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Risk Factors of Ventilator-Associated Pneumonia in Critically Ill Stroke Patients: Multivariate Logistic Regression Analysis

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Background: Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring more than 48 hours after initiation of mechanical ventilation. It is the most common nosocomial infection in the ICU, and increases mortality (1). Post-stroke respritaory infections are reported as 1-to-22%, median ~10% (2).To find out the specific risk factors for developing VAP, we performed a surveillance analysis on stroke patients who required mechanical ventilation for more than 48 hours.

Methods: After obtaining approval from the Human Studies Committee of the University of Louisville to retrospectively analyze the prospectively collected patient data, we reviewed the electronic records of our stroke patients admitted between 2004 and 2007.
VAP was diagnosed and confirmed by Clinical Pulmonary Infection Score (CPIS) supported with culture results on days 0 and 3(2). We analyzed host and disease specific and care-related risk factors. Factors with $p<0.20$ in the univariate analysis were considered for the multivariate logistic regression model. In the univariate analyses, categorical variables were compared with the $\chi 2$ test, and continuous data with unpaired t test and Kruskal-Wallis test (SPSS for Windows ver.16).

Results: Within 318 stroke patients admitted to ICU, 68 patients needed to be ventilated for more than 48 hours, and 31 of them developed VAP. Only 4 of the VAP were early-onset pneumonias. Univariate analysis showed APACHE II< GCS<9, emergent intubation, acute neurological worsening, use of proton pump inhibitors(PPI), and hemorrhagic stroke as potential risk factors. After forward stepwise algorithm, APACHE II, GCS<9, COPD, emergent intubation, hemorrhagic stroke, and PPI use were shown as independent risk related factor of the VAP risk model.(Table) Additionally, patients with VAP had longer duration of mechanical ventilation and ICU stay.

Conclusions: In the light of this prospective cohort data, we concluded that stroke patients who were sicker at admission, who had hemorrhagic stroke or conversion, and who got acute neurological worsening and requiring emergent intubation in the course were more likely to develop VAP. Therefore, such patients with higher risks are recommended to be followed closely, and all VAP preventive bundle strategies to be applied in the ICU environment. Additionally, we recommend using alternative gastric protective approaches instead of routine use of PPI.

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Risk Factor	No-VAP (n=37)	VAP (n=31)	Univariate p-value	Multivariate OR & 95% CI
GCS<9 (%)	16	39	0.05	4.5 (1.1-19.5)
APACHE □	17.6±5.8	20.0±6.7	0.12	1.1 (1.0-1.2)
COPD	14	39	0.017	5.0 (1.0-24.0)
Malignancy	3	23	0.11	8.6 (0.8-89.1)
Emergent Intubation (%)	30	58	0.018	14.1 (2.1-93.9)
Hemorrhagic Stroke (%)	8	32	0.01	7.8 (1.1-55.8)
Acute Neurological Worsening (%)	22	55	0.019	
PPI for ulcer prevention(%)	51	74	0.055	6.8 (1.2-39.9)
Albumin	2.8±1.8	2.4	0.066	0.4 (0.3-1.0)

Surveillance of Ventilator-Associated Pneumonia in Aneurysmal Subarachnoid Hemorrhage Patients

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Background: Subarachnoid hemorrhage (SAH) from rupture of cerebral aneurysms is associated with significant mortality and morbidity. About 10-25% of patients die before reaching the hospital, and of those who survive about 40-50% develop significant neurological deficits (1). Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring more than 48 hours after initiation of mechanical ventilation. About 20% of post-aneurysmal SAH patients develop VAP (2). We performed a surveillance analysis on aneurysmal SAH patients who required mechanical ventilation for more than 48 hours to determine host and disease-specific and care-related risk factors.

Methods: After obtaining approval from the Human Studies Committee of the University of Louisville to retrospectively analyze the prospectively collected patient data, we reviewed the electronic records of our aneurysmal SAH patients admitted between 2004 and 2007. VAP was diagnosed and confirmed by Clinical Pulmonary Infection Score (CPIS) supported with culture results on days 0 and 3 (3). We analyzed host and disease specific and care-related risk factors. The $\chi 2$ test was used for categorical data and unpaired t test or Kruskal-Wallis test for continuous data.

Results: Of the 86 aneurysmal SAH patients admitted to the ICU, 45 patients needed to be ventilated for more than 48 hours (52%), and 16 of them developed VAP (19%). More than 80% of SAH patients required either a surgical or endovascular procedure. The majority of VAP cases were late-onset pneumonias (88%), and the duration of mechanical ventilation was longer in the patients who developed VAP. About 20% of VAP patients were also diagnosed with sepsis. However, duration of ICU stay was not influenced by VAP or sepsis. Four patients who did not developed VAP were diagnosed with stroke during their ICU stay. All cause mortality was not affected by VAP.

Conclusions:
In this preliminary report of a prospective cohort trial, it appeared that — unlike the vast majority of neuro-ICU patients — VAP did not contribute to additional morbidity or mortality in the aneurysmal SAH patients. In most patients VAP occurred late in the course of ventilation. In summary, the severity and progress of aneurysmal SAH make the biggest impact in its own morbidity and mortality outcomes.

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Risk Factor	Patients with No-VAP (n=29)	Patients with VAP (n=16)	p-value
ICU Admission GCS<9 (%)	19	59	0.01
Hunt-Hess Score	2.9±1.4	2.5±0.9	0.49
Clinically Proven Vasospasm (%)	28	31	1.00
Mechanical Ventilation (days)	9±8	17±7	<0.01
Day of VAP Diagnosis	-	10±8	-
Sepsis (%)	0	19	0.05
Stroke in the ICU (%)	14	0	0.28
Duration of ICU Stay (days)	18±10	22±11	0.18
Mortality (%)	21	13	0.69

Effect of a Computerized Standard Order Set on Ketamine Utilization in a Burn Center

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Background: Ketamine has been shown to be an effective analgesic in the care of burn patients. There has been no data published on the effect of computerized physician order entry or standard order sets on the use of ketamine in a burn population.

Methods: In this retrospective database analysis we compared all the orders written for ketamine and all dosages of ketamine given in a burn center for a 1 year period of time, including six months prior to, and six months after the implementation of a computerized standard order set for the use of ketamine.

Results: In the 6 months prior to standard order set implementation there were 197 orders for ketamine. After correction for daily patient census, a median of 4.76% of patients each day had ketamine ordered. 194 doses of ketamine were given with a median daily dose of 0.69 mg/kg. In the 6 months after standard order set implementation, there were 475 orders for ketamine. After correction for daily patient census, a median of 9.52% of patients each day had ketamine ordered ($p < 0.0001$). 475 doses of ketamine were given with a median daily dose of 1.12 mg/kg ($p = 0.0011$).

Conclusion: Following the implementation of a computerized standard order set there was a significantly greater incidence of ketamine utilization, and significantly larger doses were given.

Illustrations:
Ketamine Doses Number of doses Mean dose mg/kg Standard deviation Median dose mg/kg p-value
Prior to standard order set 194 1.80 3.22 0.685
After standard order set 475 3.79 9.28 1.121 0.0011

Ketamine Orders Number of orders Mean % of patients ordered ketamine daily Standard deviation Median % patients ordered ketamine daily p-value
Prior to standard order set 197 4.96% 3.85% 4.76%
After standard order set 475 11.10% 8.50% 9.52% <0.0001

Ketamine Doses	*Number of doses*	*Mean dose mg/kg*	*Standard deviation*	*Median dose mg/kg*	p-value
Prior to standard order set	194	1.80	3.22	0.685	
After standard order set	475	3.79	9.28	1.121	0.0011

Ketamine Orders	*Number of orders*	*Mean % of patients ordered ketamine daily*	*Standard deviation*	*Median % patients ordered ketamine daily*	p-value
Prior to standard order set	197	4.96%	3.85%	4.76%	
After standard order set	475	11.10%	8.50%	9.52%	<0.0001

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Retrospective Review: Severe Hypoglycemic Events in the ICU Occurred either on Intermittent Insulin (IIT) or on Continuous Insulin Therapy (CIT)

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Introduction: Since the Van den Berghe trial reported improved outcomes with intensive insulin therapy, ICU teams endeavor to maintain glucose (glu) control. We utilize either IIT or CIT, generally aiming to keep glu between 80-150 mg/dL. We monitor incidence of hypoglycemia and decided to investigate clinical characteristics surrounding severe hypoglycemia (SHYPO; glucose < 40 mg/dL) in our mixed medical-surgical ICU population with a goal of developing an intervention to decrease SHYPO.

Hypotheses: With aggressive glu control goals, SHYPO occurs in ICU patients treated with insulin whether IIT or CIT is administered. SHYPO events may occur with discontinuation of nutritional therapy.

Methods: Sixty SHYPO events that occurred over an 8 month period were retrospectively reviewed as a pilot study for a performance improvement project. Institutional Review Board approval was obtained for this study and subject consent was waived. Glu measures were made using Accu-Chek devices (Roche Diagnostics, Indianapolis, IN) and were typically measured on fingerstick samples. Demographic and clinical data were extracted from medical records. Data were tabulated to characterize these patients and events. Data are presented as descriptive statistics (mean ± SD; %ages).

Data: 37 male and 23 female patients with SHYPO were 58 ± 15 yrs old. 48.3% of patients were previously diagnosed with diabetes mellitus. 25% of SHYPO patients were on steroid therapy; 41.7 % of patients had Cr > 1.5 mg/dL; and 13.3% of patients were on dialysis. Of note, 45% of events occurred during CIT whereas 48.3% of events occurred when IIT was utilized and 6.7% occurred without insulin. 61.6% of events were associated with discontinuation of nutritional therapy. 35% of these SHYPO measures were repeated within 5 min for confirmation. 51.6% of events were treated without repeat measure. Despite our insulin infusion protocol that requests repeat glu measure 15 min after treatment of SHYPO, we noted that only 45% of these events were followed by glu measure within 30 min of SHYPO.

Conclusions: Our pilot study did not collect data to determine overall ICU prevalence of treatment with IIT vs CIT, nevertheless we were surprised that more of these events occurred with IIT than CIT. Many pts in our ICU that are initially treated with CIT are transitioned to IIT but some are treated with IIT originally. Further studies will determine the risk of SHYPO on each regimen by determining the incidence of SHYPO on IIT vs CIT days. As we hypothesized many of these events occurred with temporary discontinuation of caloric intake (enteral and/or parenteral nutrition) and these may be preventable. We are concerned regarding the lack of consistent follow-up of SHYPO and are initiating a performance improvement process to re-educate staff about treatment of SHYPO. Efforts to maintain glu in lower ranges are associated with risks and patients on either IIT or CIT appear to be at risk of SHYPO. Frequent and labor intensive monitoring and treatment is required to protect patients from adverse sequelae of SHYPO.

The Association between Etomidate-Induced Adrenal Insufficiency and Outcome in Critically Ill Patients

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Background: Etomidate is the most commonly used drug to facilitate emergency tracheal intubation in critically ill patients because of its hemodynamic stability; however adrenal suppression has been a documented detrimental side effect. Although relative adrenal insufficiency (RAI) has been associated with worse outcome in critically ill patients, it is not clear whether the use of etomidate for intubation is a relevant and independent risk factor for developing clinically significant RAI or if etomidate-induced adrenal suppression is associated with worse patient outcome.

The objectives of the present study were to investigate the association between etomidate-induced adrenal suppression and hospital mortality, and estimate the association between exposure to etomidate and RAI within 48 hours of the exposure.

Methods: Retrospective study of critically ill patients admitted from 2000 through 2005 at the University of Washington hospitals who had adrenal function testing performed at any time during their hospitalization. Adrenal insufficiency was defined as an increase in cortisol levels <9 ug/dL after stimulation. Patients' medical records were reviewed for time of exposure to etomidate prior to testing. Patients included in the main analysis were those who either had documented etomidate administration within 48 hours of testing or never received etomidate. The primary endpoint was hospital mortality; the secondary endpoint was hospital length of stay. Data were analyzed using univariate and bivariate summaries of baseline characteristics between patients exposed or not to etomidate (chi-square statistics or Student's t-test). Multivariate logistic regression was used to estimate the association between etomidate exposure and mortality.

Results: There were 558 patients admitted to the ICU and undergoing adrenal testing, and of those 23 received etomidate within 48 hours prior to testing. Compared with patients not exposed to etomidate, those who received etomidate were more likely to be female, otherwise there were no differences in age, admission severity score, blood pressure, body temperature, white blood count, mechanical ventilation, baseline cortisol level and stimulation test ($p=.81$). Unadjusted mortality was significantly higher in patients with RAI (42% RAI, 27% normal response, $p <.01$), but not in patients receiving etomidate (30% exposed, 33% non-exposed, $p =.77$). Adjusted ORs of death were 1.72 (95%CI 1.17, 2.52, $p<.01$) for RAI and 0.71 (95%CI .27, 1.88, $p=.49$) for exposure to etomidate. There was no interaction on mortality between RAI and etomidate exposure ($p=.12$). Hospital length of stay was not different among patients exposed to etomidate, whether survivors or non-survivors.

Conclusions: These data support the evidence that relative adrenal insufficiency is associated with worse outcome in critically ill patients. However, there was no indication that administration of etomidate modified this relationship or was associated with worse outcome in this population. Due to potential exposure misclassification and the small sample size, it is possible that we were unable to detect a smaller effect of exposure to etomidate.

Intraperitoneal Injection of a Caspase 3 Inhibitor Can Decrease Neuronal Apoptosis after MCAO

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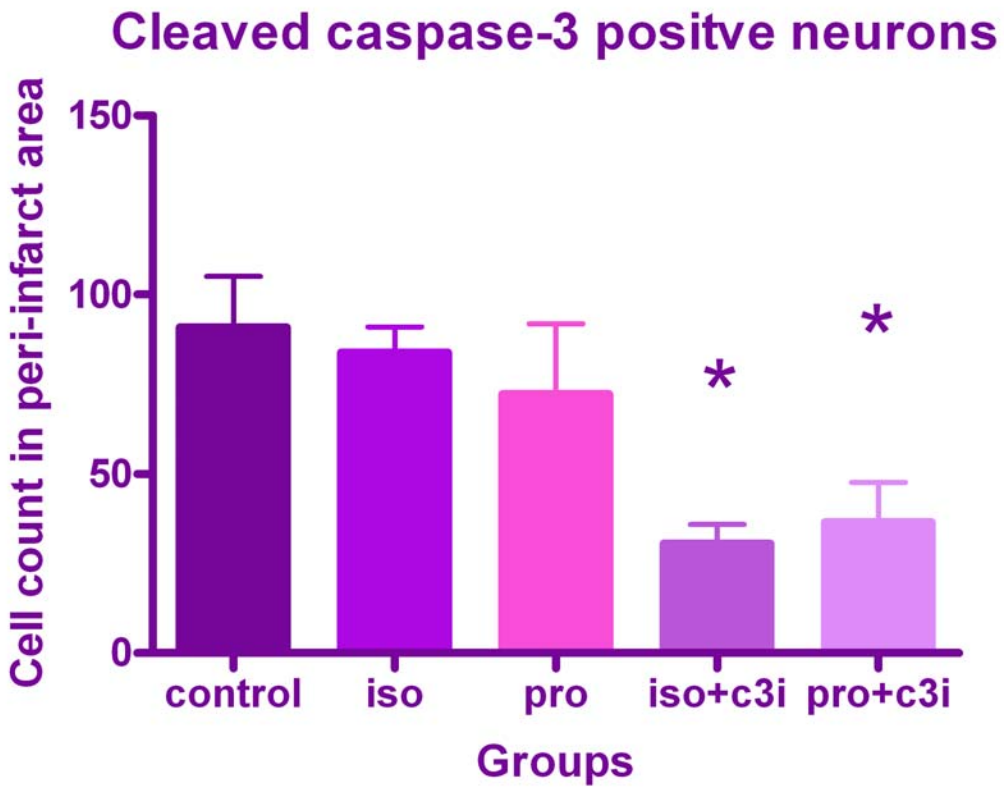
Introduction: In recent years, neuroprotection researchers have used caspase inhibitors to reduce neuronal damage caused by ischemia (1,2,3) . Most of the trials have shown positive effects when these substances were administered intracranially (2). There is very limited evidence that caspase blockers can be used systemically and still have a beneficial effect. We hypothesized that caspase inhibitors could cross the hematoencephalic barrier during ischemic events like stroke.

Materials and Methods: To test this hypothesis, 250 to 350g male Sprague Dawley rats of an average age of six months were examined after MCAO. The control group (group 1) received no treatment following the surgery (n=6). Group 2 received 90 minutes of 1% isoflurane while inside an exposure chamber (n=5). Group 3 received 35 mg/kg/h of Propofol i.v. for 90 minutes (n=5). Group 4 received the 1% isoflurane treatment for 90 minutes followed by 3 systemic injections of a caspase 3 inhibitor (100 µg Z-DEVD-FMK, BD Pharmingen, San Jose, CA) which were given immediately after, 24 hours after and one week after isoflurane treatment (n=5). Group 5 received 35 mg/kg/h of Propofol for 90 minutes followed by the same caspase 3 treatment regimen as group 4 (n=5). Animals were euthanized two weeks after MCAO. Brains were harvested, sectioned, and a series of adjacent sections were stained for TUNEL and cleaved caspase-3. The numbers of positively stained neurons were counted within the peri-infarct area using Optical Disector (Stereology Resource Center, Chester, MD). Statistical analysis was performed using Graphpad Prism 5 with the two-tailed unpaired t-test at a 95% confidence interval, after ANOVA (* $p<0.05$).

Results: The number of neurons that were positive for TUNEL, two weeks after permanent occlusion of the middle cerebral artery, were not significantly different in the groups that were treated with propofol and isoflurane alone compared to the control group. However, the number of positive TUNEL neurons were significantly lower in animals that received Z-DEVD-FMK in comparison with the animals that did not received the caspase inhibitor (see figures). These results were confirmed with the significant reduction in cleaved caspase 3 positive neurons in the groups treated with the caspase inhibitors compared to the control group and the rats treated with anesthetics alone.

Conclusion: Systemic administration of caspase 3 inhibitor has a positive effect in the histological outcome of ischemic brains. With the significant reduction in apoptotic cells, we demonstrated that the caspase inhibitor can reach intracerebral targets after intraperitoneal injections and blocks the apoptotic cascade, decreasing the deleterious effects of programmed cell death.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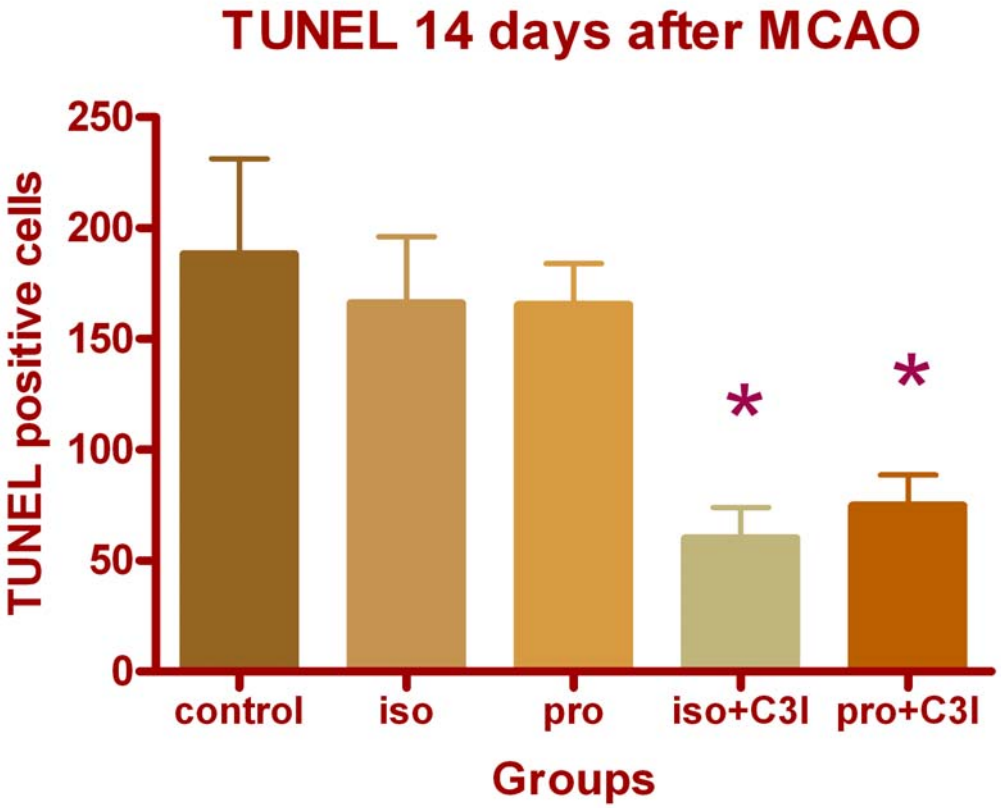
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Profound Hypotension for Three Minutes Results In Cortical and Hippocampal Neuronal Loss in SpragueP Dawley Rats

Rafael E. Chaparro, M.D.[1]; Carolina Quiroga, M.D.[1]; Rachel Karlnoski, Ph.D.[1, 2]; Diana Erasso, B.S.[1]; Enrico Camporesi, M.D.[1,2]; Devanand Mangar, M.D.[1, 2]

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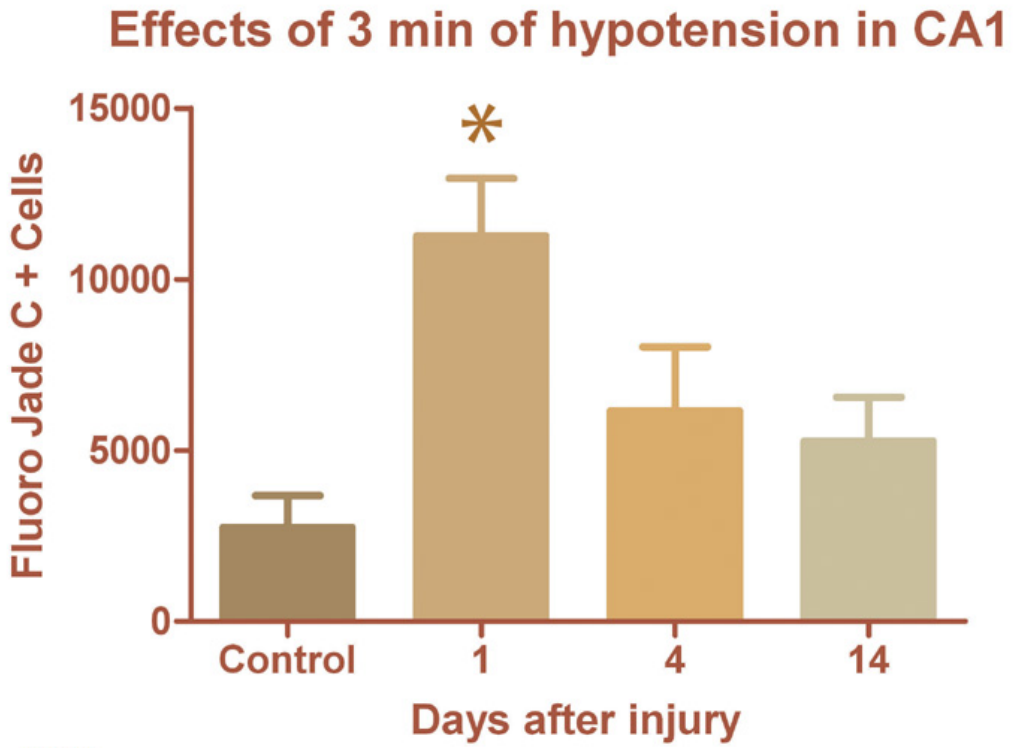
Introduction: Cognitive tests have revealed different degrees ofdysfunction after surgery,the underlying cause of this condition seems to be multifactorial.Hypotension per se may not be the culprit but can be responsible for some neuronal loss. We used a rat hemorrhagic shock model to assess functional outcome and to measure the relative neuronal damage at 1, 4 and 14 days post-hypotension.

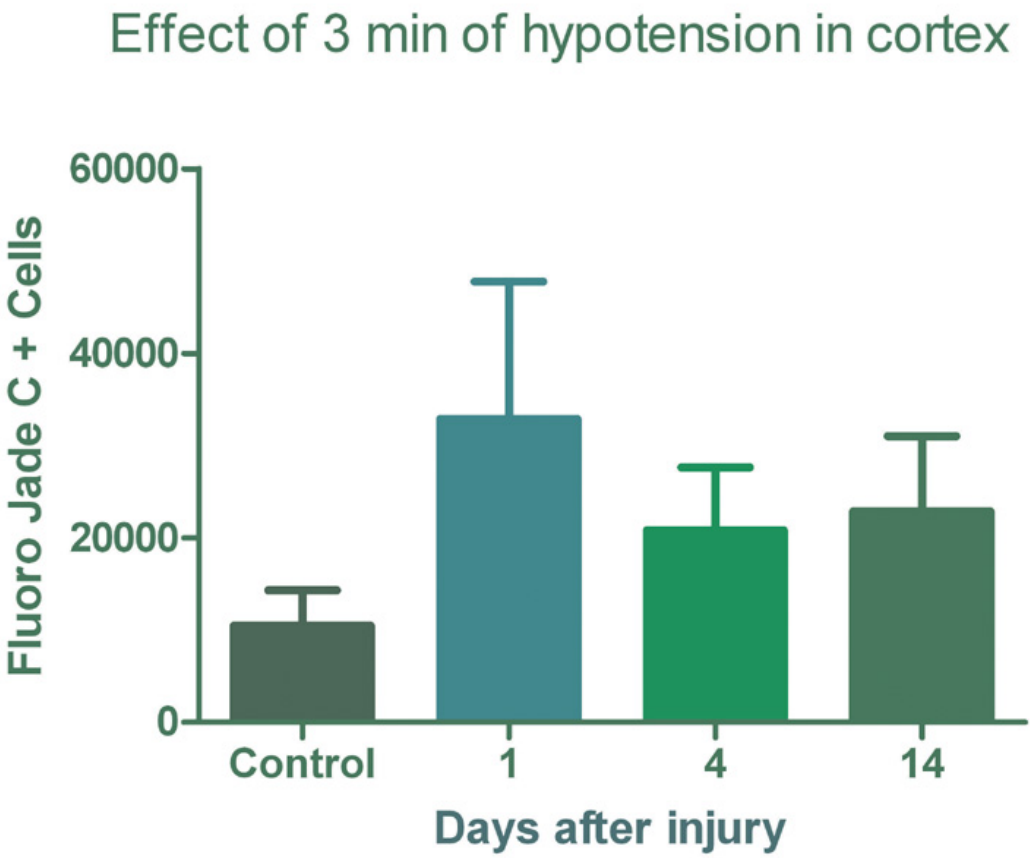
Methods: Six month old, 250g to 350g Sprague-Dawley male rats were subjected to severe hypotension induced by withdrawal of arterial blood from the right femoral artery, while under Isoflurane anesthesia. The mean arterial blood pressure was maintained between 20-30 mm Hg accompanied with isoelectric EEG for one minute per hour, for a total of 3 minutes per rat in a two hour period. Shed blood was immediately returned to venous circulation, returning systemic pressure to normal. The rats were separated into four groups as follows; groups 1, 2 and 3 received 3 minutes of hypotension - 1 minute every hour - and were evaluated at 1, 4 and 14 days, respectively. An additional group of rats, group 4, received a sham operation. A neurological assessment including motor abilities, sensory system evaluation and retrograde memory was performed at 1, 4 and 14 days post-hypotensive insult. Brains were harvested and stained for fluoro-jade C. Image analysis of fluorojade-stained brain sections were used to quantitatively detect neuronal damage (necrosis and apoptosis) after the hypotensive insult. We used stereology (dissector) to quantify fluoro-jade C positive cells in cortex and CA1 hippocampalregion.Statistical analysis was performed using Graphpad Prism 5 with the two-tailed unpaired t-test at a 95% confidence interval, after ANOVA.

Results: Significant differences in cell injury were seen between control rats and rats that received 3 minutes of hypotension solely at one day after the insult represented by numerous fluoro-jade positive hippocampalcells, We demonstrated a similar trend in the frontal cortex; however the differences were not significant.

Discussion: The present observations that repeated hypotensive episodes lead to hippocampal damage may have clinical implications. Patients with hemodynamic TIAs, cerebral arteriosclerotic disease, or orthostatic hypotension may experience repeated nonfatal circulatory deficiencies. This observation suggests that in this hemorrhagic model in Sprague-Dawley rats, brief periods of hypotension result in neuronaldamage or distress in the hippocampal CA1 region one day after insult. However, these “distressed” neurons recover by day 4. We did not find any significant changes in behavior in this study.


Effects of 3 min of hypotension in CA1
15000
10000
5000
0
Fluoro Jade C + Cells
*
Control
1
4
14
Days after injury

p = 0.0021


Effect of 3 min of hypotension in cortex
Fluoro Jade C + Cells
60000
40000
20000
0
Control
1
4
14
Days after injury

Increased Mortality among ICU Patients Geographically Distant from a Closed Model ICU Team's Primary ICU

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Background: As closed system organizational models of Intensive Care increase, the effect of limited bed availability within a given ICU may require more patients to be 'boarded' in multiple, geographically remote ICUs. It is unknown whether in a closed system model, patient location affects the efficiency and quality of care.

Hypothesis: Medical patients boarded in an ICU located one floor below the Medical Intensive Care Unit (MICU) but still managed by the medical service are associated with more days on a ventilator, increased lengths of ICU stay and worse survival.

Methods and Design: We obtained the data for this study from a prospectively developed cohort of 19,244 consecutive admissions to the Medical (MICU) and Surgical (SICU) ICUs of a tertiary care university hospital from Jan 2000 to April, 2008. A total of 8424 patients were admitted to the MICU service, of whom 7851 were admitted to the MICU and 573 patients were boarded in the SICU which is located one floor below the MICU. No formal triage policy dictating where patients were boarded existed during the time period; admission to the SICU was based on no beds being available in the MICU, not by diagnosis. Demographic, case-mix and acute physiology data were collected using APACHE III. Multivariate regression, multivariate logistic 1 digit matching technique, the◊regression, propensity score with the greedy 5 t-test for continuous variables and the chi-squares test for binary variables were performed.

Main Outcome Measure: Days receiving mechanical ventilation, number of indwelling catheters and endotracheal tubes pulled, ICU and hospital lengths of stay and mortality.

Results: No differences in age, gender or readmission status were found between the two groups. Despite an absence of a formal triage policy when boarding patients, more patients with an admitting diagnosis of sepsis, liver failure, and congestive heart failure were admitted to the MICU (33.86% v. 20.94%, p<0.0001 , 3.97% v. 1.57%, p<0.0001, 6.24% v. 4.19% , p=0.02, respectively). Patients with thrombotic vascular disease, cardiac events were found in higher proportions in the SICU (13.61% v. 5.66%, p<0.0001, 3.84% v. 1.50%, p=0.004 respectively).

Despite SICU boarded patients having a lower Acute Physiology Scores (52 v. 59, p<.001) and Apache III scores (64 v. 71, p<.001) they had a higher mortality after adjusting for age, case mix, critical care status and severity of illness (OR=2.27, 95% CI= 1.74- 2.98, p<0.001). On the contrary the average ICU Length of stay (LOS) in the SICU was 32% lower than MICU (% decrease=32, 95% CI; 26 to 38 , P<0.001). In addition the SICU cohort had an average ventilator days per patient that were 0.54 times (or 46%) lower than MICU (% decrease= 46, 95% CI; 36 to 56, P< 0.0001). After propensity score matching the two groups in-hospital mortality was found to be significantly increased (25% v. 16%, p<.001) and ICU LOS and ventilator days per patient significantly decreased (2.61% v. 4.21%, p<0.001, 2.72% v. 4.91%, p<0.001, respectively)

Conclusion: Boarding ICU patients in locations outside a central location in a closed system team model is associated with in an increase in hospital mortality and decreases in ICU length of stay and ventilator days. Examination of factors such as timing, duration and quality of rounds, response time to urgent notifications of patient condition changes, and other process measures may add understanding to explain these observations.

Clinician Practice Relating to Antibiotic De-Escalation in Suspected Ventilator-Associated Pneumonia

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Background: Treatment guidelines for Ventilator-Associated Pneumonia (VAP) emphasize early empiric broad-spectrum antibiotics. However, empiric broad-spectrum antibiotics are often continued unnecessarily and given to patients at low risk of true infection. Antibiotic de-escalation is a strategy that strives to limit the use of unnecessarily broad-spectrum antibiotics and encourage the discontinuation of antibiotics in patients with low risk of true infection.

Hypotheses: We hypothesized that ICU clinicians are reluctant to narrow antibiotic spectra of activity despite data suggesting it is safe, and that they are also reluctant to stop antibiotics in patients unlikely to have true infection once they have started treatment.

Methods: From November 2007 to May 2008, four surgical intensive care units at a tertiary care hospital were screened daily for patients beginning treatment for suspected VAP. Patients were followed prospectively to see if: 1) Antibiotic coverage was narrowed based on sputum culture results 2) Antibiotics were stopped in patients at low risk of true VAP (Clinical Pulmonary Infection Score <6 on days #1 and #3). Assessment of appropriate narrowing of antibiotic spectra was made by one of the co-investigators who is an infectious diseases specialist.

Results: During the study period there were 44 cases of clinician-suspected VAP. In 34 cases sputum cultures grew a pathogenic organism, but in only 21(65%) of these cases were antibiotics tailored to culture data. Additionally, 22 cases were considered “low-risk” for true infection, but in only 2 (10%) of these cases were antibiotics stopped after the third day of treatment.

Conclusions: At our institution, the rates of appropriate antibiotic de-escalation in cases of suspected VAP is poor. Studies looking at the reasons for these practices, and ways to improve them, are needed. In a future second phase of our study, a dedicated ICU pharmacist will provide decision support to the ICU team in situations when de-escalation is indicated. Post-intervention rates of de-escalation will be compared to pre-intervention rates. Reasons for not de-escalating will also be collected and analyzed.

Chronic Application of Pyridostigmine Compensates for Immobilization-induced Up-regulation of Nicotinic Acetylcholine Receptors

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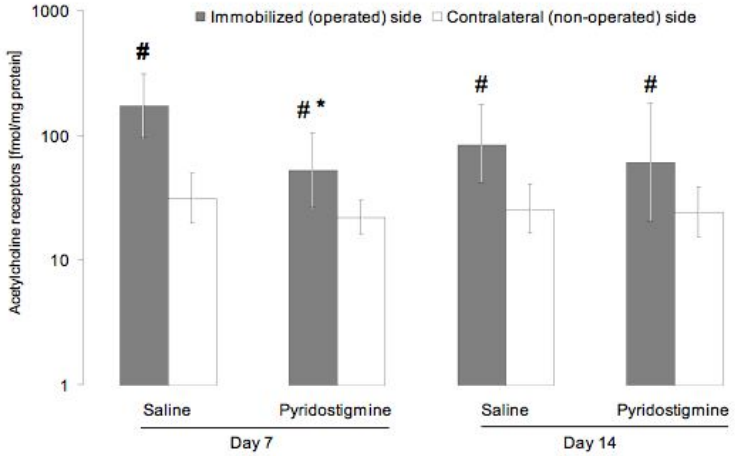
Background: Critical illness often results in immobilization of limb and respiratory muscles, leading to neuromuscular weakness and up-regulation of nicotinic acetylcholine receptors (nAChRs), and thus, complicating the use of muscle relaxants. Pyridostigmine, widely used to improve muscle function in patients with myasthenia gravis, reversibly blocks acetylcholinesterase activity and, thus prolongs and intensifies the physiologic action of acetylcholine in the synaptic cleft. Chronic administration of pyridostigmine in high doses, as previously shown, has the potential to decrease nAChR number. We investigated the effects of chronic pyridostigmine infusion on pharmacodynamics of atracurium and expression of nAChR following immobilization.

Material & Methods: After approval, 40 rats were immobilized in one hind-limb by pinning knee and ankle joints and received either continuous pyridostigmine (15mg/kg/day) or normal saline as a subcutaneous infusion via implanted osmotic pumps. The contralateral (non-operated) leg served as control. Osmotic pumps were removed 24 h before measurements to exclude direct effects of pyridostigmine on muscle function. At 7 and 14 days after immobilization, pharmacodynamics of atracurium and expression of nAChRs were evaluated. The effective dose (ED) of atracurium and its concentration to establish a steady-state 50% twitch depression on the immobilized leg were determined. nAChRs were quantitated using 125I -bungarotoxin.

Results: Immobilization for 7 and 14 days, respectively, significantly ($p<0.05$) increased ED5, ED50 and ED95 of atracurium in the saline group. This was associated with a profound up-regulation of nAChR. On day 7, however, chronic infusion of pyridostigmine significantly ($p<0.05$) reduced ED values, infusion rate and atracurium plasma levels at 50% twitch depression in the immobilized tibialis muscle, while immoblization-induced up-regulation of nAChRs was significantly ($p<0.05$) attenuated. On day 14, resistance to atracurium was still significantly ($p<0.05$) diminished in the pyridostigmine group, evidenced as reduced ED values and a decreased infusion rate (relative to the saline group). Although immobilization significantly ($p<0.05$) increased nAChR expression at this time, there were no differences in nAChR numbers between the immobilized (operated) sides of both experimental groups.

Conclusion: Chronic administration of pyridostigmine has the potential to improve neuromuscular transmission by compensating for the immobilization-induced up-regulation of membrane nAChRs in the tibialis muscle after intermediate-term (7 days) immobilization. Due to decreased nAChR up-regulation, hyposensitivity (resistance) to non-depolarizing muscle relaxants, usually associated with increased nAChR numbers, is attenuated in animals treated with pyridostigmine. After long-term immobilization (14 days), however, the beneficial effects of chronic infusion of pyridostigmine on nAChR expression were no longer significant. Tolerance towards pyridostigmine may explain this observation.

Figure 1. Expression of Nicotinic Acetylcholine Receptors



•# p<0.05 versus contralateral (non-operated) leg
•*p< 0.05 versus saline group (group effect)

Chronic Administration of Pyridostigmine Improves Immobilization-Induced Neuromuscular Weakness

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Introduction: Immobilization is a key factor for the development of muscle weakness in critical ill patients, causing failure to wean from mechanical ventilation. Pyridostigmine increases acetylcholine (ACh) levels in the synaptic cleft by reversibly blocking acetylcholinesterase. The increased ACh concentration improves neuromuscular transmission in patients with myasthenia gravis. We hypothesized that chronic pyridostigmine infusion ameliorates muscle function after immobilization.

Material & Methods: 40 rats were immobilized in one hind-limb by pinning knee and ankle joints and received either continuous pyridostigmine (15mg/kg/day) or normal saline as a subcutaneous infusion via implanted osmotic pumps. The contralateral (non-operated) leg served as control.Osmotic pumps were removed 24 h before measurements to exclude direct effects of pyridostigmine on muscle function. On 7 and 14 days after immobilization, neuromuscular transmission was investigated by mechanomyography.

Results: On day 7 and 14, immobilization significantly impaired evoked and tetanic muscle tensions, while tibialis muscle mass was significantly reduced. On day 7, however, chronic infusion of pyridostigmine significantly increased muscle contraction and tibialis muscle mass on the immobilized side. On day 14, animals of the pyridostigmine group showed increased evoked muscle tension on the immobilized side, while there were no differences in tetanic tensions and tibialis muscle mass. Tetanic fade was significantly more pronounced on the immobilized side in the pyridostigmine group. Specific evoked tensions (tension per mg tibialis muscle mass) were significantly decreased on the immobilized leg in the saline group. At this time, pyridostigmine infusion significantly increased specific evoked and specific tetanic tensions on the immobilized side. On day 14, however, the functional studies indicated no differences in specific tetanic tensions between groups and sides.

Conclusion: Chronic infusion of pyridostigmine improves neuromuscular transmission after intermediate-term immobilization (7 days). The elevated specific tensions on day 7 suggest that the improvement of muscle function is not only due to the prevention of muscle atrophy, but also results of an altered nerve to muscle transmission. On day 14, the beneficial effects of chronic infusion of pyridostigmine on muscle function were no longer significant. Tolerance towards pyridostigmine may explain this observation.

Summary: Pyridostigmine increases acetylcholine levels in the synaptic cleft by blocking acetylcholinesterase.This study shows that chronic infusion of pyridostigmine improves muscle weakness after immobilization.

		saline			pyridostigmine			saline			pyridostigmine		
relative Tibialis Muscle Mass [mg/g]	*contralateral side*	0.59	±	0.03	0.58	±	0.04	0.70	±	0.07	0.65	±	0.03
	immobilized side	0.43	±	0,03 #	0.50	±	0,05* #	0.43	±	0,1#	0.50	±	0,09#
Evoked muscle tension [N]	*contralateral side*	3.7	±	0.7	3.6	±	0.66	4.1	±	0.7	3.9	±	0.3
	immobilized side	2.0	±	0,59 #	3.0	±	0.54* #	2.1	±	0,52 #	2.7	±	0,76* #
Specific muscle tension [N/g]	*contralateral side*	6.3	±	1.2	6.4	±	1.0	5.9	±	0.9	6.0	±	0.5
	immobilized side	4.6	±	1,12 #	6.0	±	1.01*	5.0	±	1,1#	5.4	±	1.0
Peak tetanic tension [N]	*contralateral side*	8.1	±	0.9	7.8	±	1.0	9.2	±	1.4	8.7	±	0.7
	immobilized side	5.1	±	1,87 #	7.1	±	0.65* #	5.2	±	1,6#	6.5	±	1,8#
Specific tetanic tension [N]	*contralateral side*	13.7	±	1.3	13.6	±	1.4	13.3	±	2.1	13.5	±	1.2
	immobilized side	11.8	±	3.9	14.4	±	0,98*	12.0		2.0	12.9	±	1.9
Train-of-Four- Ratio	*contralateral side*	0.99	±	0.01	0.98	±	0.10	0.98	±	0.15	0.97	±	0.01
	immobilized side	1.00	±	0,3#	1.09	±	0,03#	1.00	±	0.03	0.99	±	0.03
Tetanic Fade [%]	*contralateral side*	43	±	11	59	±	14	51	±	12	47	±	40
	immobilized side	46	±	5	52	±	6*	37	±	8	47	±	28*

# p<0.05 versus contralateral (non-operated) leg
* p< 0.05 versus saline group (group effect)

Pressure Support as Main Ventilatory Strategy in Critically Ill Patients with and without Lung Injury: Impact on Mortality and Incidence of Complications

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University of Pittsburgh[1]; Clinica Palermo Fundacion Hospital San Carlos[2]

Background: Multiple ventilatory strategies may be used in the management of critically ill patients depending on the underlying cause of respiratory failure, degree of pulmonary dysfunction, or even specific institutional guidelines. Patients with acute lung injury may require more complex /sophisticated ventilatory support, which may also need heavy sedation and muscle blockade. These patients are exposed to a higher risk for ventilatory-derived complications. Spontaneous breathing methods such as pressure support ventilation (PSV) may be a safe alternative to more commonly used ventilatory modes. Accordingly, we assessed the impact of PSV on tidal volume (Vt), mean airway pressure (MAWP) and subsequent multiple organ dysfunction score (MODS), pneumothorax and mortality in ventilator dependent critically ill patients with lung injury stratified by Lung Injury Score (LIS).

Methods: All adult patients admitted to two surgical/medical Intensive care units (ICU) subjected to pressure support mechanical ventilation (MV) independently of their admission diagnosis were enrolled in the study. Patients were stratified by LIS in two groups: Group 1 LIS< 2.5 and group 2 LIS > 2.5. Exclusion criteria included presence of pneumothorax on admission, varying ventilatory strategies during hospitalization, non-invasive MV, selective ventilation, inability to trigger assisted ventilation. Airway pressures and ventilatory mechanics were measured twice daily prior to any respiratory therapy interventions. Data presented as mean ± 95% CI.

Results: 166 consecutive patients with a mean age of 55 (52-58 years) years, LIS of 2.27 (95% CI 2.16-2.37) and MODS of 3.13 (2.9-3.3) were enrolled. 65.8% (109/166) had LIS < 2.5, and 34.2% (57/166) LIS>2.5. Airway pressures were, Mean PPI 25.3 (24.4 – 26.2) vs. 30.2 (29 – 31.5), PIP 32.9 (30.3 - 35.4) vs. 44.7 (36.6 – 52.9) and MAWP 15.2 (14.7 – 15.7) vs. 21.2 (18.9 – 23.6). Incidence of pneumothorax was 1% (0 – 5.2) vs. 2.4% respectively (p>0.05) and 1.6% (0.8-31) for the complete cohort. Mortality was 11.4% (3.8 – 24.6) vs. 25% (9.8 – 46.7) respectively (overall mortality 21% (14.9-28.2)). Tidal volume was independent of LIS, MODS, level of pressure support (PS) or PEEP in the stratified analysis, and its correlation to PS was poor (r2=0.08). Higher ventilatory support defined by higher plateau airway pressures was related to higher MODS score (MODS 0-3, 25 cm H2O; MODS 4-9, 31 cm H2O; MODS >9, 39.8 cm H2O). The level of PEEP was not significantly different among those who did or did not developed pneumothoracies (9.5 vs. 10.5 cmH2O, p=0.13). Higher tidal volumes were associated with less pneumothorax (OR 0.99, p=0.02). Neither MAWP nor PPI correlated with tidal volume. Incidence of atelectasis was 6.4% (3.2-11.2).

Conclusion: These data demonstrate that PSV is a safe strategy in the management of patients with acute lung injury. Furthermore, PSV may also be beneficial since it was associated with low incidence of atelectasis and barotrauma and with comparable mortality to other ventilatory approaches. The incidence of barotrauma in the group of patients with LIS>2.5 was not significantly different from that of patients with LIS<2.5, which reinforces the safety of the technique.

Automatic Transmission of Data from the Operating Room to the Intensive Care Unit

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Introduction: Pre-transport coordination and communication are essential for safely transporting critically ill patients [1]. We have traditionally relied on verbal communication of data when transferring patients from the operating room (OR) to the intensive care unit (ICU). In patients undergoing cardiac surgery at Columbia University Medical Center, usually the resident in the OR calls the ICU team to give a brief verbal report after the patient has been weaned off cardio pulmonary bypass. This information is usually cursory as the OR physicians are pre-occupied with patient care at this critical juncture. Hence the ICU team does not get a detailed picture of the status of the patient in the OR. Furthermore the ICU team is unable to monitor any subsequent changes in the patient condition. On transporting the patient to the ICU usually the OR resident gives a report to the ICU team comprising of the ICU fellow, the ICU resident and the nurse. The accuracy and the length of this briefing is dependent on the resident experience, the questions asked by the ICU team, and the time demands on all health care providers. The purpose of this study is to present the methodology of information transfer between two locations and to discuss the potential benefits of this system in improving communication between various health care providers.

Methods: In the operating room we use CompuRecord system (Philips Clinical Information Systems, USA) for generating intra-operative anesthesia record. This information system automatically imports physiological data from patient monitors, ventilators, and anesthesia machines. Other data like medical history, critical events in the OR, drugs and blood products administered, and the echocardiaography report are manually entered by the anesthesiologist.

Our goal was to automatically import data from CompuRecord in real time to a secure website accessible to the ICU team. The gold standard we used for selection of data points to be included in our report was the ICU Admission Note. The ICU admission note is a form designed by a group of physicians from cardiac surgery, cardiac anesthesia, and cardiology who identified the information that should be available on patient admission to the ICU. This form has been used for admitting patients in the ICU for many years. [2]

The template which we use for transmission of data is shown in Figure 1. Apart from the data imported from CompuRecord, the physicians in the OR were also able to enter their comments about the complications of the case. This report was made available on a secure webpage after IRB approval. This report was also printed in the ICU prior to the arrival of the patient. The OR physician also paged the ICU fellow by pressing a single button on this webpage, prior to leaving the OR.

To improve effective communication between various health care providers, our system incorporated tools of effective communication like SBAR (Situation, Background, Assessment, and Recommendation) [3].

Results: We were able to introduce a system for automatic transmission of data from the OR to the ICU in real time. With this system we were able to greatly increase the ability of the ICU team to monitor patient progress in the OR. Similar to the previous study by our group which showed 200% increase in quantity of available data[2], we were also able to improve the quantity of data transmitted to the ICU prior to patient arrival without interfering with patient care responsibilities of the OR physicians. Subjectively this has greatly improved the quality of communication at the point of transition of care in the ICU. As was done in a prior study by our group[4], the quality of the data is being evaluated by a cognitive study using ethnographic methodology.

Discussion: The transition of care of a critically ill patient is an important event entailing high degree of risk [5, 6]. Furthermore, lack of effective communication has been shown to be a contributing factor in the majority of sentinel

events and root cause analysis[3]. Thus effective communication becomes crucial in transition of care of patients after cardiac surgery as these patients are prone to significant hemodynamic lability. The ability of the ICU team to effectively respond to these physiological perturbations after cardiac surgery is dependent on advance preparation,[7] and effective communication at the time of transition of care . With the advent of computerized record keeping in the OR, it is now possible to transmit the patient status at critical points to the ICU team prior to patient arrival in the ICU. This automatic transmission of patient information along with alteration of pre-admission ICU workflow will result in decrease in incidence of sentinel events during transition of patient care.

References

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Figure1: Template for transmission of data

OR , Date:

Name: MRN: DOB: Gender:

Height: Weight: ASA Classification:

Surgeon: Anesthesiologist:

Procedure:

Past Medical History:

Pre-operative Medication:

Allergies:

Intra-operative Drugs:

Intravascular Access:
☐PAC, ☐ Cordis/ CVL; ☐Left, ☐ Right; ☐ Internal Jugular, ☐ Subclavian, ☐ Femoral
☐ABP; ☐ Left, ☐ Right; ☐ Upper Ext, ☐ Lower Ext
☐PIV; ☐ Left, ☐ Right; ☐ Upper Ext, ☐ Lower Ext

Intubation: ☐ Easy, ☐ Difficult

Times (Minutes): XC: CPB: Ischemic: Circ arrest/ Antegrade:

Vasoactive Medications:

NE: , AVP: , DBT: Milr:

NTG: , Epi: , Amicar: Insulin:

Propofol: , Fentanyl: , Midazolam:

☐ Nitric Oxide

Input/ Output:

RBC: U, Cell Saver: U, FFP: U, Platelets: U

Cryoprecipitate: U, Crystalloid: ,

Urine Output: cc

Post-Operative TEE Report:

OR Complications:

- ☐ Arrythmias
  - ☐ Asystole/ Conduction abnormalitie/ Bradycardia requiring pacing
  - ☐ Ventricular arrhythmias requiring Cardioversion/ Drugs
  - ☐ Atrial Arrythmias not present at baseline
- ☐ Reinstitution of CPB
- ☐ IABP insertion
- ☐ Coagulopathy
- ☐ Unexpected surgical complications
- ☐ Others

Pacing wires: ☐ Atrial, ☐ Ventricular

Chest tubes (Number): Pleural: Mediastinal:

Submit

Severe Morbidity and Mortality in Pregnancy and Puerperium: A 12-year Review in Intensive Care Unit

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Background: We maternal morbidity and mortality have become rare in developed countries, they still remain underestimated in the developing countries the objective behind this study was a determine and explore cause of severe obstetric morbidity and mortality in our unit.

Materials and Methods: Retrospective collection of data for all obstetric patients admitted in Our intensive care unit over an 12-year period (September 1995- December 2007).
Data collected include age, reason to admission, prevalence per year, stay on the ICU, prognostic scoring:APACHE II ,obstetrical Simplified Acute physiology Score (ob-SAPS)and the outcomes.

Results: During twelve years, there were 756 obstetric admissions in our unit , 19 were still pregnant and 737 puerperium or postpartum .
Admission was planned to 16 (2,1%) parturient (valvular heart diseases or recently intra cerebral haemorrhage).The median duration of stay was 5 days (range 1-66). Median Ob-SAPS was 17,1 (range 10 – 32) and APACHE II was 11 (range 4 -33).The reason of admission in ICU ,prevalence and outcome are represented in table (1)

Reason for admission	Number of parturients	Percent %	Prevalence per year	Number of maternal death	Mortality related a reason %
Eclampsia / preeclampsia	389	51,5	35 ± 13	11	2,9
Haemorrhagic shock	149	19,7	14 ± 8	11	7,4
Severe sepsis / septic shock	71	9,4	6 ± 3	15	21,1
Cardiac diseases / puerperium cardiomyopathy	36	4,7	3 ± 2	4	11,1
Pulmonary emboli / thrombophlebitis	25	3,3	3 ± 1	3	12
Intracerebral haemorrhage	19	2,5	3± 2	5	26,3
Status epilepticus	13	1,7	2±1	0	0
Other Neurologic disorders	4	0,5	1±1	1	25
Intentional overdose drug	5	0,7	1±1	1	20
Iatrogenic/Anesthesic accident	45	6	4 ± 2	3	6,7
Total	756	100	63± 31	54	7,1%

Our statistics are relatively higher than estimations inspite of the progress made in quality of obstetric care and intensive care. this is due to the fact that :
Majority of the cases of maternal death was unbooked or relatively under investigated for antenatal care this leads us

to acknowledge the existence of risk factors related to pregnancy .Others causes unrelated to pregnancy and the pre-existing conditions pregnancy lead to an increase in morbidity and mortality .

Conclusion: The results of this study reflect morbidity gravity degree but they remain valid only our unit. National investigation is needed to find out national morbidity and maternal mortality.

Heparin-induced Thrombocytopenia Exacerbated by Unintentional Insertion of a Heparin-impregnated Central Venous Catheter: A Case Report and Call for Unified Labeling Practices

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Introduction: The Institute for Safe Medication Practices (ISMP) defines heparin as a high-alert medication. In addition to antithrombotic adverse effects, heparin exposure is associated with heparin-induced thrombocytopenia (HIT), an immune-mediated prothrombotic disorder. All forms of heparin are contraindicated in patients with active HIT or heparin allergy. Labeling designed to assist clinicians in averting medical errors with "high-alert" or “dangerous” medications is becoming routine in the pharmaceutical and health-care industries (Figure 1). Additionally, the US FDA has required manufacturers to specifically disclose the latex-containing status of medical devices (e.g., central venous catheters [CVC]) to avoid anaphylactic reactions in latex-sensitive patients (ref 1) Given similar rates of post-exposure antibody production between latex (5-8%) and heparin (8-14%) (ref 2), and severity of post-exposure complications in sensitive patients (i.e., patients with active HIT), it seems prudent to also require labeling that more clearly discloses the heparin-containing status of CVCs (Figure 2). The following case outlines the importance and potential impact of this proposal.

Case Report: A 69-year-old woman was admitted to the Surgical ICU following motor vehicle collision sustaining acetabulum and long bone fractures. Following two weeks of venous thromboembolism (VTE) prophylaxis with heparin, the patient developed HIT with extensive bilateral thrombosis, significant bullae, and skin necrosis requiring trans-metatarsal amputation of the left foot. On day 40, an infected PICC line was replaced with a right internal-jugular CVC. Over subsequent days, the patient’s trunk developed areas of skin necrosis. Anticoagulation also became difficult to control and argatroban dosage requirements increased 10-fold. After further examination by the critical care team, it was determined that the CVC was heparin-impregnated. The patient required excisional debridement of her right breast and axilla; two weeks later a mastectomy was completed. The patient continued argatroban for several weeks and was ultimately converted to warfarin therapy prior to hospital discharge.

Discussion: This unfortunate case reinforces the importance of avoiding heparin-impregnated CVCs in patients with active HIT. Moreover, labeling that clearly disclosed the heparin-containing status of the CVC might have helped prevent extension of HIT-associated thrombosis and sequelae. We recommend that the medical device industry and US FDA follow the direction of the ISMP and consider the use of heparin in any CVC or other relevant medical devices in a “high-alert” fashion. The American Association of Health-System Pharmacists advocates that the most prominent items on the pharmaceutical product label should be information in the best interest of safety with less prominence given to company names or logos (ref 3). We propose adoption of a unified packaging and device labeling system that clearly defines the heparin-containing status of all CVCs similar to what the US FDA currently requires for latex.

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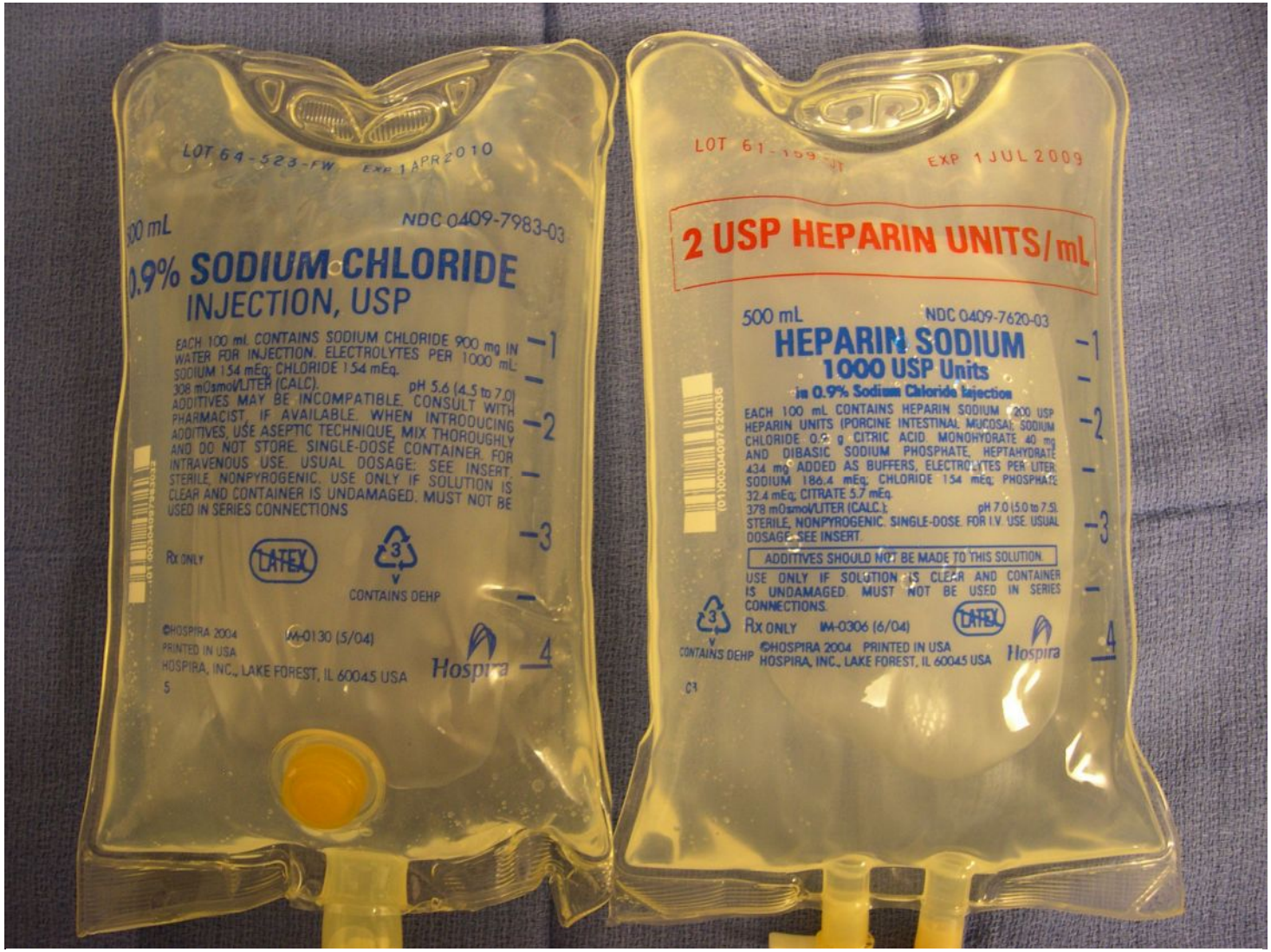

Figure 1: Two 500 ml bags of 0.9% NaCl. It is clear which contains heparin (note red color)

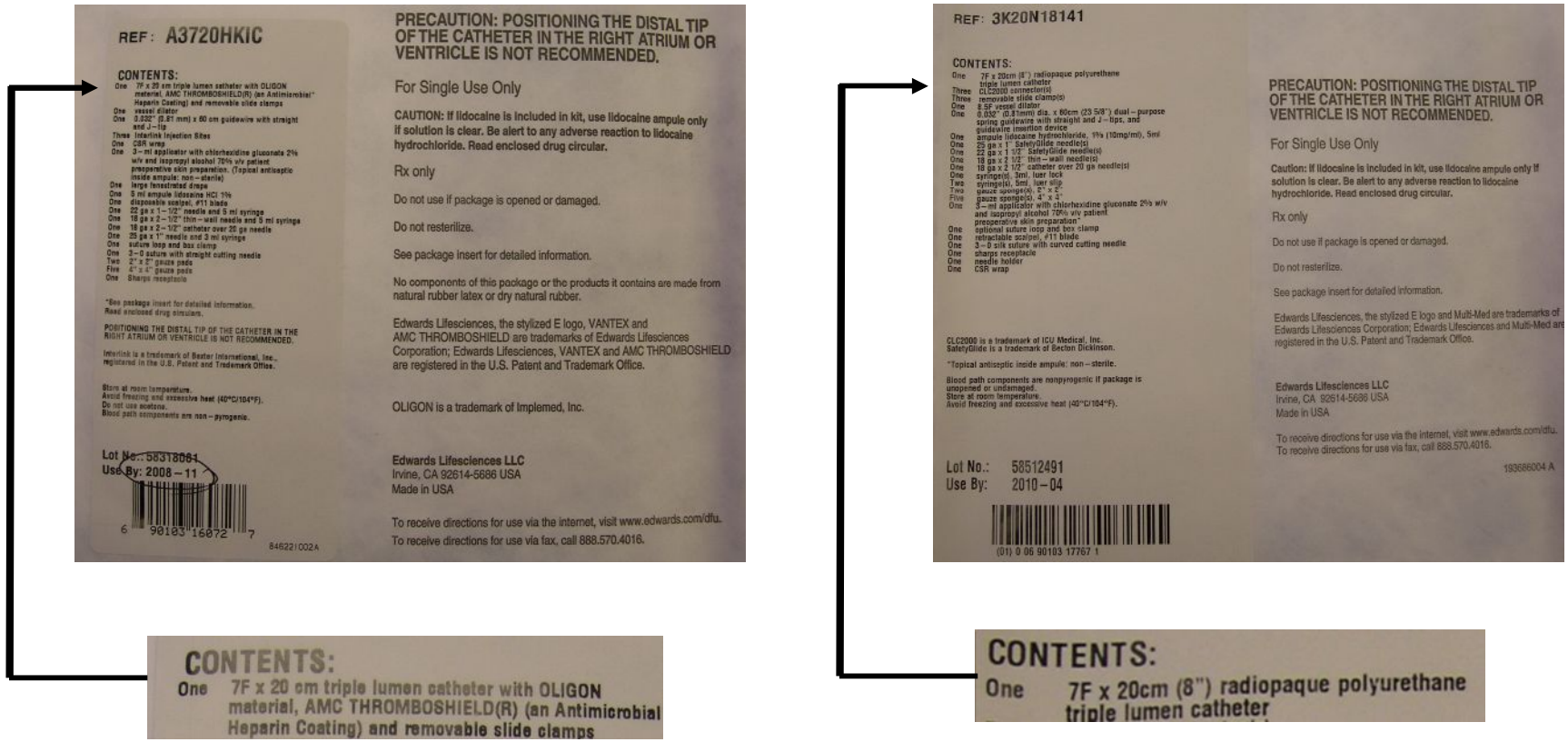

Figure 2: Two CVC line kits (left). Which kit contains the heparin coated catheter? Unless user is familiar with the reference number of the manufacturer there is no way to know that an "H" in the reference number signifies heparin. The top kit contains the heparin coated CVC.

Elevated Preoperative HbA1c in Non-diabetic Patients is Associated with Prolonged Length of Stay after Cardiac Surgery

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Purpose: Diabetes mellitus is an independent risk factor for complications after cardiac surgery. The proportion of patients undergoing cardiac surgery that have undiagnosed or latent diabetes, and the risk that this represents, is unknown. Elevated glycosylated hemoglobin (HbA1c) is an index of persistent hyperglycemia. We hypothesized that an elevated preoperative Hb1Ac might be an indicator of perioperative risk in patients undergoing cardiac surgery with diagnosed and undiagnosed diabetes.

Methods: After IRB approval we measured preoperative HbA1c in 355 patients undergoing cardiac surgery. An HbA1c level > 6.5% was considered to be elevated. Results are expressed as mean ±SD.

Results: Of the 355 patients enrolled, 103 patients (29.0% of total) had a preoperative HbA1c >6.5%. Of these, 61 (22.5% of total) had diagnosed diabetes and 42 (15.3% of total) did not have this diagnosis. Compared to patients with no diabetes and a normal HbA1c, non-diabetic patients with elevated HbA1c had a similar Parsonnet score (10.2 ± 7.7 vs. 9.7 ± 8.7, p = 0.71) but a significantly longer hospital length of stay (LOS): 7.0 ± 7.2 vs. 11.8 ± 13.0 days, p=0.006.

Conclusions: More than 15% of the patients in this study had preoperative elevation of HbA1c levels without a prior diagnosis of diabetes mellitus. These patients had a significantly longer hospital LOS, suggesting that patients with undiagnosed diabetes and preoperative hyperglycemia may be at a higher risk for postoperative complications. It appears prudent to include assessment of HbA1c in the workup of patients prior to cardiac surgery even if they do not have an existing diagnosis of diabetes. Further studies are required to evaluate whether hospital LOS may be improved by deferring elective cardiac surgery until normalization of HbA1c by glycemic control is achieved.

Non-Invasive Ventilation, Immediately Following Extubation and For One Hour Postoperatively, Improves Lung Mechanics 24 Hours Following Bariatric Surgery

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Background: We have shown that in morbidly obese patients with obstructive sleep apnea, the application of non invasive ventilation (NIPPV), using either a mechanical ventilator or the Boussignac CPAP system, improves lung mechanics 24 hours following laparoscopic bariatric surgery (LBS), compared with CPAP commenced in the recovery room (1,2). In these studies all of the patients received CPAP for at least 8 hours following surgery. The purpose of this study was to determine whether the differences demonstrated resulted from the one hour of NIPPV immediately post op, or whether it was the combination of immediate NIPPV plus overnight CPAP.

Methodology: 30 MO patients undergoing LBS with standardized anesthesia care were randomly assigned to receive NIPPV immediately following extubation in the operating room (NIPPV group), or no postoperative non invasive ventilation (control group). All of the patients had preoperative sleep studies, and none had clinically significant obstructive sleep apnea.
The NIPPV were administerd biphasic positive airway pressure (BiPAP) via a portable non invasive ventilator (BiPAP Esprit , Respironics, Pa) continuously following extubation thru arrival to PACU for a total of 1 hour, or as long as was tolerated up to 1 hour. The patients in the control were extubated to supplemental oxygen. None of the patients received non invasive ventilation following following discharge from the recovery room.
Spirometry was performed by a blinded observer in the preoperative holding area, 1 hour following admission to PACU and 1 day postoperatively.

Results: Thirty patients were enrolled into the study, 10 into the NIPPV group and 20 into the control group. There was no difference in preoperative characteristics, lung function, body mass index, neck circumference, age, apnea hypopnea index, intraoperative PEEP or opioid dosage between the groups. One hour after arrival in PACU all subjects had a statistically significant reduction in pulmonary function tests with NIPPV group having clinically and statistically significant better preservation of preoperative function. There was a mean reduction in forced expiratory volume (FEV1) from preoperative values of 27.5% in the NIPPV group in the first hour postoperatively versus 51.0% in the control group ($p<0.005$). The forced vital capacity (FVC) was reduced by 25% in NIPPV group versus 47.5% controls ($p<0.005$) and the peak expiratory flow rate (PEFR) was reduced by 33.9% in NIPPV group versus 60.9% controls ($p<0.005$).

Twenty four hours postoperatively all subjects continued to manifest statistically significant reduction spirometry values with NIPPV group having clinically and statistically significant better preservation of preoperative function. There was a mean reduction in FEV1 from preoperative values of 30.6% in the NIPPV group 24 hours postoperatively versus 43.2% in the control group ($p<0.05$). The FVC was reduced by 26% NIPPV versus 43.0% controls ($p<0.05$) and the PEFR was reduced by 25.0% NIPPV versus 60.9% in the control group ($p<0.005$).

Discussion: This was a study involving morbidly obese patients, without obstructive sleep apnea, undergoing laparoscopic bariatric surgery. Immediate post extubation non invasive ventilation that was continued for 1 hour significantly improved spirometry values at 1 hour and 1 day post operatively compared with patients that did not receive postoperative non invasive ventilation.

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2. ASA abstract # 952434 (2008)

Table 1: Spirometry values in NIPPV group versus controls at 1 hour and 1 day post operatively.

Variable	1 hour NIPPV Group % Reduction from baseline (mean)	Control Group % Reduction from baseline (mean)	% Difference in values (ARR)	p value
FEV1 1 hour postop	27.5%	51.0%	23.5%	<0.005
FVC 1 hour postop	25.0%	47.5%	22.5%	<0.005
PEFR 1 hour postop	33.9%	60.9%	27.0%	<0.005
FEV1 1 day postop	30.6%	43.2%	12.6%	<0.05
FVC 1 day postop	26.0%	43.0%	17.0%	<0.05
PEFR 1 day postop	25.0%	50.0%	25.0%	<0.05

Biological Markers in Blood of Patients with Cerebral Vasospasm Following Subarachnoid Hemorrhage

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Cerebral vasospasm is one of the most significant complications of aneurysmal subarachnoid hemorrhage (aSAH).

Objective: The goal of this study was to determine whether Nitric Oxide (NO) substrates or intermediates in blood are predictive markers for onset of cerebral vasospasm.

Methods: This prospective clinical study compared 18 patients who had cerebral vasospasm following aSAH and 16 patients who did not develop cerebral vasospasm following aSAH. Early plasma samples were obtained within 1-4 post bleed days (PBD) and late plasma samples were collected 7-14 post bleed days (PBD). Citrulline, Ornithine, Arginine levels were analyzed using an amino acid analyzer which uses an ion exchange column for separating the amino acids monitored with chromatography.

Results: On PBD 1-4, Ornithine and Arginine levels were significantly lower in patients with vasospasm 29.3 ± 3.4 nM/ml and 26.8 ± 1.6 nM/ml, compared to patients without vasospasm 41.6 ± 3.3 nM/ml and 39.4 ± 4.2 nM/m, respectively ($p=0.01$). On PBD 7-14, the Nitric oxide substrate levels trended lower in patients with vasospasm compared with patients without vasospasm; however the difference was less probably due to NO stores being replenished.

Conclusion: Immediately following aneurysmal subarachnoid hemorrhage, Nitric Oxide substrates levels are lower in patients with cerebral vasospasm. Thus, Nitric Oxide substrates may be important early markers for cerebral vasospasm.

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Sedation with Dexmedetomidine Improves Clinical Outcomes In Septic ICU Patients Compared To Lorazepam

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Introduction: New strategies for sedation in mechanically ventilated (MV) patients have yielded improvements in patient outcomes including acute brain dysfunction; however, the effect of sedation regimens across different diagnostic groups has yet to be explored. In this pilot project, we evaluated the impact of sedation using dexmedetomidine versus lorazepam, in an a priori determined subgroup of septic patients enrolled in the MENDS trial.(1)

Methods: The MENDS study enrolled adult medical/surgical MV patients and excluded those with neurological disease, severe liver failure, active coronary ischemia, and seizures. Patients were randomized in a double blind fashion to receive dexmedetomidine (DEX)-based (maximum 1.5 mcg/kg/hr) or lorazepam (LZ)-based (maximum 10 mg/hr) sedation for up to 5 days, titrated to a target Richmond Agitation-Sedation Scale score. Patients were evaluated for delirium using the Confusion Assessment Method for the ICU. Patient demographics and outcomes were compared for the two sedation regimens separately in the septic and non-septic groups, assessing for interactions due to the presence of sepsis.

Results: Of the 103 patients who were randomized to study drug in the MENDS study, 39 patients were admitted with sepsis, with 19 in the DEX group and 20 in the LZ group. Baseline demographics, ICU type and admission diagnoses of this septic subgroup were balanced between DEX and LZ groups, with the median (interquartile range, IQR) age being 57 (49, 66) vs. 55 (44, 65), p=0.66 and APACHE II scores of 30 (24, 32) vs. 28.5 (25, 32), p= 0.86, respectively. Median DEX dose was 0.9 mcg/kg/hour and LZ dose was 3.3 mg/hr in the septic patients. DEX vs. LZ septic patients achieved the targeted RASS score 65% of days versus 35% (p=0.02), had improved clinical outcomes (Table 1) and a lower risk of death at 28-days [Hazard ratio 0.3 (0.1, 0.9), p=0.036]. Tests for interactions between treatment groups and sepsis showed that the presence of sepsis impacted the beneficial effects of DEX for delirium/coma free days (interaction p=0.12), delirium free days (interaction p=0.09), MV free days (interaction p=0.036) and 28 day mortality (interaction p=0.12). Cardiovascular hemodynamics were similar between the 2 groups and there were no differences in cardiac, hepatic and endocrine laboratory data.

Conclusion: In this subgroup analysis of septic patients from the MENDS trial, sedation incorporating dexmedetomidine reduced the duration of delirium and coma and length of time on the ventilator, and reduced the risk of dying as compared to lorazepam. This serves as a hypothesis generating analysis to help direct further prospective study in such patients.

(1) Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007;298:2644-2653.

Additional File #1:

Table 1. Patients Outcomes in patients with and without sepsis

	Patients with sepsis			Patients without sepsis		
Outcome variable	DEX (N=19)	LZ (N=20)	P value	DEX (N=33)	LZ (N=31)	P value
Delirium/coma free days	8 (4,10)	1.5 (1,4)	0.002	5 (1,10)	4 (1,7),	0.38
Delirium free days	10 (8, 10)	7.4 (4,8)	0.007	9 (5,10)	7 (6,10.5)	0.87
Coma free days	10 (9, 12)	7 (1,9)	0.003	10 (8,12)	8 (6,10.5)	0.045
MV free days	9.5 (0,12)	2 (0,9)	0.04	4.2 (0,10)	5.4 (0,10)	0.8
28-day mortality	21%	50%	0.036	15%	13%	0.8

Serum Tryptophan Levels Are Independent Risk Factors for Transitioning to Delirium in Mechanically Ventilated ICU Patients

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Introduction: Delirium, highly prevalent in critically ill patients, is associated with poor outcomes, including death. The synthesis and release of serotonin, dopamine and norepinephrine, neurotransmitters implicated in the pathogenesis of delirium, depend upon the ratio of their precursor amino acids (tryptophan, tyrosine and phenylalanine, respectively) in the plasma to the other large neutral amino acid (LNAA) that compete to cross the blood brain barrier via the large amino acid transporter (LAT-1).(1,2) This pilot study aimed to determine if alterations of tryptophan (Trp), tyrosine (Tyr), and phenylalanine (Phe) plasma levels were associated with a higher risk of transitioning to delirium in critically ill patients.

Methods: We enrolled mechanically ventilated (MV) medical and surgical ICU patients from within the MENDS study (3) after excluding those with neurological disease, severe liver failure, active cardiac ischemia, or substance abuse. Plasma amino acid concentrations were determined on days 1 and 3 using liquid chromatography. Three independent variables were calculated by dividing the plasma concentrations of Trp, Phe, and Tyr by the sum of all LNAA concentrations (valine, leucine, lysine, isoleucine, tryptophan, tyrosine and phenylalanine). Delirium was assessed daily using the CAM-ICU. Markov regression models were used to analyze the associations between plasma LNAA ratios and transition to delirium after adjusting for age, APACHE II, prior cognitive status and sedative exposure.

Results: Markov modeling requires at least 2 assessments in order to study transitions of cognitive status; hence 97 of the 103 patients enrolled in MENDS were included in the analysis. Patients had a high severity of illness (median APACHE II, 28; IQR, 24 to 32) and 42% of patients were admitted with sepsis and/or acute respiratory distress syndrome. Patients with high or very low tryptophan to LNAA ratios were at increased risk of transitioning to delirium ($p<0.0001$), after adjusting for potential confounders. Alternatively, phenylalanine and tyrosine levels were not associated with transition to delirium ($p=0.80$ and 0.65, respectively). In keeping with our earlier studies, older age ($p=0.0002$), and exposure to lorazepam ($p=0.0001$) and to fentanyl ($p=0.005$) were also associated with a higher probability of transitioning to delirium, while dexmedetomidine exposure was not ($p=0.75$).

Conclusions: In this pilot study, plasma tryptophan to LNAA ratios were associated with transition to delirium in mechanically ventilated ICU patients, suggesting that serotonin is important in the pathogenesis of ICU delirium. Future studies aimed at studying the role of amino acid precursors of neurotransmitters are warranted.

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Effect of Intensivist Co-Management on Clinical Outcomes in Patients with Major Burn Injury

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Background: The structure and organization of critical care units has been the subject of an increasing number of studies demonstrating improved patient outcome related to the presence of dedicated high-intensity intensivist staffing.(1-3) High-intensity models are defined as those intensive care units (ICUs) where trained intensivists manage or co-manage all patients. The Burn Center at the study institution consists of a 10 bed burn intensive care unit and a 10 bed intermediate care unit. In the latter part of 2005, the traditional multi-disciplinary burn team added an intensive care physician to participate in co-management of all patients admitted with major burn injury. Data from the hospital quality management database suggested decreased mortality for all patients admitted to the burn unit after the change took place. This study is performed to examine this effect.

Methods: Cohort study of all patients meeting criteria for major burn injury for periods before and after implementation of the intensivist model. Patient acuity was assessed using the Abbreviated Burn Severity Index (ABSI). (4) Based on historical mortality, our power analysis predicts need for approximately 300 patients to demonstrate significance. We report data on the first 141 patients. Patient demographics and mortality data were compared using t test and $\chi 2$ statistics.

Results: From April, 2004, through June, 2007 141 patients were admitted with criteria for major burn injury as described by the American College of Surgeons.

	No Intensivist(n=50)	Intensivist(n=91)	
Age	51.0±17.3	44.6±17.8	p<0.05
Female	17	21	p=0.16
%TBSA Burn	38.8±20.3	40.6±21.2	p=0.62
ABSI	8.57±2.68	9.06±2.41	p=0.32
Mortality %	34%	19%	p<0.05

All-Cause Mortality:
Absolute Risk Reduction 0.15 (CI 0.01-0.31)
Number Needed to Treat 7 (CI 3-188)
Relative Risk Reduction 0.45 (CI 0.02-0.69)

Conclusions: Our data including 141 patients with major burn injury suggest a trend in decreased all-cause mortality after the addition of a trained intensivist to the multi-disciplinary burn team. While the study is not designed to identify what aspects of intensivist involvement are responsible for the observed result, possibilities include improved monitoring and assessment of the patients, better execution of evidence based guidelines, enhanced use of daily goal sheets and positive cultural changes among members of the care team. Ongoing research is needed to determine the strength and significance of this trend, potential to generalize these findings to other institutions and identify the factors intensivists may bring to critical care of the burn patient contributing to improved outcome.

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Association of Hemoglobin and Mortality in Severely Anemic, Critically Ill Patients

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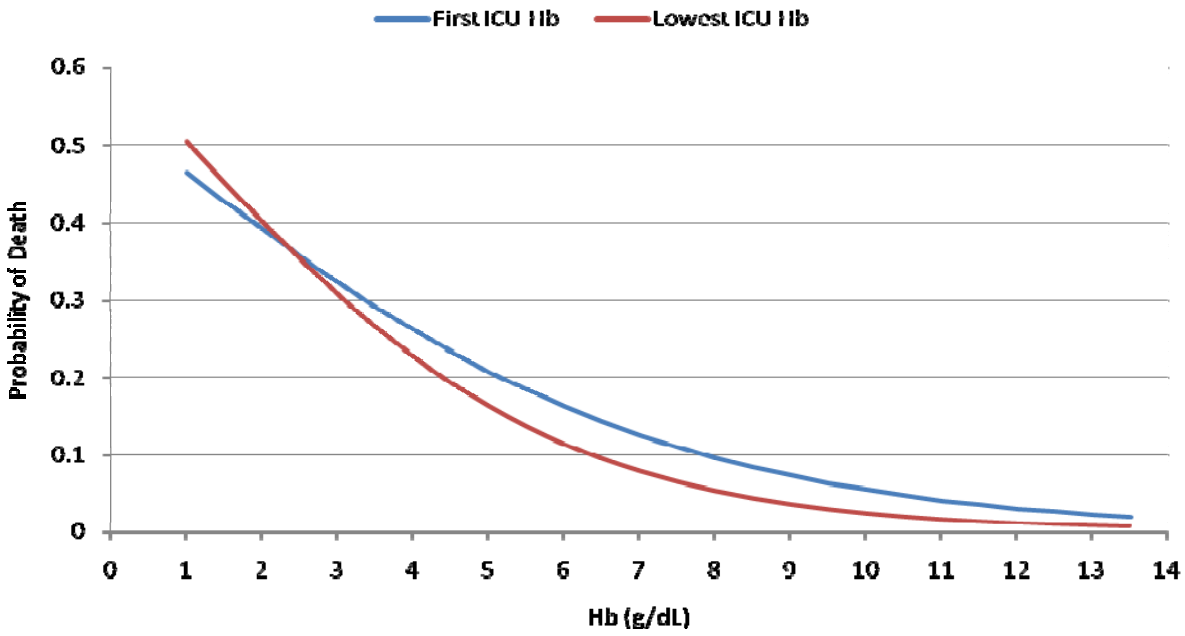
Following drop in hemoglobin (Hb) concentration, a relatively large reserve capacity alongside with several adaptive mechanisms ensure that tissue oxygen consumption is not affected.[1,2] Once a critical Hb concentration is reached, oxygen consumption is compromised and ischemia develops. If left uncorrected for long enough, irreversible organ injury and imminent death will follow. This critical Hb level is likely to be affected by several factors and it varies from patient to patient. Few studies have looked at the survival of patients with low Hb levels who refused allogeneic transfusions.[3-6] However, these studies mostly focused on surgical patients, and there are limited data on critically ill patients.

Following IRB approval, data of critically ill patients who developed severe anemia (as defined by Hb<8.0 g/dL within first 48 hours of ICU admission) and who refused allogeneic blood transfusions were reviewed. Patients who were younger than 18 years old, pregnant, post cardiac surgery, treated with artificial Hb-based oxygen carriers, and those admitted with diagnosis of traumatic brain injury or acute myocardial infarctions and patients who expired within first 24 hours of admission were excluded. All patients received anemia management including diagnosis and treatment of iron deficiency if present, followed by recombinant erythropoietin, folate and IV iron guided by Hb level.

A total of 160 admissions (143 patients) met the criteria. Patients had a mean age of 60.1±16.9 years and 65.3% were female. Mean APACHE II score was 22.6±8.0. Mean initial Hb value during the first 24 hours of ICU admission, lowest Hb during ICU stay and Hb at discharge/death were 6.4±2.0, 5.3±1.6, and 6.2±2.0 g/dL, respectively. Median ICU length of stay and days to lowest ICU Hb were 3.5 and 1 day, respectively. ICU mortality rate was 16.3%, and mean initial and lowest ICU Hb values were significantly lower in expired versus survived patients: 5.5 vs. 6.5 g/dL (p=0.012); and 4.5 vs. 5.5 g/dL (p=0.013), respectively. Although mean APACHE II score of expired patient was higher compared with those who survived (23.8±7.3 vs. 20.0±8.0, p=0.030), there was no difference in age or gender ratio. After adjusting for APACHE II score, lower first and lowest ICU Hb values remain statistically significantly associated with higher ICU mortality (OR=1.361, 95% CI 1.068-1.736 per g/dL, p=0.013, for first ICU Hb; and OR=1.585, 95% CI 1.197-2.099 per g/dL, p=0.001, for lowest ICU Hb). Figure shows the logistic regression curves for probability of death versus first and lowest ICU Hb levels in these patients.

This study shows that Hb is a predictor of mortality in severely anemic, critically ill patients, independent of severity of their disease, and lowest ICU Hb is more significantly associated with mortality compared with first ICU Hb. Nonetheless, the mortality rates in these patients, even in very low ranges of Hb, are rather low, indicating a relatively good tolerance of low Hb concentrations in these patients, likely to be a result of meticulous management of anemia and other blood conservation modalities in this patient series.


First ICU Hb
Lowest ICU Hb
Probability of Death
0.6
0.5
0.4
0.3
0.2
0.1
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Hb (g/dL)

Outcomes of Transfusion in Critically Ill Severely Anemic Patients

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A number of observational studies have shown that critically ill patients who receive allogeneic blood transfusions have worse outcomes compared with not-transfused patients. These unfavorable outcomes include increased ICU, hospital and overall mortality,[1-3] higher risk of developing acute respiratory distress syndrome,[4,5] longer length of stay,[2,3] and higher risk of infections.[6,7] A landmark randomized trial has also shown that outcomes in critically ill patients treated with a restrictive transfusion approach (transfused if hemoglobin [Hb] <8 g/dL) is not worse than those who were transfused if Hb <10 g/dL.[8] However, it is still not clear if transfusion has any benefits in severely anemic patients in ICU.

Following IRB approval, outcomes of 150 ICU admissions of 133 critically ill patients who refused allogeneic blood transfusion and had at least one Hb below 8 g/dL within first 48 hours of admission to ICU were compared with a cohort of 150 admissions of 139 transfused patients, matched for age, gender, initial ICU Hb level and APACHE II score. Patients admitted with traumatic brain injury, acute myocardial infarction, or status post cardiac surgery were excluded. All patients received anemia management including diagnosis and treatment of iron deficiency if present, followed by recombinant erythropoietin, folate and IV iron guided by Hb level.

Overall, patients had a mean age of 62.4±16.6 years, mean initial Hb level of 6.6±1.6 g/dL, and 61.0% were female. Mean age, gender ratio, initial ICU Hb and APACHE II score of the transfused and untransfused admissions were similar. A median of 3 units of allogeneic blood was given in transfused admissions. ICU, out-of-ICU, and overall hospital mortality rates were not statistically significantly higher in untransfused versus transfused admissions: 16.7% vs. 13.3% (p=0.419); 10.0% vs. 8.0% (p=0.545); and 26.7% vs. 21.3% (p=0.279), respectively. Ten percent of untransfused admissions developed at least one positive blood culture during ICU stay, as opposed to 12.0% of transfused admissions (p=0.580). However, 17.3% of transfused admissions developed rise in cardiac enzymes (either CK, CK-MB or TnT above normal range) versus only 8.0% of untransfused admissions (p=0.015). Median ICU length of stay of transfused and untransfused admissions was similar (3.0 vs. 3.5 days, p=0.293). Despite similar initial Hb levels, lowest and discharge Hb levels were significantly lower in untransfused admissions versus transfused ones: 5.5 vs. 6.3 g/dL (p<0.001) and 6.4 vs. 8.5 g/dL (p<0.001), respectively.

This study shows that in spite of having lower Hb levels during ICU admission, mortality outcomes, ICU length of stay and blood infections in severely anemic, critically ill patients treated with no transfusion are not worse that those who are transfused. On the other hand, heart ischemia as indicated by rise in cardiac enzymes may be more common in transfused patients. Therefore, these patients can be safely managed without use of allogeneic transfusions, if their anemia is properly managed.

Right Ventricular Dysfunction in Patients with Ventricular Assist Devices

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Introduction: Right ventricular dysfunction (RVD) is associated with worse outcomes in cardiac surgery but has received little attention. This study's objective was to identify variables associated with RVD and outcomes among patients with RVD who receive ventricular assist devices (VADS).

Methods: Data for the 233 consecutive patients receiving a VAD at our center from 1996 to 2007 were recorded prospectively. RVD was graded as none or mild, moderate, or severe by echocardiography. These and other clinical data were prospectively collected. Bivariate and multivariate analyses were performed.

Results: Patients with severe RVD were not different from patients without severe RVD with respect to gender, NYHA class, etiology of heart failure, ionotrope requirement, and requirement of life support. Significant bivariate preoperative and outcome variables associated with severe RVD are listed in table. Using multivariate analysis, variables independently associated with severe RVD included 1) right ventricular stroke work index (RVSWI) (OR=0.998, p=0.002); 2) ejection fraction percent by surface echo (OR=0.893, p=0.003); and 3) placement of right VAD (RVAD). RVADs were more common among these patients compared to patients with normal RV function (OR=10.917, p=0.001). Preoperative variables independently associated with RVAD placement at time of LVAD placement included 1) RVSWI (OR=0.991, p=0.001); 2) cardiac arrest within twenty-four hours prior to surgery (OR=18.8, p=0.02); and 3) severe right ventricular dysfunction (OR=16.1, p=0.002). Finally, severe RVD was associated with both longer lengths of stay (OR=1.06, p=0.012) and fewer days at home (OR=0.98, p=0.001), as well as significantly higher hospital mortality (OR=3.12, p=0.02).

Conclusion: With the increasing incidence of heart failure and a limited supply of donor hearts, VAD demand is increasing. Improved perioperative management in areas such as reducing right heart strain may improve outcomes. Due to either primarily right ventricular failure or to biventricular failure, patients with right ventricular dysfunction are at significantly higher risk of morbidity, mortality, and resource use. Using predictors for patients with RVD who are more likely to receive an RVAD may improve our selection for patients who would benefit from biventricular assist devices or even VADs themselves.

Variables Associated with Right Ventricular Dysfunction

	Degree of Right Ventricular Dysfunction		
	Normal (n=77)	Moderate (n=65)	Severe (n=77)
PREDICTORS			p-value
Ejection Fraction (%)	14.97	14.04	12.17 0.01
Cardiac Index	2.36	2.16	1.99 0.001
RVSWI	621	511	368 <0.0001
AST	60.47	57.37	120.43 0.02
PT	11.65	12.08	12.89 0.001
OUTCOMES			p-value
ICU LOS (days)	8.92	9.66	13.62 0.05
Home time (days)	193.61	175.78	75.91 0.0007
Mortality (%)	12	7.69	22.08 0.01

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Moderate Hyperglycemia Is Not Associated with Adverse Outcomes in Heart Transplant Patients

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Hyperglycemia has been reported as a risk factor for complications after cardiac surgery. The importance of intraoperative versus postoperative glucose control is not determined. Some studies show no effect of intraoperative glucose control on postoperative complications whereas other studies indicate a beneficial effect of glucose control, beginning intraoperatively. One study demonstrated risk of postoperative hypoglycemia when tight intraoperative glycemic control was attempted. We analysed the relationship between intraoperative glu > 160 mg/dl, and postoperative adverse outcomes in both diabetic and non-diabetic heart transplant patients.

Methods: We analysed retrospectivly data from 239 heart transplant patients at our institution from Jan 2003 to Dec 2005. The Columbia University Physician Assistant Cardiothoracic Surgery Clinical Research Project was used. Data included demographics, preoperative risk factors, intraoperative peak and mean blood glucose levels, and postoperative complications.
Postoperative adverse outcomes were defined as renal failure, stroke, deep sternal wound infection, sepsis or endocarditis, respiratory failure, or death within 30 days. We assessed the associations of peak intraoperative glu with postoperative adverse outcomes using t-tests or Fisher's exact tests at the bivariate level and the logistic regression model at the multivariate level.

Results: Peak intraoperative glu varied between 78-427 mg/dl and mean intraoperative glu varied between 78-419 mg/dl. Glu > 160 mg/dl occurred in 90% of patients. Overall, 30% of the patients experienced postoperative adverse outcomes, including 8 deaths. Peak intraoperative glu was not significantly associated with any recorded postoperative adverse outcomes ($p>0.05$) in either diabetic or non-diabetic patients. Peak glu > 200 was not significantly associated with one-year mortality ($p=0.5$). Mean glu levels > 160 mg/dl were associated with renal failure ($p=0.0342$) and sepsis ($p=0.0213$). Intraoperative hyperglycemia may not be a reliable predictor of postoperative complications in heart transplant patients unless glu is very high. Steroid-induced hyperglycemia in transplant patients may represent a different metabolic derangement than stress-induced hyperglycemia, described after major surgery.

Conclusions: We did not observe any predictive value of peak glu for adverse postoperative outcomes in heart transplant patients. Association between mean glu > 160 and some outcomes indicate that intraoperative glu in heart transplant patients may be predictive of postoperative complications only at higher levels than have been reported for open heart patients, not receiving steroids.
Our data must be interpreted with caution. Limitations of this study include the retrospective cohort design, the modest sample size, and the heterogeneity of the study subjects. The results reported in this study need to be confirmed in prospective controlled studies before any definite conclusions can be made.

The LIFETEST Procedure

Survival analysis by max glucose 2 levels: < 210 and > = 210