

**Scientific Session**  
**Oral Abstracts Presentations**

- 8:00 a.m.      *Effects of Mild Hypothermic Cardiopulmonary Bypass on Glucose, Lactate, Free Fatty Acids and Ketone Bodies Metabolism in Man*  
**Pierre Rouge, M.D.**  
Rangueil University Hospital.  
France
- 8:15 a.m.      *Eliminating Catheter-Related Blood Stream Infections In The Intensive Care Unit*  
**Sean Berenholtz**  
Johns Hopkins University  
Baltimore, Maryland
- 8:30 a.m.      *Nuclear Factor- $\kappa$ B Decoy Attenuates Monocrotaline-Induced Pulmonary Hypertension and Neointimal Formation in Young Rats*  
**Yukako Hotta**  
Tokyo Women's Medical University  
Tokyo, Japan
- 8:45 a.m.      *Stretch Induced Up-Regulation of Matrix Metalloproteinases in a Murine in Vitro Lung Ventilation Model*  
**B. Murat Kaynar**  
Beth Israel Deaconess Medical Center; Brigham and Women's Hospital  
Boston, Massachusetts
- 8:55 a.m.      Presentation of Registration Travel Awards  
(Sponsored by Baxter Healthcare)

## Effects of Mild Hypothermic Cardiopulmonary Bypass on Glucose, Lactate, Free Fatty Acids and Ketone Bodies Metabolism in Man

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### Background

We have investigated the influence of mild hypothermic (33°C) cardiopulmonary bypass (CPB) on energetic metabolism in adult patients undergoing uncomplicated elective valve replacement surgery. This study aims to clarify during the perioperative period the relationships between arterial glucose (G), lactate (L), pyruvate (P), free fatty acids (FFA), ketone bodies (KB) : $\beta$ -hydroxybutyric acid ( $\beta$ OH) and acetoacetic acid (AcA).

### Method

After procedure approval by the institutional reviewboard and written informed consent, 30 consecutive patients undergoing valve replacement with the use of CPB were prospectively enrolled into this study. Anesthesia, conduct of bypass and perioperative treatments were identical for all patients. Hemodynamic parameters and blood samples were obtained at selected 8 periods : just before anesthesia induction (B); 10 minutes before the initiation of CPB (PRE) and 1 hour after (PER); 30 minutes after the end of CPB (POST); at the time of ICU admission (ICU); 3,6,18 hours after the ICU admission (3ICU, 6ICU, 18ICU). Our findings were analysed by non parametric tests used as appropriate.

### Results

All patients had an uncomplicated clinical course and were extubated within 12 hours after ICU admission. Table 1 shows the evolution of biochemical data. There was no statistical correlation between these biochemical endpoints and hemodynamic or oxygen metabolism data. In contrast, there were significant correlations (Snedecor rank correlations) between G and P ( $r=0,381$ - $p<0,001$ ); G and L( $r=0,457$ -  $p<0,001$ ); L and P ( $r=0,678$ - $p<0,001$ ); and finally between FFA and KB ( $r=0,431$ - $p< 0,001$ ).

Table 1 : time course of biochemical parameters

m sem	B	PRE	PER	POST	ICU	3ICU	6ICU	18ICU	Friedman test
G (mmol.l <sup>-1</sup> )	10.1 0.3	9.8 0.4	9.4 0.4	13.3** 0.6	9.7 0.5	10.5 0.4	12.1** 0.4	11.4* 0.4	p<0.001
FFA ( $\mu$ mol.l <sup>-1</sup> )	0.155 0.03	0.324** 0.05	0.381** 0.04	0.116 0.02	0.124 0.02	0.337* 0.03	0.291* 0.03	0.233* 0.03	p<0.001
L (mmol.l <sup>-1</sup> )	1.4 0.1	1.3 0.1	2.0** 0.1	2.1** 0.1	1.9* 0.1	2.0** 0.1	2.4** 0.2	2.4** 0.2	p<0.001
P ( $\mu$ mol.l <sup>-1</sup> )	54 4	53 4	67** 4	79** 5	79** 8	83** 6	92** 9	96** 8	p<0.001
L/P ratio	27.8 1.8	27.3 1.8	33.2 2.8	29.9 2.1	26.2 1.8	27.0 1.8	28.3 1.9	28.1 2.1	NS
$\beta$ OH ( $\mu$ mol.l <sup>-1</sup> )	102 18	105 23	381** 76	196* 49	195* 39	468** 96	332** 53	219* 44	p<0.001
AcA ( $\mu$ mol.l <sup>-1</sup> )	131 17	126 19	212** 25	171 17	197* 17	278** 43	255** 19	193* 19	p<0.001
AcA/ $\beta$ OH ratio	1.7 0.2	1.6 0.2	0.9** 0.1	1.4 0.2	1.6 0.2	0.8** 0.1	1.2 0.2	1.5 0.2	p<0.001

Wilcoxon test (Tx versus B) - \* p < 0.05 - \*\* p < 0.01

## **Discussion**

The effects of hypothermic CPB on glucose homeostasis are well known<sup>1</sup>. They are consistent with our data. The significant relationship between the hyperglycemia and L-P's parallel rise with stability of L/P ratio may be explained by the inhibition of the Krebs cycle and the concomitant increase in hepatic and muscular glycogenolysis. The stimulation of lipolysis, attested by the clear increase of FFA, responsible for an acceleration of KB formation may be explained by circulating catecholamines and heparin. Consistent with the probable insulin resistance<sup>1</sup>, the stimulation of FFA's  $\beta$ -oxydation with NADH accumulation in excess may explained the decrease of KB ratio observed during CPB (PER) and 3 hours after ICU admission (3ICU). In conclusion, our data suggests that two metabolic indicators related to the redox-theory, may be significantly disturbed by the endocrine response to the hypothermic CPB, even in the absence of tissue dysoxia.

References :

- 1. *JPEN* 1988; 12:574-578.**

## Eliminating Catheter-Related Blood Stream Infections In The Intensive Care Unit

SM Berenholtz MD MHS\*, PJ Pronovost MD PhD, PA Lipsett MD, T Dorman MD and TM Perl MD MSc, Department of Anesthesiology/ CCM, Johns Hopkins University, Baltimore, Maryland, USA

**Objective:** To determine whether a multifaceted systems intervention would eliminate catheter-related blood stream infections (CR-BSIs).

**Design:** Prospective cohort study in a surgical intensive care unit (SICU) with a concurrent control ICU

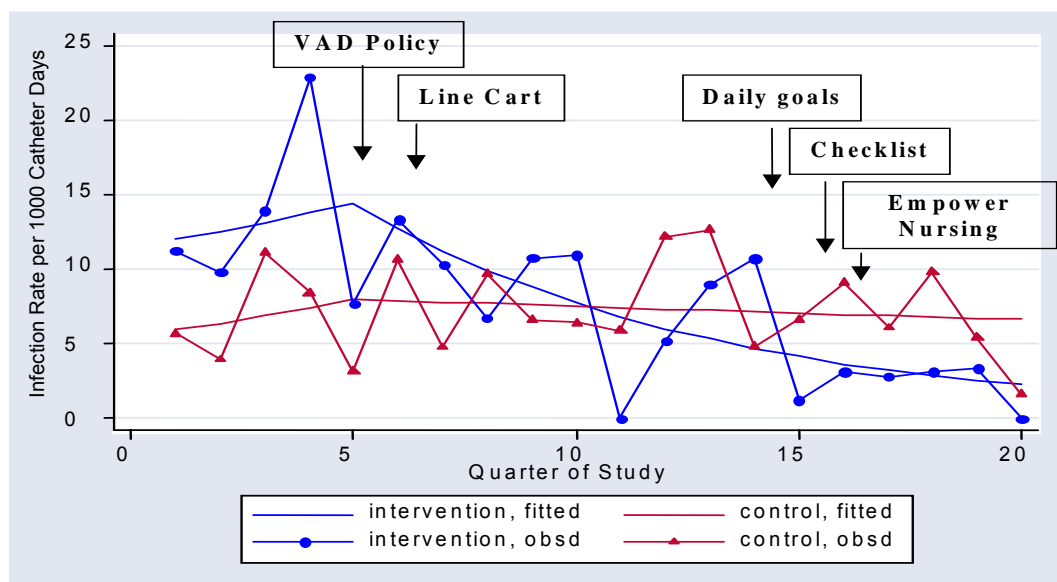
**Patients:** All patients with a central venous catheter in the ICU at The Johns Hopkins Hospital

**Intervention(s):** To eliminate CR-BSIs, a quality improvement team implemented five interventions: 1. Educating staff, 2. Creating a line insertion cart, 3. Asking providers daily whether catheters could be removed, 4. Implementing a checklist to ensure adherence to evidence-based guidelines for preventing CR-BSIs, and 5. Empowering nurses to stop the procedure if a violation was observed. For education we developed an institutional vascular access device (VAD) policy and web-based educational program to increase awareness of evidence-based infection control practices including hand hygiene, chlorhexidine skin prep, maximal barrier precautions, maintaining a sterile field, and subclavian vein placement as the preferred insertion site. All physicians were required to complete a 10-question test successfully before they were allowed to insert a central venous catheter. To help facilitate adherence to the guidelines, we created a line insertion cart containing all the equipment needed for catheter insertion. In addition, we modified our daily goals form and added a question for each patient about whether catheters could be removed. Finally, nurses completed a checklist to ensure that physicians complied with the guidelines. For nonemergent catheter placement, ICU leadership empowered nurses to stop the procedure if they observed a violation in compliance.

**Measurement(s):** The primary outcome variable was the rate of CR-BSIs per 1000 catheter days from January 1, 1998 through December 31, 2002. Secondary outcome variables included adherence to evidence-based infection control guidelines during catheter insertion.

**Main Results:** Prior to the intervention, we found that physicians followed infection control guidelines during 62% of the procedures. Over the intervention time period, the rate of CR-BSIs in our SICU fell from 11.3/1000 catheter days to 0/1000 catheter days ( $p=0.001$ ); there was no change in the control ICU, 5.7/1000 catheter days to 1.6/1000 catheter days ( $p=0.56$ ) (Figure 1). We estimate that these interventions may have prevented 43 CR-BSIs, 8 deaths, 559 additional ICU days and \$1,824,447 in additional costs per year.

**Conclusions:** Multifaceted interventions that helped to ensure adherence with evidence-based infection control guidelines nearly eliminated CR-BSIs in our SICU.



## **Nuclear Factor- $\kappa$ B Decoy Attenuates Monocrotaline-Induced Pulmonary Hypertension and Neointimal Formation in Young Rats**

Yukako Hotta, M.D., Yasuko Yambe, M.D., Shoichi Uezono, M.D., Hideaki Oda, M.D., Ph.D. and Makoto Oxaki, M.D., Ph.D. 1 Department of Anesthesiology, Tokyo Women's Medical University, Tokyo, Japan.

### **Background**

The alkaloid monocrotaline (MCT)-induced pulmonary hypertension (PH) in adult rats has been reported. However, this animal model produces only mild PH with medial hypertrophy of pulmonary arteries and, more importantly, lacks abnormal endothelial cell proliferation, known as neointimal formation, in the development, PH with a marked proliferative-inflammatory component three weeks following single injection of MCT. Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a transcription factor that is rapidly activated at the site of inflammation and thus might have been involved in the progression of PH in MCT-injected young rats. We hypothesized that suppression of NF- $\kappa$ B activity reduces MCT-induced PH by inhibiting the NF- $\kappa$ B dependent inflammatory cascades. To achieve effective suppression of NF- $\kappa$ B *in vivo*, transfection with synthetic double-stranded NF- $\kappa$ B decoy oligodeonucleotides was utilized in this study.

### **Method**

Four groups of eight 4-week-old male Sprague-Dawley rats were evaluated. Two days prior to and immediately after MCT (60mg/kg) administration, either NF- $\kappa$ B decoy or scrambled decoy was transfected into the pulmonary artery through the direct jugular vein injection using a hemagglutinating virus of Japan-liposome method. Untreated group received only MCT without decoy transfer. Uninjured group received sham operation (i.e. no MCT, no decoy). Three weeks later, hemodynamics (mean arterial blood pressure and mean pulmonary artery pressure) were measured under anesthesia with ketamine, xylazine and isoflurane. Then rats were exsanguinated and lungs were excised for morphometric analysis of the pulmonary arteries to determine the degree of pulmonary arterial neointimal formation quantified with vascular occlusion score (VOS) as described previously<sup>1</sup>. Briefly, the severity of neointimal formation was graded as: zero (absence of neointimal formation); one (lumen occlusion of less than 50%); two (lumen occlusion of greater than 50%) and an average score for 50 vessels were calculated for each animal. Statistical analysis was performed with ANOVA and Newman-Keuls multiple comparison testing. A P value of less than 0.05 was considered statistically significant.

### **Results**

Successful introduction of NF- $\kappa$ B decoy into pulmonary vessels was confirmed by using fluorescein isothiocyanate (FITC)-labeled decoy. As summarized in the Table, NF- $\kappa$ B decoy transfection markedly attenuated MCT-induced PH and neointimal formation and thereby improved the survival rate and percent increase in body weight.

### **Conclusion**

This study provides direct evidence of the functional importance of NF- $\kappa$ B in the MCT-induced PH experimental rat model. Decoy against the transcription factor NF- $\kappa$ B attenuates pulmonary vascular remodeling in MCT-injected young rats.

Reference: 1. Okada, K., Bernstien M.L., Zhang W., Schuster D.P., Botney M.D. (1998) Am J Respir Crit Care Med., 158:939-950.

Physiological and pathological profiles of the four experimental groups

<b>Group Name</b>	<b>Untreated</b>	<b>SCD</b>	<b>NF-κB</b>	<b>Uninjured</b>
Conditions	MCT+ No Decoy			
Number	8	8	8	8
Survival Rate (%)	63	63	100	100
% Increase in BW	128±20†	137±23†	181±43†	217±33†
Mean AoP (mmHG)	95±8†	82±13†	111±8†	116±3†
Mean PA P (mmHG)	50±7†	46±6†	46±6†	20±2†
PA/A	0.52±0.07†	0.56±0.10†	0.56±0.10†	0.18±0.02†
VOS	0.82±0.49†	0.68±0.47†	0.21±0.47†	0.08±0.02†

Data are expressed as mean ± SD, \* p<0.05 vs untreated, †p < 0.00 vs. uninjured (SCD: Scramble decoy, NF-κB: NF-κB decoy)

**Stretch Induced Up-Regulation of Matrix Metalloproteinases in a Murine in vitro Lung Ventilation Model** A. Murat Kaynar, M.D.,<sup>1</sup> Steven D. Shapiro, MD.<sup>2</sup><sup>1</sup> Dept. of Anesthesia and Critical Care, Beth Israel Deaconess Medical Ctr; Dept. of Medicine, Brigham and Women's Hospital.

**Introduction:** The pathogenesis of ventilator induced lung injury (VILI) and its contribution to acute respiratory distress syndrome (ARDS) is studied at molecular level in recent years. An injurious, in vitro single lung ventilation model is presented in this abstract, where the other lung acts as the internal control. This in vitro approach may circumvent some of the interindividual differences observed in other models of lung injury.

**Methods:** An in vitro single lung ventilation model of the rat was adapted to mice in this study with the approval of Institutional Animal Care&Use Committee. The aim was to evaluate the response of matrix metalloproteinases (MMP) produced within the lung to a stretch injury imitating VILI. The novelty of this model lies in the use of the same animals lung as the internal control. In this study, 8-12 week old C57 B/L6 female mice were used (n=12). Following a lethal dose of pentobarbital, anterior chest wall was removed and lungs were perfused with phosphate buffered saline (PBS). The lungs and heart were then removed en-bloc and placed into a Harvard Apparatus *isolated/perfused lung* system. The lungs were perfused with Krebs-Henseleit solution (without albumin) during the experiment at a constant pressure of 20 cmH<sub>2</sub>O, gassed with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The lungs were ventilated with 8 ml/kg of tidal volume (Tv) at an FiO<sub>2</sub> of 100%. Afterwards, the right main stem bronchus was ligated and only the left lung was exposed to cyclic Tv's (10, 20 and 30 ml/kg) at a rate of 100/min. The experiment was terminated after 3 hours. Both lungs were homogenized in the presence of proteinase inhibitors (PMSF 1 mM, 1-10 Phenanthroline 1 mM, Leupeptin 500 μM, Pepstatin A 500 μM). Four animals were used in each Tv group. The lung homogenates were then analyzed using gelatin and casein zymograms for MMP activity. This technique requires the use of a non-denaturing sample buffer system. Gelatin (24 h) and casein (4 days) zymography from control and ventilated lungs were incubated and stained with Coomassie Blue.

**Results:** Increase of activated MMP9 gelatinase (migrating at 92-82 kDa) and to a lesser degree, of activated MMP2 gelatinase (migrating at 72-68 kDa) was observed in a dose dependent fashion. Faint caseinolytic bands at 22 kDa was observed, which may be the processed MMP12. Subsequent incubation with EDTA confirmed the MMP identity of these bands. Initial Western analysis confirmed MMP9 identity of the gelatinolytic bands.

**Conclusion:** By cleaving matrix components, MMPs could play a role in the disruption of alveolar epithelium and basement membranes in VILI. Gelatinases, MMP2 and MMP9, are known to degrade almost all basement membrane constituents. During acute inflammation, polymorphonuclear neutrophils (PMN), eosinophils, monocytes and lymphocytes are recruited to sites within tissue, they perform some of their functions by releasing MMPs into the pericellular space. But, when present in excess, MMPs can stimulate further inflammation. MMP2 is synthesized by a wide variety of cells (fibroblasts, endothelium, epithelium). MMP9 is produced mainly by inflammatory cells but also by cells that synthesize MMP2 (e.g. endothelial or alveolar epithelial cells). This study used a novel in vitro single lung ventilation model and showed increased MMP2 & -9 expression solely from the lung tissue with mechanical ventilation. And these results will support a future in vivo experiment.

This study was supported by the NIH training grant T-32

## American Society of Critical Care Anesthesiologists Young Investigator Award

9:00 a.m.

Young Investigator Award

**Presenter: William E. Hurford, M.D.**

Systemic Inflammation Increases Immobility-Induced Neuromuscular  
Weakness

**Recipient: Heidrun Fink, M.D.**

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## Systemic Inflammation Increases Immobility-Induced Neuromuscular Weakness

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**Background:** Inflammation and immobility are two main causes discussed in the pathogenesis of critical illness myopathy. Aim of this study was to reflect this pathology and its effect on muscle force generating capacity and muscle histology in a double-hit rat model.

**Material and Methods:** 53 male Sprague-Dawley rats received 3 i.v. injections of either corynebacterium parvum (c.p.) or saline on days 0, 4, and 8. The groups were further divided to have one hind limb (op-leg) immobilized by pinning knee and ankle or sham immobilized. The respective other leg served as control (non-op-leg). On day 12 the individual force generating capacity (single and tetanic twitch) was measured in both legs. The animals were then killed and the muscles excised for histological evaluation (H&E and PAS stain). Statistical evaluation was done with repeated measurement ANOVA ( $p < 0.05$ ).

**Results:** 11 animals died following the bacterial injections, in 2 animals immobilization was insufficient. Single twitch and tetanic twitch are reduced in the op-leg following immobilization as well as inflammation. The combination of immobilization with inflammation further reduced muscle force generating capacity in the op-leg as well as the non-op-leg. Muscle weight of the tibialis cranialis was reduced in the op-leg of the saline + immobilization group as well as in the op- and non-op leg of both c.p. groups. Additional immobilization aggravated loss of muscle mass in the c.p. group. Histological evaluation showed an increase in inflammatory cells in the muscles of all c.p. animals regardless of mobility or op-/non-op-leg. Immobilization and inflammation in the op-leg had an additive effect in terms of inflammatory cells (see table). There were no differences in fiber type composition between the groups.

Group	Single twitch (N)		Tetanic twitch (N)		Inflammatory cells	
	<i>op-leg</i>	<i>non-op-leg</i>	<i>op-leg</i>	<i>non-op-leg</i>	<i>op-leg</i>	<i>non-op-leg</i>
Saline + sham immobil.	2.00 ± 0.73* <sup>§</sup>	2.32 ± 0.62	6.68 ± 1.0* <sup>§</sup>	7.43 ± 0.77 <sup>§</sup>	12.4 ± 9.9 <sup>§</sup>	11.6 ± 6.7 <sup>§</sup>
Saline + immobi.	1.28 ± 0.56* <sup>§</sup>	2.21 ± 0.69 <sup>#</sup>	2.92 ± 1.0* <sup>§</sup>	7.68 ± 0.78 <sup>§#</sup>	19.1 ± 14.1 <sup>§</sup>	8.6 ± 6.5 <sup>#§</sup>
c.p. + sham immobil.	1.42 ± 0.21* <sup>§</sup>	2.19 ± 0.91 <sup>#</sup>	2.92 ± 0.47* <sup>§</sup>	5.71 ± 1.15 <sup>§#</sup>	25.3 ± 15.9* <sup>§</sup>	28.8 ± 21.0 <sup>§</sup>
c.p. + immobil.	0.93 ± 0.24* <sup>§</sup>	1.71 ± 0.60 <sup>#</sup>	1.89 ± 0.55* <sup>§</sup>	4.87 ± 1.48 <sup>§#</sup>	41.6 ± 20.7* <sup>§</sup>	26.8 ± 21.8 <sup>#§</sup>

\*  $p < 0.05$  immobilization vs. sham immobilization, <sup>§</sup>  $p < 0.05$  c.p. vs. saline

<sup>#</sup>  $p < 0.05$  op-leg vs. non-op leg

**Conclusion:** The clinical symptoms of muscle weakness during critical illness myopathy can be depicted in our model of chronic inflammatory response. Inflammation and immobilization as isolated factors already reduce the force generating capacity. The combination of both factors (double-hit) have an additive effect on muscle weakness. Interestingly, inflammation and immobilization together also have a systemic effect in terms of muscle contraction. i.e. muscle force of the non-op leg is also reduced. Histologic evaluation showed a picture of myositis without changes in fiber type composition in the affected muscles, indicating that the inflammatory component is in itself a main factor in the pathogenesis of critical illness myopathy.

Study supported by an educational grant from Kommission für klinische Forschung, Klinikum rechts der Isar (#KKF 56-03).