over Gr4 (p=0.66; median difference=5.45mL, or 0.27 minutes). **Conclusions**: There is an information hierarchy among physiologic variables. The availability of beat-to-beat derived metrics, and then CVP provided incremental improvement in the ability of physiological signals to identify ongoing hemorrhage.

29 (Selected for poster)

EFFECTS OF RECIRCULATION OF DIALYSATE ON CARBON DIOXIDE REMOVAL CAPABILITIES OF A MEMBRANE LUNG

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Objectives: A low-flow extracorporeal CO2 removal (ECCO2R) device combining gas exchange and hemofiltration has been recently developed. A possible advantage of this technique is that dialysate recirculation (DR) could enhance membrane lung CO2 removal (VCO2ML). We studied the effects of DR on VCO2ML and ventilation in an animal model. **Methods**: Three conscious spontaneously breathing sheep were connected to a custom made extracorporeal circuit. Blood flow (BF 250 ml/min) was generated and blood decarboxylated (gas flow, GF 10 L/min, ambient air) employing a ECCO2R device (Hemolung, Alung Technologies, Pittsburg, PA). A hemofilter was connected in series after the ML. Dialysate flow (DF) was generated and re-circulated before the ML with a peristaltic pump. We tested four DFs (0, 50, 100, 150 ml/min) in randomized order for 20 minute each, 8 to 9 times per animal, resulting in total of 26 test repetitions. Before each repetition a baseline 20 minute period without GF and DF was evaluated. Arterial and circuitry blood samples were collected at the end of each 20 minute period. Hemodynamics and ventilatory variables were recorded continuously by an automated data collection system. **Results**: VCO2ML and CO2 removal efficiency were not changed by DR. No effect on spontaneous ventilation and arterial blood gas analysis was observed during application of DR. Only the absence of GF proved to effect respiratory variables significantly. ***Conclusions:*** *Dialysate recirculation before a membrane lung (ML) did not prove to ameliorate ML carbon dioxide removal capabilities or affect spontaneous ventilation in spontaneously breathing animal model.*

BF (ml/min)	**250**	**250**	**250**	**250**	**250**
GF (L/min)	**0**	**10**	**10**	**10**	**10**
DF (ml/min)	**0**	**0**	**50**	**100**	**150**
VCO2ML (ml/min)	0	40.2±0.8	39.4±0.9	39.6±0.9	39.0±0.8
CO2 Removal Efficiency (%)	NC	31.3±0.6	30.5±0.7	31.1±0.8	29.9±0.7

VCO2NL (ml/min)	136.0±1.5	127.4±1.4*	128.3±1.7*	128.5±1.7*	127.0±1.6*
MV (lt/min)	8.47±0.13	7.33±0.13*	7.71±0.11*	7.44±0.13*	7.62±0.12*
RR (apm)	30.7±0.5	28.5±0.4*	28.5±0.4*	28.1± 0.4*	27.8±0.4*
Arterial pH	7.391±0.008	7.400±0.008	7.393±0.008	7.395±0.008	7.394±0.006
Arterial pCO2 (mmHg)	35.3±0.5	33.9±0.6	34.7±0.7	34.0±0.4	34.6±0.5
Arterial HCO3- (mEq/L)	21.0±0.4	20.6±0.4	20.7±0.4	20.6±0.4	20.8±0.3

Table 1
Summary of the Experimental Results
(Average±SEM). *: statistically significant compared baseline, $p<0.05$ (One Way ANOVA RM, All Pairwise Multiple Comparison, Holm-Sidak correction).
BF: Gas Flow, GF: Gas Flow, DF: Dialysate Flow, VCO2ML: membrane lung carbon dioxide removal, VCO2NL: natural lung carbon dioxide removal, MV: minute ventilation, RR: respiratory rate.

30 (Selected for podium)

WHAT IS THE MEANING OF A MEASURE OF HEART RATE VARIABILITY?

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Objectives: The measures of heart rate variability (HRV) can be classified into multiple domains of variability, depending on their theoretical background and method of computation; however their physiological interpretation and degree of mutually independent information remain unknown, especially given that multiple measures of variability across domains are correlated with each other. The objective of this study was to investigate independence and ability to detect change of a set of measures of HRV in silico. **Methods**: To understand the physiological meaning of HRV we used a physiologically-based mathematical model from Kotani et al. (2005). By altering its parameters, this model is able to produce R-R interval time series showing the scale-invariant properties of both healthy subjects and patients affected by heart diseases. We used Kotani's model to generate a set of R-R interval time series in the healthy case, and in altered physiological conditions (i.e. when the values of selected parameters of the model are modified) in order to investigate 1) the degree of independence of a set of measures of variability from multiple domains based on their mutual information, and 2) their ability to sense changes in the physiological parameters of Kotani's model, and to track them over time. **Results**: Our results show that in the healthy cardiovascular system state of the model, the investigated HRV measures present low mutual information, and therefore high degree of statistical independence. When the physiological conditions are altered by modifying the values of the parameters of Kotani's model, the measures follow those changes either increasing or decreasing their values. Each HRV measure resulted sensitive to multiple changes in the physiological conditions, in particular sympathetic and parasympathetic activity, baroreceptor activity, contractility of the heart, and respiration. Correlation analysis confirmed that the alteration of HRV measures due to changes in the physiological conditions leads to higher levels of correlation among the measures. **Conclusions**: The results suggest that each measure of HRV is a nonspecific sensor of the cardiovascular system. Because of the independence of HRV measures under baseline conditions, as well as their partial correlation following physiological changes, the combination of multiple measures into composite indexes can enhance the "common" information related to physiological changes. This approach could be used to improve our understanding of cardiovascular physiology, and translate the acquired knowledge into clinical applications.

31 (Selected for poster)

EXTRACORPOREAL CARBON DIOXIDE REMOVAL: EFFECT OF SHORT TIME INFUSION OF THREE DIFFERENT METABOLIC ACIDS

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Objectives: Acidification of blood entering a membrane lung (ML) with lactic acid has demonstrated to be a technique able to enhance CO2 removal of a ML (VCO2ML). In this preliminary study we evaluated the effects of short term infusion of different metabolic acids on VCO2ML of a commercially available CO2 removal device (Hemolung, Alung Technologies, Pittsburg, PA). **Methods**: Three conscious spontaneously breathing fasted sheep were connected to a custom made extracorporeal circuit optimized for safe acid infusion. The circuit consisted of a Hemolung device, a hemofilter and a peristaltic pump capable of re-circulating dialysate before the ML. Extracorporeal blood flow was set to 250 ml/min, dialysate flow was set to 100 ml/min. Citric (0.4 M), lactic (4.4 M) and acetic (4.4 M) acid were infused in the dialysate at a fixed rate of 1.5 mEq/min. Metabolic acids were tested for two hours each, in randomized order. Re-equilibration time between steps lasted 60 min. Arterial and circuit blood samples were collected at 30', 60' and 120' from beginning of acid infusion. Hemodynamics and ventilatory variables were collected continuously by an automated data collection system. **Results**: Infusion of citric, acetic and lactic acid at 1.5 mEq/min decreased pre-ML blood pH and consequently augmented pCO2 in a similar manner. This rise in pCO2 caused analogous increases in VCO2ML during infusion of the acids as compared to baseline. No effects on arterial gas analysis were observed, but citric and lactic acid infusion caused an acute rise in ventilation. See table for results. **Conclusions**: In this preliminary data, acidification of blood with lactic, acetic or citric acid demonstrated to have the same effectiveness in augmenting carbon dioxide removal of a ML. Acetic acid showed different influence on physiological parameters compared to citric and acetic acid.

	Baseline	**Acetic**	**Citrate**	**Lactic**
pH art	7.4±0.05	7.39±0.03	7.36±0.037	7.37±0.053
PCO2 art (mmHg)	35.9±3.5	36.4±2.73	33.7±2.3	36.3±3.53
HCO3- art (mEq/L)	22.2±2.54	21.6±2.5	18.9±1.7	20.4±4.4
VCO2 ML (ml/min)	37.4± 3.4	53.1 ± 5.6*	51.9± 3.6*	55.4±4.7*
Efficiency (%)	29 ± 4	40± 7*	43±4*	44±5*
pH post acid	7.38±0.04	7.15±0.02*	7.08±0.04*/$	7.07±0.07*/$
PCO2 post acid (mmHg)	34.5±2.6	54.4±4.6*	56.7±6.1*	60.7±9.2*
VCO2 NL (mmHg)	126.9±30.8	123.7±23.9	145.7±17.1*/$	146±23.6*/$
RR (min-1)	25±6.7	24.6±6.2	26.5±6*/$	30.2±7.2*/$/#
MV (L/min)	6.8±1.7	6.5±1.5	7.7±1.6*/$	8.4±2*/$/#

Table 1
Summary of the Experimental Results
(Average±SD). * vs. Baseline, $ vs. Acetic, # vs. Citrate : statistically significant, $p<0.05$ (One Way ANOVA, post HOC : Tukey).VCO2ML: membrane lung carbon dioxide removal, VCO2NL: natural lung carbon dioxide removal, MV: minute ventilation, RR: respiratory rate.

32 (Selected for poster)

EXPLORING THE EFFECTIVENESS OF HOST-INDUCED STRESSORS AGAINST INVASIVE PATHOGENS USING AN AGENT BASED MODEL

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Objectives: Some components of the acute-phase response (APR) are directed specifically against pathogens on a systemic level with little self-harm (e.g. complement; antibodies); while others (e.g. fever; anemia/hypoxia; iron and zinc sequestration) can cause significant self-harm, even though they may be acknowledged as helpful, like in the case of fever. There are also local stressors at inflamed sites that can be harmful to host cells and pathogens alike (e.g. depleted nutrients; acidosis; hypoxia; increased free radicals). We propose that, even though non-specific host-induced stressors can induce

notable self-harm, pathogens tend to be harmed relatively more because they are rapidly replicating during stressful conditions. We explore the utility of non-specific stressors in host defense via an agent based modeling approach. **Methods**: We create an agent based model (ABM) of a simplified host immune response to pathogen that uses only a basic defense strategy of generic host-induced stress. Host cells and pathogens begin with a certain level of "energy" governing their viability to sustain stress and ability to reproduce. A key difference between the two is that pathogens replicate (splitting their energy between two daughter cells) at a lower energy level than host cells. The host can do harm to pathogens at the local, regional, or systemic level by inducing a stress that also equally reduces energy to its own cells at the respective level; and the pathogens have strategies which do harm to the host as well. **Results**: The systemic stressor strategy (which harms the whole host, as well as the pathogen) is a remarkably effective defense, especially when dealing with a rather virulent pathogen. However, the systemic stressor (modeling the APR stressors) must be carefully managed; otherwise, the host dies due to excessive loss of host cells (sepsis). This defense works best when allowed to vary dynamically based on information privy to the host (e.g. self-health or pathogen number), thereby allowing these responses to be host-driven. While the local, non-specific stressor (modeling the inflammatory milieu) had limited efficacy as a defense on its own, it greatly enhanced the efficacy of the systemic stressor. We also see that, in some cases, there is evidence of anti-synergistic effects when two strategies are employed together. **Conclusions**: We have gained insight into the role of host-induced stressors implemented at different levels (local, regional, systemic) and see that the timing and magnitude of these stressors is vitally important in arriving at a successful host response. The implications about the effectiveness of the most basic of host defense strategies against infection are quite revealing. During a severe infection, there may be features of patient health that appear to our observations as subnormal or dysfunctional. However, it would be helpful to have a better understanding of these features from the perspective that the host may be using such mechanisms as a strategy to starve or cripple the pathogen in a way that is ultimately more harmful to the pathogen than to the host.

33 (Selected for poster)

DAMAGE CONTROL RESUSCITATION IN A PATIENT ON ECLS WITH EMPYEMA

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Objectives: According to Joshi et al. (Chest, Mar 2013) the need for thoracotomy while on extracorporeal life support (ECLS) is 3.2% and in-hospital mortality is 39%. Compared with the reported mortality of surgical site bleeding of 22-32% according to the 2007 ECLS Registry Report, a thoracotomy on ECLS imparts a 22-53% increase in relative risk of death. The causes of ECLS coagulopathy are multifactorial. Fibrinolysis is upregulated while platelets and the contact pathway of coagulation is activated by ECLS circuitry. To mitigate the risk of thrombosis, unfractionated heparin (UFH) is titrated to an increased activated clotting time. Here, we report our successful management of massive hemorrhage incurred during thoracotomy for a severe S.areus + Acinetobacter empyema in a patient on venovenous-ECLS using our hospital's massive transfusion protocol augmented by ECLS physician and hematology-directed hemostatic resuscitation. **Methods**: The electronic medical record, anesthesia intra-operative documentation, perfusionist charting, inpatient pharmacy and blood bank accounts were reviewed to create a consolidated coagulation record. Chest tube output, blood component therapy amounts (units (U)), thromboelastogram (TEG), anticoagulation and coagulation factor infusions (UFH, factor VIIa, prothrombin complex concentrate), and aminocaproic acid doses were compared for the 24 hours pre- and post-thoractomy. Statistical analysis was completed using a one-way ANOVA in SPSS and student's-t test in Excel. **Results**: For the 35 days while on ECLS, chest tube output was 15L (392+804ml/day). 76U of packed red blood cells (PRBC), 18U of fresh frozen platelets (FFP), 18U of apheresis platelets, and 140U of cryoprecipitate were transfused. Thoractomies 1, 2, 3, and 4 took place on ECLS day 10, day 12, day 28, and day 32 respectively. Intraoperative blood loss was 2000cc for thoracotomy(T) #1, 750cc for T#2, 1000cc for T#3, and 0cc for T#4. Mean TEG Coagulation Index (CI) did not change significantly between time points and was in the hypercoagulable range (4.67-6.80, all $p>0.06$). Greatest blood loss occurred when CI was 5.23 and INR>1.5. After cessation of aminocaproic acid (measured within 6 hours), the mean percent of clot lysis at 30 minutes (LY30) increased from 0.1±0.2% to 6.0±4.9% ($p=0.05$). **Conclusions**: Aggressive maintenance of coagulation and pharmacologic inhibition of fibrinolysis are necessary to make emergency surgery on ECLS survivable. Standard interpretations of Coagulation Index may underestimate the need for procoagulant activity in ECLS patients undergoing major surgery. Rebound fibrinolysis can occur with cessation of aminocaproic acid and may require close monitoring and prolonged infusion to manage bleeding.

34 (Selected for podium)

CLASSIFYING NEONATAL SPELLS USING REAL-TIME TEMPORAL ANALYSIS OF PHYSIOLOGICAL DATA STREAMS – VERIFICATION TESTS

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Objectives: Background: The term neonatal spell is an inclusive term for cardiorespiratory events that occur in the neonatal intensive care unit (NICU). A spell may include one or a combination of pauses in breathing, decrease in blood oxygen saturation, or decreased heart rate. There are three main classifications of spell each with two or three subtypes. We have completed a detailed review of the literature to determine the unique temporal pattern of change in heart rate, breathing pattern and blood oxygen saturation that has been described for each of the subtypes of spell. Spells may occur in the preterm infant as a consequence of their physiological immaturity or as a clinical sign of more serious conditions such as infection and brain hemorrhage. The need to determine the cause of neonatal spells frequently leads to invasive investigations and interventions. Objective: To perform pre-clinical verification of algorithms to identify and classify neonatal spells from high fidelity physiological data streams captured from standard bedside monitors. **Methods**: Algorithms for recognizing and characterizing neonatal spells have been developed for the Artemis platform using the real time processing capabilities of infoSphere Streams[1]. The algorithms have undergone pre-clinical verification. The algorithms rely on the ability to detect relative changes in heart rate, blood oxygen saturation and pauses in respiration in real time. Before clinical testing, the functional behavior of each algorithm was assessed against 24 hours of clinically annotated physiological data to assess the accuracy of the algorithms. **Results**: This pre-clinical verification study against a manually annotated trace demonstrates high levels of correlation with each of the algorithms in the system. The relative change detection algorithms for heart rate and blood oxygen saturation correlate 97.8% (total events 229) and 98.3% (total events 119) of the time respectively. The breath pause and apnea detection algorithms correlated 98.9% (total events 2943) and 96.8% (total events 33) of the time respectively. **Conclusions**: This study has demonstrated that physiological rule-based computational algorithms can be used to detect the various forms of spells in human physiological data. There is great potential for the list of potential causes to be reduced with further research using this tool to demonstrate associations between various spell profiles and different conditions. We have begun clinical validation of the algorithms in a prospective simultaneous comparison trial against the gold standard of polysomnography. Data from fifty spontaneously breathing preterm infants that are known to be having spells will be used to test and refine the output of the algorithms. This trial will form the basis for further studies on ventilated infants with the long-term goal of developing an advanced clinical decision support tool to assist in the real-time management of all neonatal spells.

35 (Selected for poster)

EXTENDING THE NOXIOUS STIMULATION RESPONSE INDEX FOR VOLATILE NARCOSIS

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Objectives: Assessing the level of analgesia during surgical interventions is still challenging. Today, there are new methods available like the surgical stress index (SSI), the analgesia nociception index (ANI) and the number of fluctuations of skin conductance (NFSC). All these methods are based on the analysis of vital signs. Due to the fact that vital signs cannot directly be predicted, these methods can only represent the current state of the analgesia and do not allow a reliable prognosis. An index based on pharmacologic models in combination with ANI or SSI can make such indices more reliable. The noxious stimulation response index (NSRI) is such an index based on pharmacokinetic (PK) and pharmacodynamic (PD) models. Currently the NSRI is only available for total intravenous anesthesia (TIVA). To allow a combination of the model-based NSRI with other signal-based indices like ANI or SSI, the authors present an extension to the NSRI undergoing narcosis based on volatile drugs in this work. **Methods**: During a clinical trial at the University Hospital in Aachen, datasets of eight surgical interventions with a balanced anesthesia using gases were recorded. All standard vital signs have been acquired using a special software developed in context of this research. Furthermore, manual applied drugs, anesthesia and surgical events have been recorded using the same software synchronously by an additional person. Recorded data has been pre-processed and analyzed post-hoc using the Matlab/Simulink Software (Mathworks, Natick, USA). Based on the recorded data, the pharmacokinetic and pharmacodynamic models used in the noxious stimulation response index have been implemented and extended. The NSRI for volatile narcosis has been implemented based on the end-tidal concentration of the anesthesia agent measured by the anesthesia machine using response surface models. Finally, the NSRI has been computed for the surgical interventions and has been correlated with painful events

like for example skin incision or intubation. **Results**: Using response surface modeling, the model could be successfully extended and the parameters determined. The NSRI could be successfully computed post-hoc for patients undergoing volatile narcosis. The computed values are comparable with those of patients undergoing TIVA. Furthermore, the NSRI for volatile narcosis could be verified in context of painful events and post-hoc assessment of the depth of narcosis. **Conclusions**: The NSRI could be successfully extended and verified for volatile narcosis. Furthermore, the influence of hypnotic and analgesic drugs can be considered as well. This is important for propofol applied for intubation and opioids applied for increasing the analgesia. In the future, the NSRI will be combined with vital-sign-based indices like ANI or SSI in order to allow a prognosis and achieve more reliable results.

36 (Invited podium)

SMART ECLA - CLOSED LOOP CONTROL OF O2 AND CO2 FOR MANAGEMENT OF EXTRACORPOREAL LUNG ASSIST

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Objectives: The management and operation of extracorporal lung support systems requires skilled and specifically trained personnel at the bedside during the whole time of operation. While this is routine in the operating theatre, when applied in the intensive care unit, the operating scheme changes. Here we see a reduced level of interaction between operator and machine in intermittend or event driven intervals. In order to maintain the same safety and operating standard, the machine should be capable of higher levels of autonomous operation. This applies both for security features (alarms, safety mechanisms, early failure detection) as well as for the adjustment of machine operation. **Methods**: In order to address the mentioned issues the "Smart ECLA" system was designed. Addressing veno-venous extracorporal lung support, oxygenator and cannulae were taken from a standard extracorporeal circuit. As hemolysis is a key feature in long term extracorporeal circulation we chose a Medos Deltastream rotational blood-pump. We wanted to steer the pump externally so an own motor console based on a Maxon motor controller was designed. A remote controllable gas supply was designed based on gas flow controllers for Air and O2, so both mass flow and Oxygen concentration of the fresh gas can be set electronically. Blood flow and pressure before and after pump and oxygenator as well as blood parameters (partial pressures of CO2 and O2, K, ph) are continuously measured and transmitted via a distributed CAN bus network. Related Safety critical tasks (e.g. sensor supervision or low level process control) are performed in these distributed sensor/actuator nodes. Additional to the ECLA Sensors a full patient monitoring including continuous cardiac output monitoring was used. All signals are processed in a central dSpace control unit, where higher control algorithms are implemented. In a hierarchical control scheme the inner control loop consists of controllers for CO2 and O2 partial pressures at the output of the oxygenator. So these can now be set independently of each other and of external factors (e.g. oxygenator wear, input concentrations). Based on a simplified physiological model several control algorithms for optimal setting of the ECLA parameters have been implemented. Among others we implemented a robust control for arterial oxygen saturation and venous CO2 partial pressure. These control loops were specifically designed to account for the large process parameter variation. The overlying blood flow optimizer sets the extracorporeal blood flow as low as possible for the desired target values. Additional safety features have been included as well. **Results**: System development, safety features and control performance have been evaluated in 15 animal experiments. After full instrumentation of the anaesthetized 45-60 kg pigs, two cannulae were placed in both femoral veins. The return cannula was placed in the jugular vein. Ventilatory insufficiency was simulated by using a hypoxic gas mixture for ventilation. Subsequently a test program for system identification (different operating points), control evaluation (set value changes, provoked control disturbances) and specific safety critical situations (e.g. induction of bubbles, cannulae suction) was performed. **Conclusions**: We could show that an ECLA system with enhanced capabilities is able to provide safe and reliable operation. Control targets could be met (within physical constraints) and safety features provide assistance and reliable alarms in critical situations.

37 (Selected for poster)

TECHNICAL VERIFICATION AND ANALYSIS OF IMPLEMENTATION OF WEARABLE SENSORS FOR PROVIDING TELEMEDICAL SERVICES IN HOME ENVIRONMENT

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Deep understanding of patterns and characteristics of physiological signals and their variation during daily activities is crucial for the development of advanced methods for diagnosis and treatment of patients suffering from chronic diseases including cardiac disorders, asthma or diabetes. The aim of the research was to design, implement and verify a wearable health monitoring system for tracking and analyzing of human physiological signals. The presented system incorporates body processing unit consisting of a Bluetooth module, dedicated ECG sensor, a temperature sensor and movement sensors placed on the human body or integrated with clothes and a network gateway to forward the acquired data to a remote medical server. The system works as a part of a telemedical service which provides remote access to monitoring data via web-based graphical user interface for authorized users (family or physician). Experimental results for a group of human who were performing various physical activities(e.g. sitting, standing, working, running) show maximum 5% absolute error in comparison with certified medical devices. The results are promising and indicate that custom-developed wireless wearable monitoring system faces challenges of multi-sensor human health monitoring during the performance of typical daily activities and open new opportunities in threating and evaluating the treatment of numerous patients. This project was funded by the National Research Center based on the decision number DEC-2011/01/N/ST7/06779.

38 (Selected for poster)

INTEGRATIVE "OMIC" ANALYSIS OF ORGAN-WIDE CO-REGULATION PATTERNS HIGHLIGHTS PATHOGEN-DEPENDENT ACTIVATION OF 25-HYDROXYCHOLESTEROL DURING SEPTIC DISEASE PROGRESSION

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Objectives: The incomplete understanding of the complex pathogenesis of sepsis contributes to the difficulty in finding reliable diagnostic biomarkers and disease-specific treatments. An early and directed diagnosis and treatment, however, is imperative, because of the rapid progression of sepsis into life-threatening conditions. Thus, systems ("omic") approaches under controlled conditions may aid in deriving verifiable hypotheses from molecular patterns and to explore diagnostic and therapeutic options. **Methods**: Liver, lung, spleen and blood samples from C57BL/6 mice subjected to polymicrobial (PCI) or S. pneumoniae infections (leading to peritonitis or pneumonia, respectively) for organ-wide screenings of transcriptomic features were taken after 6 h and 24 h (n = 4 each) and compared to uninfected controls. Co-expressed genes were clustered by self-organizing maps (SOM) and mapped using grid-wise topology-preserving enrichment analysis with respect to knowledge derived from pathway and promoter binding template databases. Validation of candidate genes and pathways was carried out at the effector levels including, a targeted metabolomics kit covering concentrations of oxysterols (BIOCRATES Life Sciences AG, Austria). **Results**: Whilst the host response to lobar pneumonia exhibited distinct features of the main pathways for the biosynthesis of steroids via cholesterol in the liver, a pronounced and early inflammatory regulation was identified organ-wide during peritonitis. Promoter analysis linked participation of interferon regulatory factors and signal transducer and activator of transcription (STAT1) to these inflammatory responses. Mapping of metabolomic features revealed an exclusively fast and sustained organ-wide accumulation of 25-hydroxycholesterol (25OHC) in polymicrobial sepsis, which was not observed during the response to pneumonia. Subcellular-level resolved responses by STAT1 to 25OHC were verified in liver and lung homogenates, showing a dominant up-regulation in the cytosolic and differences in the nuclear fraction of the target and remote organ in response to peritonitis. Interferon-dependent STAT1 regulation of 25OHC, which is also involved in antiviral responses, further implies distinct regulation and may lead to selective disruptions in primary bile acid homeostasis as found by pathway analysis. Metabolomic changes were subsequently validated in plasma samples. **Conclusions**: Results derived from organ-wide "omic" data analysis using tailored methods for multiple mappings of co-regulation patterns highlighted the early and specific transcriptional and metabolomic induction of inflammatory features and derivatives from cholesterol. The identified features, comprising, 25-hydroxycholesterol regulated by conserved pathways and transcription factors, may be suitable to support patients' intrinsic defense mechanisms and derive directed diagnostic options.

39 (Selected for poster)

INTEGRATING MATHEMATICAL MODELS OF PULMONARY GAS EXCHANGE, ACID BASE AND RESPIRATORY CONTROL FOR SIMULATION OF CHANGES IN MECHANICAL VENTILATION DURING SUPPORT MODES

LARRAZA S, DEY N, KARBING DS, WINDING R, NYGAARD R, REES SE

Objective: Setting mechanical ventilation (MV) is a difficult and time consuming process, where the goals of effective oxygenation, carbon dioxide (CO2) removal and rapid weaning are balanced against the risks of mechanical ventilation including lung injury, poor acid-base status and patient exhaustion. Decision Support Systems (DSS) have been developed to manage or generate advice for setting MV. Previously, a DSS has been developed to provide advice for controlled modes of MV using physiological models. The aim of this study was to further develop the models of the DSS to include those necessary to provide advice during support modes of MV, i.e. a model of respiratory drive. **Methods:** The current DSS incorporates model components to simulate the effects of changes in ventilator settings in controlled modes of MV. These components describe pulmonary gas exchange and mechanics, oxygenation and acid-base of blood, interstitial fluid and tissue, circulation, and metabolism. A previously published model of chemoreflex response including a compartment representing cerebrospinal fluid (CSF) was modified and integrated to the system. The integrated model was calibrated to normal conditions, and used to simulate the respiratory response to increasing inspired fraction of CO2 (FiCO2) these being compared to results from published experiments. The integrated model was also prospectively evaluated against data describing the response to 3-5 step changes in tidal volume of 50 ml in patients undergoing MV in volume support mode. All data were collected with ethical approval and informed oral consent. **Results**: Simulations of respiratory response to increased FiCO2 are in qualitative agreement with published results. To date, 9 patients have been enrolled in the ongoing clinical protocol. For each patient it was possible to tune the model for the patient specific acid-base status, metabolic production of CO2, pulmonary gas exchange status, and chemoreflex response, at baseline ventilator settings. The integrated model could then simulate changes in respiratory frequency consistent with those measured following step changes in volume support. **Conclusions**: The integrated model is parameterizable, can be tuned to the individual patient from clinically available data, and simulates adequately the respiratory response to changes in volume support. Including the integrated model into the DSS may be useful to simulate the patient's respiratory rate after changes in MV settings and may enable the DSS to provide advice during support modes of MV.

40 (Selected for poster)

DOES ADVANCED TREATMENT OF EXISTING PHYSIOLOGIC DATA ALLOW FOR EARLIER DETECTION OF OCCULT HEMORRHAGE?

HOLDER AL, GUILLAME-BERT M , CHEN K, HUGGINS P, DUBRAWSKI A, HRAVNAK M, PINSKY MR, CLERMONT G

Objective: Frequently obtained vital signs as is currently used in the clinical setting may not be the most sensitive means of detecting ongoing occult hemorrhage. We hypothesize that adding features derived from a dynamic analysis of waveform signals will create physiologic metrics more sensitive and specific in identifying hypovolemia than data collected intermittently or beat-to-beat because waveform-derived variables may provide deeper insight into dynamic physiology than more commonly used signals. **Methods**: Eleven female Yorkshire pigs were anesthetized and intubated, then after a 30 minute baseline stabilization period they were bled at a rate of 20 cc/min to a mean arterial pressure (MAP) of 30 mmHg. The pigs were maintained at a MAP between 30 and 40 mm Hg for 90 minutes, then resuscitated using Hextend at a 1:1 ratio to blood lost. We collect continuous waveform data on arterial pressure (AP), pulse oximetry plethysmograph (SpO2) and right atrial pressure (CVP) at a frequency of 250 Hz as well as beat-to-beat measures of heart rate (HR). For each animal, harmonic analysis of all waveform signals was performed in a moving 5 minute window and principal components of the power spectrum were computed (PCA). Once all metrics were computed, we created hierarchy "levels" based on the incremental increase in data granularity, from level "a" data (only intermittently collected data) to level "c" data (intermittent, beat-to-beat, and processed waveform data). For every level of data complexity, we learned a mapping between those signals and the amount of blood lost using regressive random forest. This regressive model was used to predict the binary "bleeding state" of the pig. The robustness of the prediction was evaluated using 10-folds-leave-one-out cross validation where each fold was attached to one testing pig. Hierarchy levels were compared by their activity monitoring operating characteristic (AMOC) profiles. **Results**: At a fixed number of false positive alerts of bleeding (per 100 min), we were able to detect hemorrhage after 87.0 mL of blood lost, or 4.35 minutes after hemorrhage onset, using a random forest regression model that included metrics extracted from beat-to-beat data and PCA of Fourier transformations of waveform data ("c" level data). This is 212.0 mL (10.6 minutes) earlier than a random forest model including intermittent vital signs alone ("a" level data) ($p<0.01$). **Conclusions**: Using derived features of raw waveforms and beat-to-beat data may inform bedside physicians of hypovolemia caused by occult hemorrhage much earlier than intermittent data alone.

GROUND AND FLIGHT ASSESSMENT OF THE FEASIBILITY OF A MOBILE SYSTEM TO INITIATE ACUTE CARDIO/PULMONARY/RENAL SUPPORT

GEORGE PANTALOS 1, TREY KENNEDY 1, GLENN HOVER 2, RICHARD WARD 1

1. University of Louisville
2. United States Air Force School of Aerospace Medicine

Objectives: Seriously injured soldiers may experience shock and acute multi-organ failure necessitating evacuation to a higher level care center. We explored the ability to initiate cardiac/pulmonary/renal support (CPRS) to stabilize a patient at a theater hospital prior to transport and to maintain support during transport to a definitive care hospital. **Methods**: A circulation test loop filled with a blood analog fluid (40% glycerin/water, $\mu = 3.6$ cP) was used to test this concept. The loop incorporated femoral artery and vein cannulae (19 Fr and 23 Fr, Medtronic BIO-MEDICUS, Minneapolis, MN) as would be used for adult ECMO with peripheral cannulation connected to the inflow and outflow ports of an integrated pump/oxygenator (pCAS, Ension, Inc, Pittsburgh, PA) with integral ultrasound flow sensors (Transonic Systems, Ithaca, NY). A dialysis cartridge (Polyflux HD-C4, Gambro, Germany) was connected in parallel with the pump/oxygenator outflow tubing. The arterial outflow pressure in the circuit was monitored and regulated to 80 mm Hg (Delta Cal, Utah Medical, Midvale UT). The top of an exchangeable 5 L dialysate bag was hung 75 cm above the dialyzer to hydrostatically drive dialysate inflow. An empty, 5 L bag collected dialysate outflow. Pump performance (RPM, flow output) was recorded for different combinations of dialyzer blood flow and total flow output from the circuit. The flight implementation of the CPRS system was evaluated in a C-130 Hercules CCATT trainer at Wright-Patterson Air Force Base and on board a rotary wing, MH-60 Black Hawk military helicopter at Rickenbacher Air National Guard Base under simulated flight conditions. **Results**: With resistances in the flow paths and pump speed (RPM) adjusted, a pump/oxygenator outflow of 3 to 5 L/min was achieved (although flows as low as 250 ml/min are possible) while blood flow through the dialyzer was 0 to 500 ml/min at an arterial pressure of 80 mm Hg; dialysate flow rate was 250 ml/min. These flow rates are sufficient for beneficial clearance of urea and creatinine and for gas exchange. The ability to secure and operate the integrated pump/oxygenator (including confirmation of blood flow achieved), controller, and dialyzer with a custom platform fastened to a special medical emergency evacuation device (SMEED) platform was successfully accomplished, demonstrating the ability to easily transport the CPRS system with a patient to any location necessary. **Conclusions**: Future consideration will include the mostly likely type of dialysate fluid composition needed. A scaled up version of the pump/oxygenator may be needed to provide greater gas transfer capability along with an anti-thrombotic blood-contacting surface treatment as patients may have bleeding and cannot be systemically anticoagulated. These data and evaluation experiences suggest that the CPRS approach to acute organ support during transport of a critically injured soldier is feasible.

Cultural program, tours and sightseeing

Important note: this part of the program is available to family members and guests of the attendees and can be customized as needed by contacting Mrs. Kata Bornemissza, cultural program coordinator for the meeting via e-mail at:
bornemisszakata@gmail.com or via phone at +1 36 30 384 2867
(Group discounts available with timely arrangements)

1. CITY TOUR IN BUDAPEST WITH WATERBUS / live guided

First in Europe! Budapest - as you can only see it with us. Until now you could choose between touring our beautiful capital on four wheels or marveling at the city from the deck of a pleasure boat. Now you don't need to choose: RiverRide is a special sightseeing tour on which you can see the sights of Budapest from a comfortable seat, first along its busy streets, and then, from one second to the next - to the gasps of some of your fellow travelers - you splash into the lapping water of the river.

Duration:	*2 hour*
Departure:	*every day at 12:00, 15:00, 17:00*
Starting:	*from Széchenyi István square 7/ 100 m. from Marriott Hotel*
Price:	*30 Eur /person*
Included:	*ticket to the bus, English speaking guide*

2. DINNER & CRUISE WITH LIVE MUSIC

Budapest has many faces. This vibrant city comes to life at night, when lights are lit up, and a new magical city shines from the twilight. We created this program for those who would like to enjoy the wonderful view of the city swimming in lights with a romantic candlelight atmosphere, and have a romantic dinner. The meals are prepared by European and world champion food sculptor, Attila Tanács, who is a true artist. The salon music is performed by 3 members of the Zoltán Kodály Awarded Rajkó Folk Orchestra, including the world-famous violinist Zsigmond Vidak who is the recipient of the Bronze Merit Cross of the Hungarian Republic.

Duration:	*2 hour*
Departure:	*every day at 19:00*
Starting:	*from Duna Palota/Zrinyi str.5/ 200 m. from the Marriott Hotel*
Price:	*40 Eur /person*
Included:	*buffet dinner, danube cruise, live music*

3. DANUBE LEGEND - SIGHTSEEING CRUISE

This is a one hour long sightseeing tour on the river Danube in Budapest. The boat departs from the city centre. On the boat's deck with the help of TV screens you will be able to view the buildings we pass. The tour will also show and review some famous figures from Hungarian history, kings and queens, poets and music artists will talk about the legends of Budapest and its hidden treasures. The program ends with the Blue Danube waltz music, a catchy tune that will remain with you long after you have returned home.

Duration:	*1 hour*
Departure:	*every day, every hour*
Starting:	*from Vigado Square deck 7/ 50 m. from the Marriott Hotel*
Ticket Price:	*15 Eur /person*

4. DANUBE BEND TOUR / live guided

The Danube Bend – an excursion into Hungary's history. This is an unforgettable tour along the "Blue Danube" with stops in Visegrád, Esztergom and Szentendre.

Visegrád: we walk on the 750 year-old stones of the formal Royal Residence (entrance fee included), learn about life in the middle ages and enjoy the fascinating panorama on the Danube valley.

Esztergom: the Northern gate of Budapest – the centre of the Catholic Church. We will visit Hungary's largest cathedral (also burial place of famous cardinals of Hungary, like Primate József Mindszenty). Afterwards, we glance across the river and enjoy the view over to Slovakia.

Szentendre: On the way back we stop in the artist's village of Szentendre. It is a small baroque city at the gate of the Danube Bend, at the meeting place of the river Danube and the Pilis mountains, in a beautiful natural environment. We walk around the baroque settlement, built on medieval ruins, and then walk-up the narrow streets to reach a panorama point to see the majestic Danube.

Duration:	*8 hour*
Departure:	*9th of August at 10:00*
Starting:	*from Marriott Hotel*
Price for group 4-20 pax:	*70 Eur /person*
Price for private tour 2-4 pax:	*400 Eur/ car*
Included:	*bus transfers, English speaking guide, lunch*

5. IMPERIAL VIENNA

On this tour we drive along the famous Ringstrasse (Vienna's main boulevard) to give you a first impression of the most important sights of Vienna and show you: the City Park, the State Opera House, the Museums of Fine Arts and Natural History, the Parliament, the Burgtheatre, the City Hall and the Votive Church. Then we take a short walk to the most beautiful parts of the city centre: Museumquarter, Hofburg (winter residence of the Habsburgs), Kärtner Strasse (shopping street), the Stephan's Cathedral etc. Finally, we provide you time for shopping in the elegant pedestrian area. There are also opportunities to visit Schönbrunn Palace or several near-by museums, or you can explore Prater, the well-known amusement park.

Duration:	*10 hour*
Departure:	*10th of August at 10:00*
Starting:	*from Marriott Hotel*
Price for group 4-20 pax:	*80 Eur /person*
Price for private tour 2-4 pax:	*500 Eur/ car*
Included:	*bustransfers, English speaking guide*

6. SIGHTSEEING IN EGER

During this tour, you will visit a small baroque town, located in the famous wine region along with the second largest Basilica in Hungary. The visit will include picturesque strolls of important historical sites. Eger is a town of medicinal baths, students and fine wines. The excellent reds and whites of this famous historical wine region are served in wine cellars that have seen the passage of several 100 years. Another force also played an important role in shaping the face of Eger, namely, Bull's Blood. Bull's Blood is a legendary red wine, a cuvee of the merlot and kékfrankos grape, which means that it taste varies sharply from cellar to cellar. In the Valley of the Lovely Woman, you will see many wine cellars that were dug into the hillside and adjacent to each other. After the tour we are going down to the Szepasszony Valley where you will have the opportunity for leisurely wine tasting and lunch.
park.

Duration:	*10 hour*
Departure:	*9th of August at 10:00*
Starting:	*from Marriott Hotel*
Price for group 4-20 pax:	*80 Eur /person*
Price for private tour 2-4 pax:	*400 Eur/ car*
Included:	*bustransfers, English speaking guide, lunch with wine tasting*