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Dexmedetomidine Protects Mice from Radiocontrast Induced Nephropathy

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INTRODUCTION: Radiocontrast nephropathy (RCN) is a clinical problem with no effective preventive therapy. RCN is proposed to result from contrast-induced intrarenal ischemia and direct cytotoxicity. Dexmedetomidine (DEX) is a relatively new sedative agent with known vasodilative and diuretic effects. We hypothesized that dexmedetomidine may protect against radiocontrast nephropathy.

METHODS: To test our hypothesis, we performed in vivo studies using a murine model of RCN and in vitro studies using cultured human kidney (HK-2) cells. After Columbia University IACUC approval, we implanted miniosmotic pumps SQ that delivered saline (vehicle) or 4ug/kg/h DEX in isoflurane anesthetized male C57BL/6 mice. Following overnight dehydration, we induced RCN in these mice by injecting iohexol (1.5mg/kg Iodine SQ) after inhibiting cyclo-oxygenase (indomethacin, 10 mg/kg SQ) and nitric oxide synthase (levo-nitroargininemethylester, 10 mg/kg). Twenty-four hours later, plasma creatinine was determined, and kidneys were collected for H&E staining and histological analysis. Proximal tubular necrosis, tubule vacuolization, and cellular apoptosis was quantified by a board certified pathologist blinded to treatment group. For mechanism investigation we assessed changes in renal blood flow and direct cellular toxicity. We measured outer medullary renal blood flow following radiocontrast induction in saline or DEX pretreated mice using laser Doppler probes. For in vitro analysis of direct renal tubular toxicity, immortalized human proximal tubule cells were pretreated with 10uM DEX or saline and then exposed to various concentrations of iohexol. Cellular viability was assessed using an MTT assay.

RESULTS: Dexmedetomidine protected mice from radiocontrast nephropathy as evidenced by reduced renal dysfunction after iohexol injection (DEX plasma creatinine: 0.8 +0.3 mg/dL, n=10 vs. Saline: 1.5 +0.3, n=7, p=0.011, mean +SEM)(Fig.1). DEX treated mice also showed significantly reduced proximal tubular necrosis, tubule vacuolization and cellular apoptosis (DEX: 0.50 +0.4 necrotic tubules/400x field, n=6 vs. Saline: 5.7 +1.6, n=6, $p<0.01$; DEX: 22.8 +8.2 vacuolized tubules/400x field, n=6 vs. Saline: 59.6 +7.0, n=6, $p<0.007$; DEX: 0.8+ 0.3 apoptotic cells/400x field, n=6 vs Saline: 8.8 +2.3, n=6, $p<0.006$)(Fig.2). DEX treated mice had significantly higher renal medullary blood flow after RCN injury (cumulative effect, $p<0.049$; and at the 90 minute post iodine time point, $p<0.028$, Fig.3A). DEX treatment failed to improve viability after iohexol exposure in isolated human proximal tubule kidney cells, n=12 at each concentration (Fig.3B).

CONCLUSION: Dexmedetomidine protects mice against radiocontrast nephropathy. Preserved renal blood flow may mediate this protection. DEX mediated inhibition of RCN does not appear to be related to decreased direct tubular cytotoxicity. Our findings may have significant clinical relevance to improving outcomes following radiocontrast exposure.

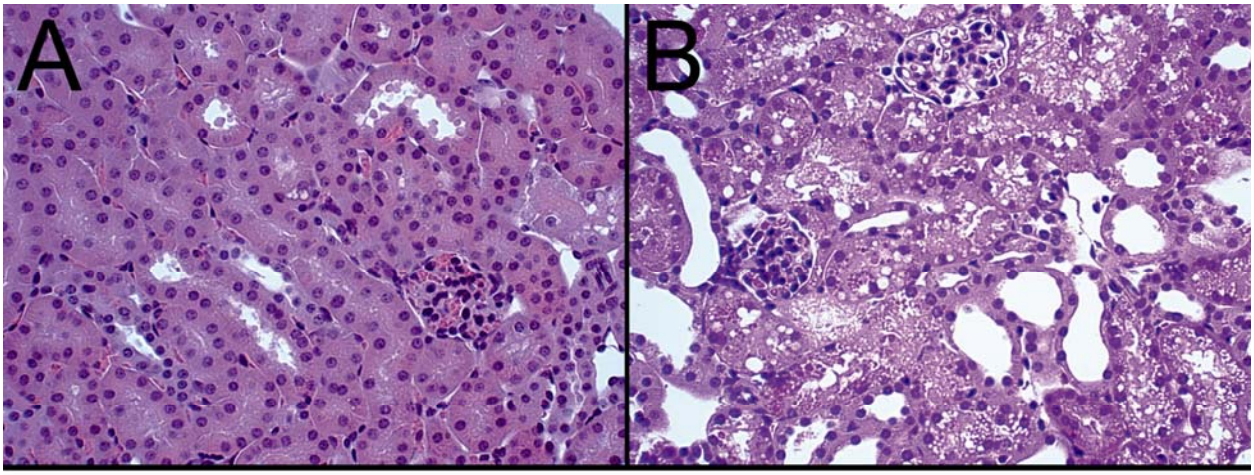

Figure 2: Haematoxylin and eosin stained renal cortex. (A) Dexmedetomidine pretreated animals. (B) Saline controls showing necrosis, vacuolization, and apoptosis characteristic of radiocontrast nephropathy.

Inducible Nitric Oxide Synthase-Mediated Sirt1 Inhibition and P53 Activation In Burn Injury-Induced Apoptosis In Skeletal Muscle

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ABSTRACT CONTEXT: Muscle wasting leads to decreased mobilization, difficulties in weaning off respirators, prolonged rehabilitation and hospitalization. We have previously shown that inducible nitric oxide synthase (iNOS), a major mediator of inflammation, plays an important role in burn injury-induced muscle apoptosis, which in turn contributes to muscle wasting. However, molecular mechanisms by which iNOS mediates apoptosis remain to be investigated. S-nitrosylation, a covalent attachment of NO to cysteine thiols has emerged as a major mediator of NO actions. Sirt1 NAD+-dependent deacetylase, a mammalian homologue of the yeast longevity gene, Sir2, is involved in apoptosis and stress resistance. Inhibition of Sirt1 upregulates acetylation of p53, which promotes p53-mediated apoptosis. We therefore investigated the effects of iNOS on Sirt1, p53 and apoptosis in vitro, in cultured skeletal muscle cells and muscle of burned rats.

METHODS AND RESULTS: Site-directed mutagenesis revealed that iNOS and NO donor reversibly inactivated Sirt1 by S-nitrosylation of evolutionally conserved cysteine residues in Sirt1 in vitro and in intact cells. Treatment of C2C12 myocytes with cytokine admixture (LPS [1 ?g/ml], TNF-? [1 ng/ml], IFN-? [20 U/ml]) for 3 days induced iNOS expression, and acetylation and increased expression of p53 in parallel with S-nitrosylation of Sirt1. iNOS inhibitor, L-NIL (200 ?M), reverted cytokine admixture-induced changes in p53 and S-nitrosylation of Sirt1. Next, we evaluated the effects of iNOS inhibitor in burned rats. Full-thickness third degree burn injury comprising 55% of total body surface area was produced under anesthesia by immersing the back of trunk for 15 sec and abdomen for 8 sec in 80°C water in male Sprague-Dawley rats (160-190 g). Then the animals were treated with iNOS inhibitor, L-NIL (60 mg/kg, b.i.d., IP), or phosphate-buffered saline for 3 days. At 3 days after burn or sham-burn, rectus abdominis was taken for biochemical analyses. Burn injury induced robust iNOS expression and S-nitrosylation of Sirt1, although Sirt1 protein expression was unaltered. Acetylation and protein expression of p53 were significantly increased in burned rats, in association with increased expression of Bax, a p53-dependent proapoptotic molecule. iNOS inhibitor, L-NIL, reverted burn-induced alterations in Sirt1, p53 and Bax, in association with reversal of burn injury-induced apoptosis, as judged by cleavage of caspase-3 and poly(ADP-ribose) polymerase, and TUNEL assay.

CONCLUSIONS: These results demonstrated that iNOS induction after burn injury was associated with S-nitrosylation of Sirt1, p53 acetylation, and increased expression of p53 and Bax, and apoptosis in skeletal muscle, all of which were reverted by iNOS inhibitor. Our data suggest that iNOS may contribute to burn injury-induced muscle apoptosis and atrophy by S-nitrosylation-mediated Sirt1 inactivation, leading to activation of the p53 pathway.

SOD Overexpression Reduces Intestinal Ischemia-Reperfusion Injury in a Natural Igm-Dependent Model

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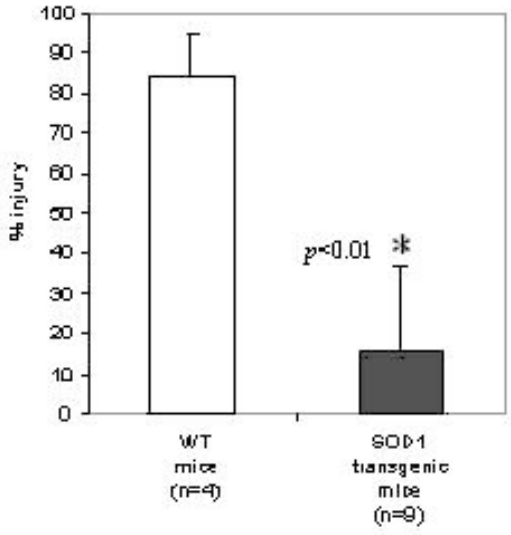
Acute mesenteric ischemia is a medical emergency with a mortality rate of 70-90%. Immediate reperfusion of the ischemic tissue is the best treatment, but may lead to acute tissue injury, called ischemia/reperfusion (I/R) injury. Two theories are suggested for the mechanism of reperfusion injury. One involves intracellular response to ischemia, while the other involves extrinsic acute inflammation. Supporting evidence for the intracellular response theory is derived from studies showing that reactive oxygen species (ROS) are generated by multiple sources during I/R, and contribute to tissue injury. Supporting evidence for extrinsic inflammation is derived from studies showing that reperfusion of ischemic tissues elicits an acute inflammatory response involving serum complement system, which is activated by natural IgM. Whether the ROS-mediated mechanism plays a role in natural IgM-mediated mechanism is still unknown. We studied this important question by using transgenic mice overexpressing a human antioxidant enzyme, superoxide dismutase (SOD1). SOD scavenges ROS by converting superoxide anions (O2-) into hydrogen peroxide (H2O2), which is then removed by glutathione peroxidase and catalase. If intracellular response contribute to extrinsic inflammation, we predicted that inhibiting ROS mechanism will protect animals from natural IgM-mediated I/R injury. In our murine model of natural IgM-dependent I/R injury, we induced intestinal ischemia by applying a microclip to the superior mesenteric artery. After 40 minutes of ischemia, the microclip is removed, and reperfusion of the mesenteric vasculature is confirmed by the return of pulsation to the vascular arcade and a restoration of pink color to the intestine. At the end of a 3-hour reperfusion period, the ischemic segment of the jejunum is harvested and the central 4cm portion is cut and used for pathological studies. Our study showed that SOD1 transgenic mice have significant reduction in intestinal I/R injury compared with wild-type littermates (Figure 1). Since in previous studies of this murine model we have established that I/R injury is mediated by natural IgM, the SOD1 protection in the current study suggests that the ROS-mediated mechanism (the intracellular response) plays a role in the natural IgM-mediated (the extrinsic inflammation) I/R injury.



Botulinum Toxin Increases Sensitivity to Atracurium, Despite Profound Up-Regulation of Nicotinic Acetylcholine Receptors on Muscle

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BACKGROUND: Systemic infection with C. botulinum causes paralysis of the affected muscles leading to respiratory failure, often requiring endotracheal intubation and mechanical ventilation. In this study, we examined the short-term effects of botulinum toxin on muscle function and pharmacology including expression of nicotinic acetylcholine receptors (nAChRs). In the view of the difficulties in maintaining an animal with generalized paralysis for prolonged periods, the effects of botulinum toxin were studied after the injection (infection) of toxin into a single muscle (tibialis).

METHODS: After IRB approval Male Sprague-Dawley rats (n=26) were injected with 2.5U of botulinum toxin into the tibialis muscle. Another group of control animals (n=25) received an equivalent volume of saline. At 0, 4 and 16 days following injection, neuromuscular function and pharmacodynamics of atracurium were evaluated. The effective dose (ED) of atracurium and its concentration to establish 10 minutes of steady-state 50% twitch depression were determined. nAChRs were quantitated using 125I-bungarotoxin.

RESULTS: On the day of injection (day 0), the tibialis muscle tensions, including tetanic tension, and muscle mass did not differ between groups and sides when examined within 4 hours of injection. On day 4, there was complete neuromuscular paralysis on the botulinum toxin-injected side, while its contralateral, non-injected side showed a decrease in evoked muscle tension. On day 16, although evoked tensions could be generated on the toxin-injected side, the evoked and tetanic tensions, including muscle mass were decreased relative to the contralateral side and to saline injected controls. At this time, Train-of-Four fade and tetanic fade were evident on the toxin-injected side. Normalized to muscle mass, the specific single twitch tensions and specific tetanic tensions (tensions/muscle mass) were reduced on the contralateral side at day 4 and the toxin-injected side at day 16. The dose-response curve for atracurium on the injected side at day 16 was shifted to the left, resulting in a lower ED50 together with a smaller slope. The ED50 values on the contralateral, non-injected side were also decreased at day 4 and 16. The atracurium plasma levels to maintain a steady-state 50% paralysis were significantly decreased in the toxin-injected group on day 16. nAChRs concentrations in the injected tibialis muscle were significantly increased in the experimental groups on day 4 and 16.

CONCLUSION: Infection with botulinum toxin follows a time-course from complete neuromuscular paralysis to severely depressed muscle function with increased fatigability. Muscle weakness was not only seen on the toxin–injected side, but also on the contralateral tibialis suggesting the spread of toxin. An increased sensitivity to atracurium was observed, despite profound up-regulation of nAChRs. The presence of fade and decreased specific tension suggest that the peri-junctional increase in nAChRs cannot compensate for the decreased release of acetylcholine one usually sees with botulinum toxin.

Table ASA 2007

		Day 0		Day 4		Day 16	
		saline	**2.5U**	**saline**	**2.5U**	**saline**	**2.5U**
Evoked muscle tension [N]	*contralateral side*	2.98 ± 0.14	2.67 ± 0.11	2.96 ± 0.07	1.75 ± 0.06 #	3.47 ± 0.16	3.35 ± 0.14
	injected side	3.06 ± 0.14	**2.81 ± 0.12**	2.88 ± 0.06	**paralysis *#†**	3.41 ± 0.16	**0.62 ± 0.04 *#†‡**
Specific muscle tension [N/g]	*contralateral side*	5.01 ± 0.21	5.16 ± 0.16	5.92 ± 0.11	3.89 ± 0.17#	5.62 ± 0.24	5.03 ± 0.19
	injected side	5.19 ± 0.22	**5.55 ± 0.19**	5.94 ± 0.10	**paralysis *#†**	5.54 ± 0.27	**2.12 ± 0.12 *#†‡**
Tetanic fade [%]	*contralateral side*	5.09 ± 0.39	6.03 ± 0.51	6.79 ± 0.31	8.51 ± 0.45	4.18 ± 0.56	7.05 ± 0.65
	injected side	10.24 ± 1.13	**8.57 ± 0.46**	6.42 ± 0.27	**paralysis**	4.63 ± 0.30	**24.48 ± 2.28*#**
ED50 [mg/kg]	*contralateral side*	0.68 ± 0.03	0.76 ± 0.03	0.65 ± 0.02	0.60 ± 0.01*#	0.70 ± 0.02	0.58 ± 0.02*#†
	injected side	0.73 ± 0.03	**0.90 ± 0.03*#**	0.67 ± 0.02	**paralysis**	0.70 ± 0.02	**0.23 ± 0.02*#†‡**
Atracurium plasmalevels	*injected side*	3.44 ± 0.11	**4.12 ± 0.35**	3.72 ± 0.13	**paralysis**	4.48 ± 0.34	**0.52 ± 0.08 #†**
nAChRs [fmol/ mg]	*contralateral side*	29.1 ± 1.0	31.3 ± 1.8	31.6 ± 0.8	28.0 ± 1.0	37.6 ± 2.9	27.1 ± 1.1
	injected side	30.1 ± 1.2	**31.6 ± 1.4**	29.6 ± 0.9	**123.5 ± 3.97*#†**	34.4 ± 1.5	**377.8 ± 18.41*#†‡**

* p<0.05 versus contralateral leg (R-L-Com
# p< 0.05 versus saline group (grou
† p< 0.05 versus day 0
‡ p<0.05 versus day 4

Impact of PEEP on ETT Cuff Geometry

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INTRODUCTION: Ventilator-associated pneumonia (VAP) carries a significant risk of increased morbidity and mortality among ventilated intensive care (ICU) patients. VAP increases ICU length of stay by 4 days, and mortality by 20-30% (1). Leak of oro-pharyngeal secretions around endotracheal tube (ETT) cuff folds have been suggested to contribute to VAP (2). The aim of this study is to understand the effects of positive-end expiratory pressure (PEEP) on endotracheal cuff fold formation.

METHODS: We used a lung/trachea model consisting of an artificial trachea, which was intubated with an #8 ETT. The ETT cuff was inflated to 20 cmH2O. Proximal end of trachea was attached to a mechanical ventilator and distal end connected to model lung.
The whole model was ventilated in volume controlled mode with varying PEEP levels (0 to 30 cmH2O) at a tidal volume of 650 ml, respiratory rate of 2/min, and cuff pressures 20 cmH2O. We imaged cross-sections of ETT cuffs in a CT scanner using lung algorithm (GE Fastscan) at 0.65 mm section intervals at end-inspiration. We then analyzed the surface area of ETT cuff folds at each section using image-J morphometry software. The images were in tiff format. We calculated average area of ETT cuff folds at each PEEP level.

RESULTS: A total of 5 experiments were performed, where the entire length of the ETT cuff were imaged. Only the cuff areas, where the whole circumference of the cuff were in contact with the artificial trachea were included in the measurements. We found a positive linear relation between PEEP and area of folds at PEEP pressures between 0 to 30 cmH2O ($y = 0.6938x + 103.55$; r^2: 0.814). The folds were in continuity in the longitudinal axis creating "channels" alongside the cuffs.

CONCLUSION: Our preliminary findings suggest a role for PEEP on the formation of ETT cuff folds, which may lead to microaspirations of oro-tracheal secretions into the lungs leading to VAP. Despite our findings, there are other variables like cuff pressures and airway diameters effecting the cuff geometry besides PEEP. We are currently studying effects of various modes of ventilation on the ETT cuff geometry in relation to PEEP. Despite the creation of the "channels", it will be difficult to draw a conclusion between the size of area folds and risk of aspiration as there would be an opposing airway pressure with increasing levels of PEEP against the fluid column collected above the cuff. Interestingly, our previous work on the relationship between PEEP and fluid leak around ETT cuffs in a similar model suggested that high levels of PEEP would decrease the volume of microaspirations. Based on our current and previous data, we will create mathematical models simulating a relation between PEEP, ETT cuff fold area changes and fluid leakage. The results of these simulations may lead to optimization of airway pressures in the prevention of VAP.

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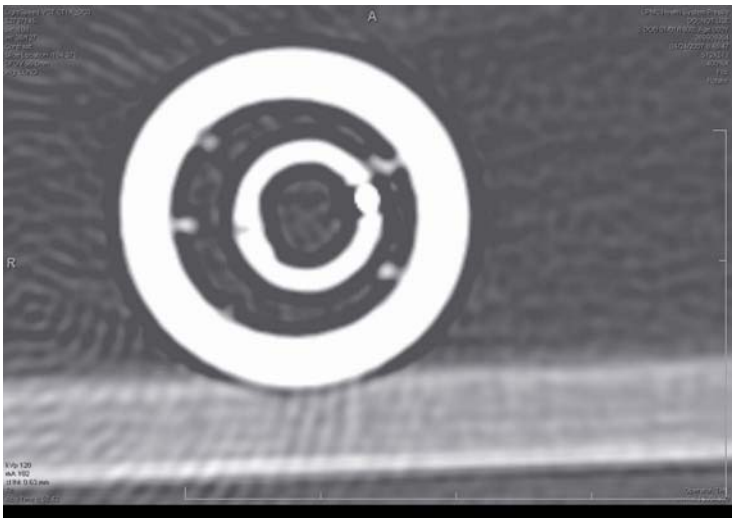

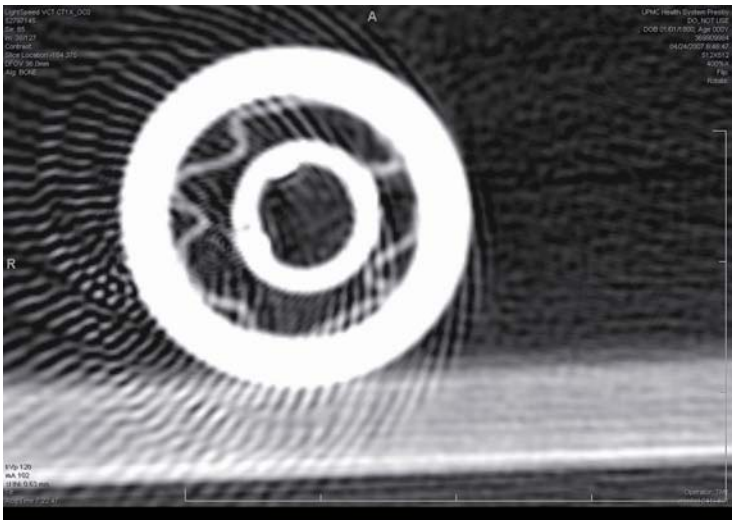

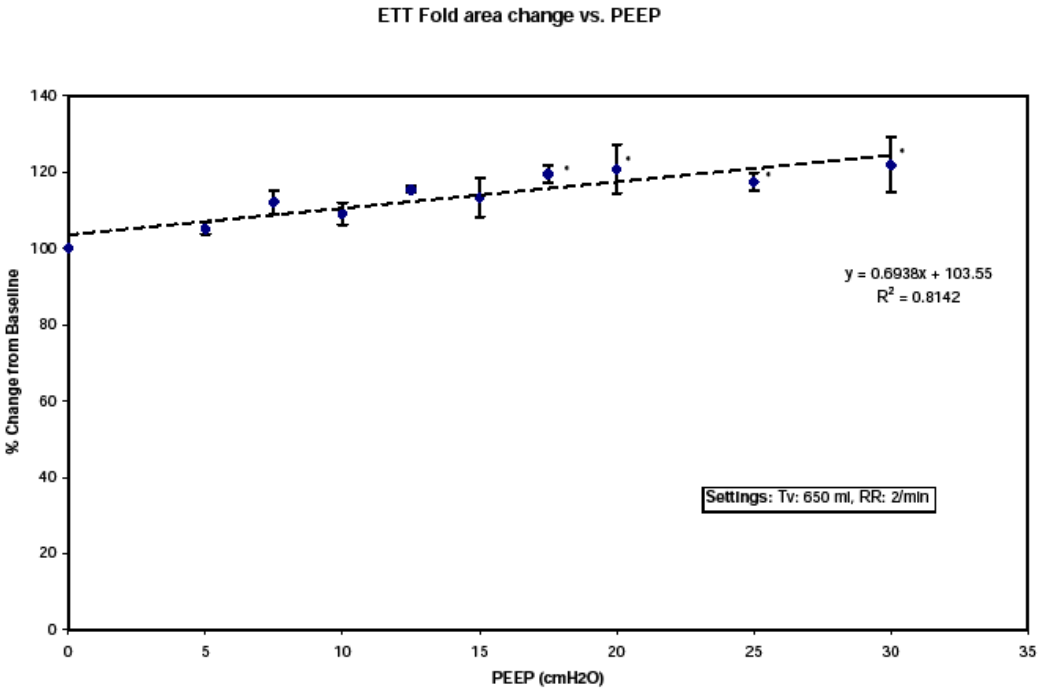
ETT Fold area change vs. PEEP
% Change from Baseline
PEEP (cmH2O)
y = 0.6938x + 103.55
R2 = 0.8142
Settings: Tv: 650 ml, RR: 2/min
0
20
40
60
80
100
120
140
0
5
10
15
20
25
30
35

A Mathematical Model of Pulmonary Regional Overdistention during Mechanical Ventilation

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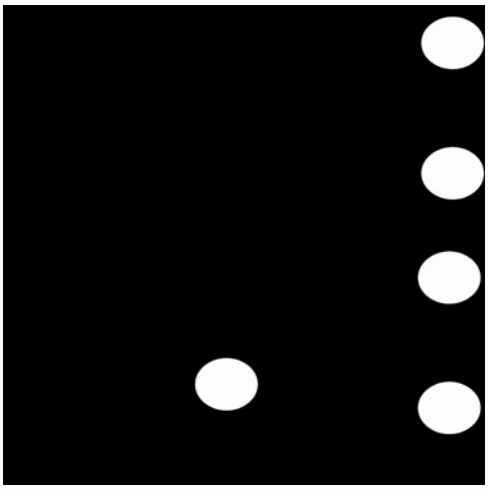
INTRODUCTION: Mechanical ventilation can harm the lungs by locally inflicting excessive stress on lung tissue. Given the heterogeneity of lung tissue, it is difficult to predict a priori optimal ventilatory strategies for an individual, and a "safe" approach for a population. We explored the feasibility of in silico approaches to identify optimal ventilatory strategies in the setting of regionally heterogeneous pulmonary mechanics.

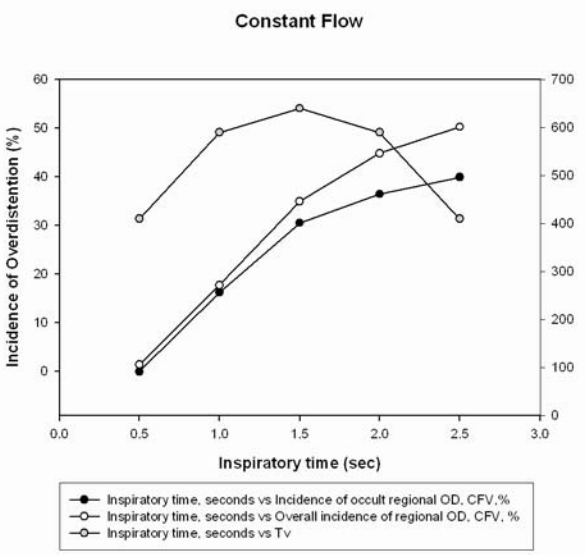
METHODS: We conducted a Monte Carlo simulation of a five-compartment model of branching airspace subjected to either volume-cycled ventilation (VCV) or pressure-regulated ventilation (PRV) (Fig. 1). Compartmental elastances were varied over clinically relevant range. Impedance configurations (200) were subjected to VCV and PRV at matched levels of minute ventilation with decelerating (DF) and constant flow (CF). Outcomes included fraction of configurations experiencing overstrain ($o \geq 1$) of at least one compartment. Settings included conventional Inspiration(I):Expiration(E) ratios, inverse ratio ventilation (I:E>1), and "extreme I:E ratio" ventilation (I:E>5).

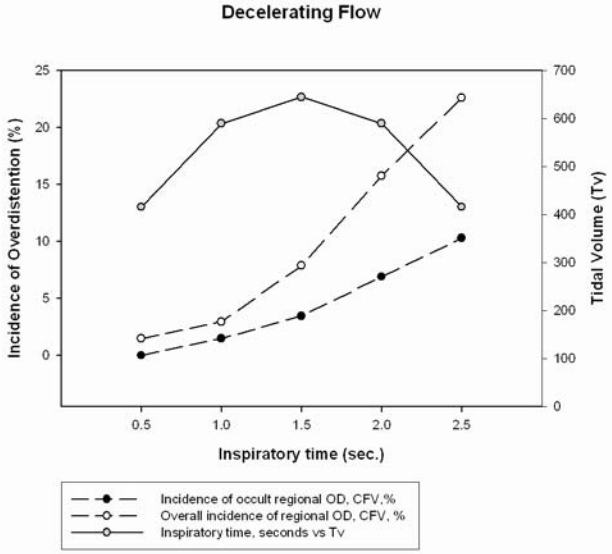
RESULTS: There was no overdistention in PRV simulations. There was overdistention in many simulations of VCV (45% in CF and 16% in DF) where compartmental volumes as high as 1.5 x the strain threshold (>40 cmH2O) were observed (Fig. 2 and 3). Yet, this was often occult (not reflected by the plateau pressure measured at the airway opening). One interesting finding was that by prolonging the I time, one would loose the beneficial/protective effects of DF as compared to CF.

CONCLUSIONS: Simulations may identify deleterious consequences of ventilator settings that are undetectable using current methods. Regional heterogeneity of peak lung strains partially explain why there is no apparent "safe" threshold plateau pressure, an insensitive "detector" of regional overdistention, particularly using VCV. Combining simulation and imaging might could guide bedside practitioner to optimize ventilation strategy in the critically ill.

REFERENCES: W.C. Burke, et al. JAP 1993
J.R. Hotchkiss, et al. CCM 2003




Constant Flow
Incidence of Overdistention (%)
Inspiratory time (sec)
Inspiratory time, seconds vs Incidence of occult regional OD, CFV,%
Inspiratory time, seconds vs Overall incidence of regional OD, CFV, %
Inspiratory time, seconds vs Tv
Respiratory Cycle: 3 sec.
PEEP: 15
Driving Pressure: 15


Decelerating Flow
Incidence of Overdistention (%)
Tidal Volume (Tv)
Inspiratory time (sec.)
Incidence of occult regional OD, CFV,%
Overall incidence of regional OD, CFV, %
Inspiratory time, seconds vs Tv
Respiratory Cycle: 3 sec.
PEEP: 15
Driving Pressure: 15

Isoflurane Protects Against Renal Ischemia-Reperfusion Injury Via Sphingosine Kinase

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INTRODUCTION: We have previously shown that isoflurane protects against renal ischemia-reperfusion (IR) injury (1). Previous studies have shown that isoflurane modulates sphingolipid metabolism in renal proximal tubule cells (2). We hypothesized that isoflurane stimulates sphingosine kinase (SK) activity and synthesis of sphingosine-1-phosphate (S1P) in renal proximal tubule cells and mediates renal protection via the S1P signaling pathway.

METHODS: All animal protocols were approved by the IACUC of Columbia University. C57BL/6 mice were anesthetized with either pentobarbital or 1.2% isoflurane and subjected to 30 min of renal ischemia. Some mice were treated with SK inhibitors (DMS or SKI-II) or an S1P1-receptor antagonist (VPC23019) before renal injury. Plasma creatinine was measured 24 h following reperfusion. For in vitro analysis, cultured human proximal tubule (HK-2) cells were treated with either room air or 2.5% isoflurane for 3-16 h at 37ºC/5% CO2 and SK activity was measured in whole cell lysate as well as cells separated into membrane and cytosolic fractions.

RESULTS: Mice anesthetized with isoflurane had lower plasma creatinine (Cr=1.3 ± 0.1, n=6) after injury compared to mice anesthetized with pentobarbital (Cr=2.4 ± 0.2 mg/dL, n=11, $p<0.01$ vs. Iso IR; Fig. 1). The renal protection mediated by isoflurane was abrogated upon treatment with the SK inhibitors DMS (Cr=2.7 ± 0.1 mg/dL, n=6, $p<0.01$ vs. Iso IR) and SKI-II (Cr=3.5 ± 0.1 mg/dL, n=5, $p<0.01$ vs. Iso IR), as well as the S1P1-receptor antagonist VPC23019 (Cr=2.6 ± 0.3 mg/dL, n=7, $p<0.01$ vs. Iso IR; Fig. 1). Treatment of HK-2 cells with 3-16 h of 2.5% isoflurane demonstrated a time-dependent increase in SK activity in both whole cell lysate fractions and membrane fractions (Fig. 2). In whole cell lysate fractions, SK activity increased 1.28 ± 0.06-fold (n=6, $p<0.01$ vs. control) and 1.37 ± 0.10-fold (n=6, $p<0.01$ vs. control) after 9 h and 16 h of isoflurane exposure, respectively (Fig. 2A). In the membrane fraction, SK activity increased 1.19 ± 0.06-fold (n=6, $p<0.05$ vs. control) and 1.22 ± 0.07-fold (n=6, $p<0.01$ vs. control) after 9 h and 16 h of isoflurane exposure, respectively (Fig. 2B). In the cytosolic fractions, there was a steady decrease in SK activity (Fig. 2B).

CONCLUSIONS: Our findings indicate that isoflurane activates SK in renal tubule cells and initiates S1P→S1P1-receptor signaling to mediate renal protection. Our findings may help to unravel the cellular signaling pathways of volatile anesthetic-mediated renal protection and lead to new therapeutic applications of inhalational anesthetics during the perioperative period.

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Effects of 3% Hypertonic Saline on Brain Edema and Neurologic Function Following Subarachnoid Hemorrhage in Rats

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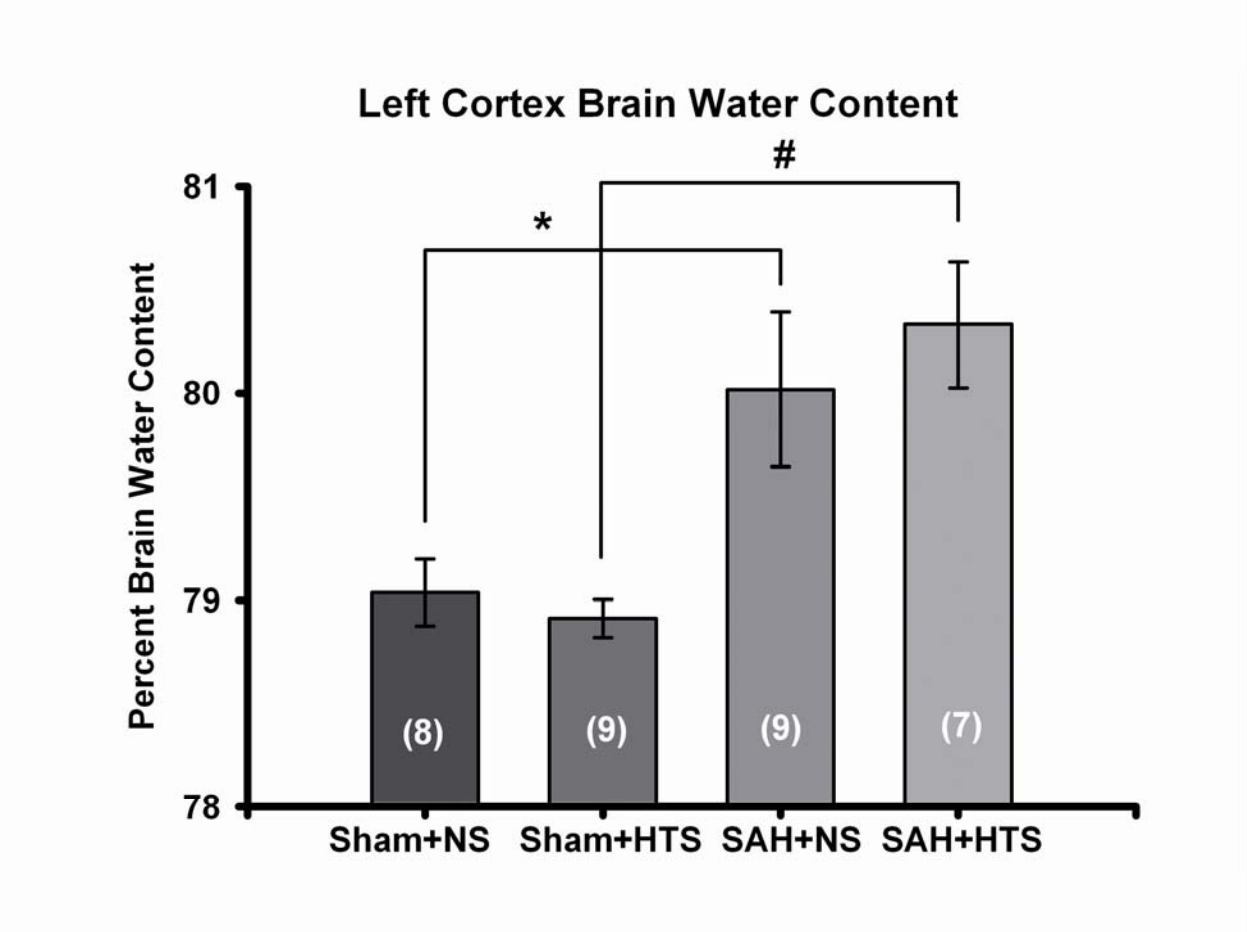
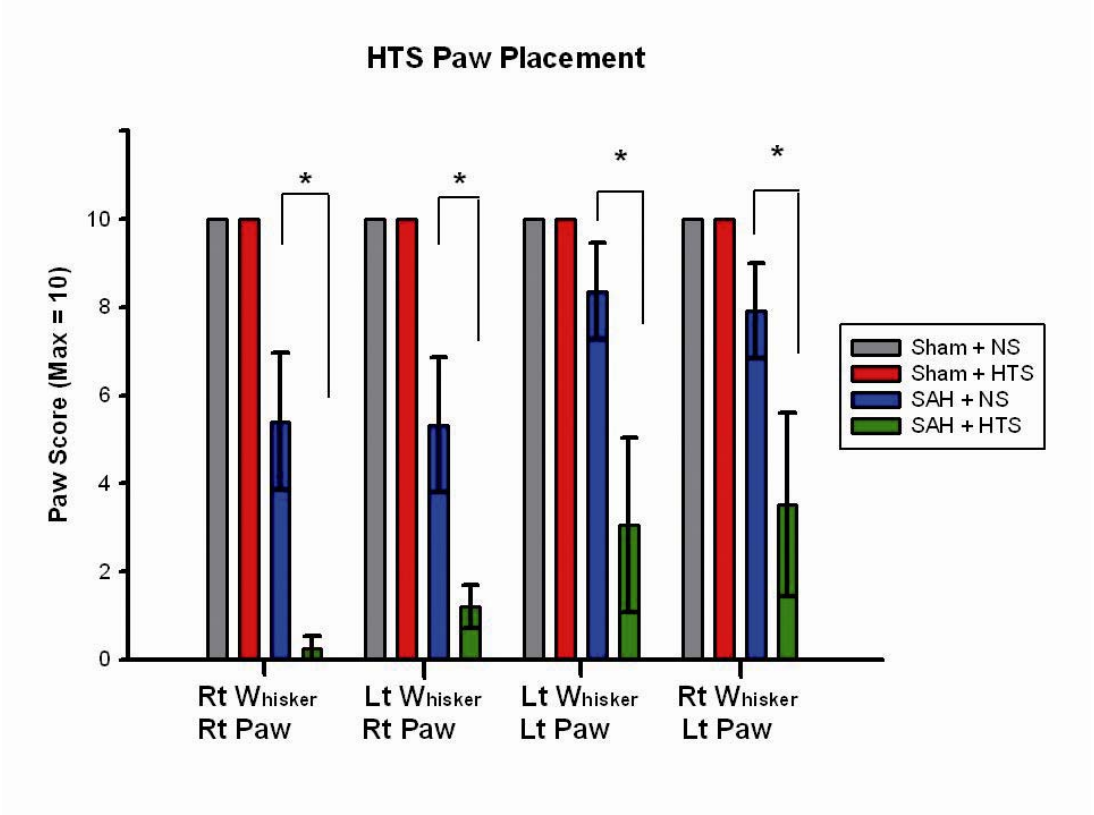
INTRODUCTION: Subarachnoid hemorrhage (SAH) is a devastating disease with high morbidity and mortality. Global cerebral ischemia occurs following spontaneous SAH as a result of an immediate rise of intracranial pressure and associated decrease in cerebral blood flow. Hypertonic saline (HTS) is increasingly being utilized after SAH to minimize secondary brain injury due to its postulated osmotic, hemodynamic, neurochemical, and immunologic properties. Although the benefits of 7.2% HTS use in brain injury have been studied, there is a paucity of data on the use of 3% HTS in the management of SAH in clinical settings. In this investigation, we used an established rodent model of SAH to study whether 3% HTS can reduce brain water content and improve neurologic function as compared to 0.9% saline solution (NS).

METHODS: A total of 52 adult male Sprague Dawley rats were used and after accounting for mortality (35%), 33 rats remained for the study. The animals were randomly divided into four groups: SAH + 3% HTS (n=7), SAH + 0.9% NS (n=9), Sham Surgery + 3% HTS (n=9), and Sham Surgery + 0.9%NS (n=8). SAH modeling under isoflurane anesthesia was done employing the 4.0 nylon suture puncture method as previously described. Animals were administered HTS or NS 1 hour post SAH with a bolus rate of 4mL/kg over 20 minutes followed by a maintenance rate of 0.5 mL/kg/hr over 100 minutes, for a total treatment time of 2 hours. Neurologic function using the previously reported modified Garcia score and the paw placement test were assessed at 24 hours post-SAH prior to sacrificing animals for brain water content evaluation. Significance was set at $p < 0.05$.

RESULTS: SAH caused a significant increase in brain water content in both the left (SAH + HTS: 80.3 + 0.3% vs. Sham + HTS: 78.9 ¬+ 0.1%; figure 1) and right (SAH + HTS: 79.9 + 0.3% vs. Sham+ HTS: 78.9 + 0.1%; figure 2) hemisphere in the HTS treated animals, however only in the left hemisphere in the NS treated rats (SAH + NS: 80.0 + 0.4% vs. Sham + NS: 79.0 + 0.2%). There was no significant difference in brain water content between HTS versus NS in the left hemisphere following SAH, however there was a significant potentiation of brain water content in the right hemisphere between 3% HTS and NS (SAH + NS: 79.2 + 0.3%). Neurologic score using the modified Garcia scale was not significantly different between the HTS group and NS group. However, the paw placement test showed significantly lower scores after SAH in the HTS as compared to the NS group.

CONCLUSION: 3% HTS does not decrease brain edema nor improve neurologic deficits as compared to NS when administered as a bolus and short infusion after SAH. Although 7.2% HTS has been shown to improve ICP after SAH, such beneficial effects may be mitigated at the lower 3% HTS concentration. In fact, our study showed HTS to potentiate brain edema and worsen neurologic deficits in the rat SAH model. HTS has also been associated with adverse effects including renal failure, coagulopathy, and electrolyte disturbances. Given the potential adverse effects of HTS therapies and the lack of benefit found in our study, more investigation is required to evaluate the clinical use of 3% HTS in the setting of SAH.




HTS Paw Placement
Paw Score (Max = 10)
0
2
4
6
8
10
*
*
*
*
Sham + NS
Sham + HTS
SAH + NS
SAH + HTS
Rt Whisker
Rt Paw
Lt Whisker
Rt Paw
Lt Whisker
Lt Paw
Rt Whisker
Lt Paw

Intracellular Ca2+ Transient can be Characterized by Hybrid Logistic Function in Aequorin-Injected Rabbit Papillary Muscle

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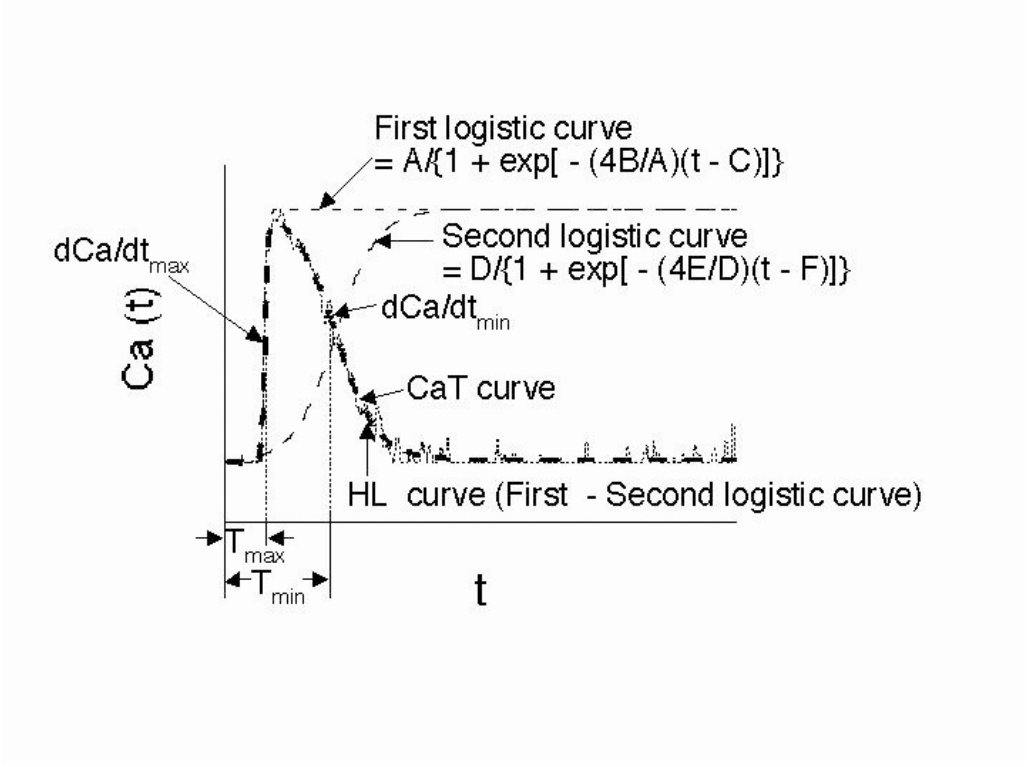
BACKGROUND: Intracellular calcium transient (CaT) regulates myocardial contraction and relaxation. By measuring the isometric tension in the ferret papillary muscle, we previously demonstrated that generated tension change fits well the difference between the first and second S-shaped logistic functions, named the hybrid logistic (HL) function. In the present study, we investigated whether CaT curve can be reliably fit by HL function.

METHODS: We investigated the potential application of HL function for analyzing CaT in seven isolated rabbit right ventricular (RV) papillary muscles. CaT was measured by using aeqorin, the calcium sensitive bioluminescent protein. We fit CaT curve using HL function equation with the least squares method; $Ca(t) = A/\{1 + \exp[- (4B/A)(t - C)]\} - D/\{1 + \exp[- (4E/D)(t - F)]\}+ G$. We calculated the maximum of the first derivative of Ca (dCa/dtmax), time to dCa/dtmax (Tmax), minimum of the first derivative of Ca (dCa/dtmin), and time to dCa/dtmin (Tmin) from the best-fit HL function curve (thick dashed curve). We compared the calculated values and actually observed values from original CaT curve (thin dotted curve).

RESULTS: The correlation coefficient (r) value of HL fit for CaT curve was 0.9924. There were significant correlations between calculated and observed dCa/dtmax, between calculated and observed dCa/dtmin, and between calculated Tmin and observed time to dCa/dtmin, but no significant correlation between calculated Tmax and observed time to dCa/dtmax.

CONCLUSION: CaT curve fits well with HL function curve in the isolated rabbit RV papillary muscle. HL function curve accurately predicts amplitude and time course of CaT curve. This approach provides new insight into the integration in CaT as a regulatory initiative of cardiac cycle.


First logistic curve
= A/{1 + exp[- (4B/A)(t - C)]}
Second logistic curve
= D/{1 + exp[- (4E/D)(t - F)]}
dCa/dtmax
dCa/dtmin
Ca (t)
CaT curve
HL curve (First - Second logistic curve)
Tmax
Tmin
t

Hypovolemia Does Not Affect Rate of Left Ventricular Contraction and Relaxation in Excised, Cross-circulated Canine Heart

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JR Tokyo General Hospital

BACKGROUNDS AND GOALS: Hypovolemia results in hypotension due to decrease in left ventricular (LV) stroke volume. We have showed that a logistic relaxation time constant (É—L) is a superior lusitropic index during the LV pressure (LVP) falling phase to the conventional monoexponential relaxation time constant (É—E) and that É—L is independent of LV preload. In the present study, we investigated the effect of decreasing LV preload on É—L and É—E during the LV contraction and other relaxation phases.

MATERIALS AND METHODS: The isovolumic LVP curve was analyzed at LV volumes (LVVs) of 18 mL, 14 mL and 10 mL during 2-Hz pacing in seven excised, cross-circulated canine hearts. É—L and É—E were evaluated by curve-fitting for the four phases of the cardiac cycle using the logistic function P(t) = PA/[1 + exp(t/É—L)] + PB and the monoexponential function: P(t) = P0oexp(-t/É—E) + P?. The four phases is following: the period from the onset to the maximum time derivative of LVP (LV dP/dtmax) (Phase I), from LV dP/dtmax to peak LVP (Phase II), from peak LVP to the minimum time derivative of LVP (LV dP/dtmin) (Phase III) and from LV dP/dtmin to LV end-diastolic pressure (Phase IV). We compared the goodness of the logistic and monoexponential fits using correlation coefficient (r) and residual mean squares (RMS).

RESULTS: There is no significant difference between É—L and É—E during Phases I–IV with the decrease in LVV. The logistic r values at Phases I–IV at three LVVs were always significantly larger than the monoexponential r values. The logistic RMS values at Phases I–IV at three LVVs were always significantly smaller than the monoexponential RMS values. Conclusions: Hypovolemia does not affect the rate of the isovolumic LV contraction and relaxation. The logistic fit is always superior to the monoexponential fit at all four phases regardless of the change in LVV. Each phase of the LVP curve is of a logistic nature. É—L is a useful index for estimation of the rate of alteration during each phase of cardiac systole and diastole.

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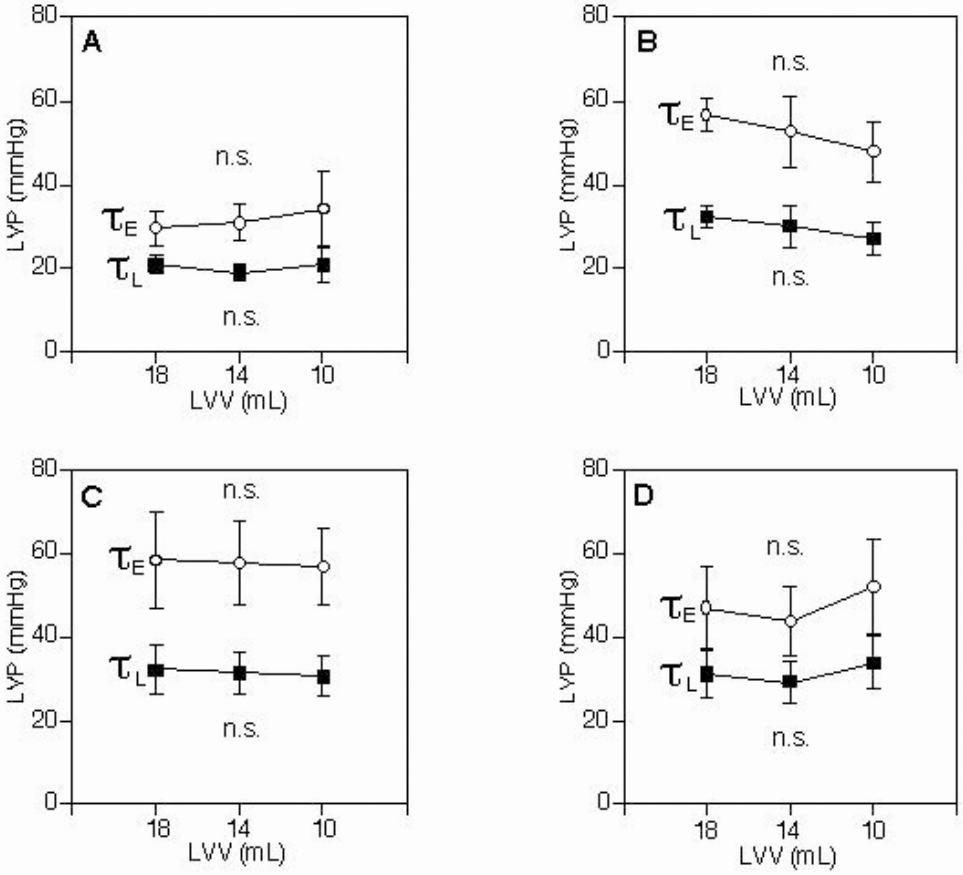
Ju Mizuno, et al: Hypovolemia does not affect speed of isovolumic left ventricular contraction and relaxation in excised canine heart. Shock: 2007 (in press)

Figure. Logistic and monoexponential time constants for four phases of the isovolumic left ventricular pressure (LVP) curves at three LV volumes (LVVs). Panels A, B, C and D show the logistic (É—L; black square) and monoexponential time constants (É—E; white circle) during phases I, II, III and IV, respectively.


A
B
C
D
80
60
40
20
0
LVP (mmHg)
18
14
10
LVV (mL)
n.s.
τ_E
τ_L

Bacterial Lipoprotein PAL Induces Apoptosis in Cardiomyocytes

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OBJECTIVE: Bacterial peptidoglycan-associated lipoprotein (PAL), an outer-membrane protein of Gram-negative bacteria, is released into the bloodstream in sepsis. PAL induces cardiomyocyte dysfunction and inflammatory responses in mice via TLR2- and MyD88-dependent mechanisms. However, it remains unknown whether or not PAL has any effect on cardiomyocyte survival.. The present study was designed to assess the effects of PAL on cardiomyocyte survival in an in vitro model of apoptosis.

SUBJECTS: Cardiomyocytes isolated from 1-2-day-old rats

MEASUREMENTS AND RESULTS: Treatment of isolated rat neonatal cardiomyocytes with PAL induced apoptosis in a dose-dependent manner as evidenced by TUNEL staining,, cell death ELISA, and cleaved caspase-3 Western blot.
PAL triggered the production of inducible nitric oxide synthase (iNOS) and nitrate. Blockade of toll-like receptor 2 (TLR2) signaling by a specific TLR2 antibody inhibited iNOS induction and PAL-induced apoptosis. Inhibition of iNOS by its specific inhibitor, L-NIL significantly inhibited PAL-induced apoptosis in cardiomyocytes.

CONCLUSION: We conclude that PAL induces apoptosis in cardiomyocytes in vitro. This is probably mediated by TLR2 and iNOS.

Bi-ventricular Pressure Volume Analysis in Spontaneously Ventilating Mice

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INTRODUCTION: Since the advent of pressure volume loop (PVL) analysis as a method of preload independent assessment of myocardial function, periodic technologic advances have led to resurgences in the utilization of this technique. Recently, conductance based catheters have been micro-scaled to allow for the physiologic characterization of transgenic mouse ventricular function. Although pressure volume analysis is rapidly becoming the standard for determining Left Ventricular (LV) performance, there are few peer-reviewed reports demonstrating the utility of this technique for assessing the function of the Right Ventricle (RV) or RV-LV interactions. We now report a series of 9 wild type spontaneously ventilating closed-chested mice, which have undergone simultaneous bi-ventricular PVL analysis.

METHODS: Nine wild type Fvb mice under isoflurane anesthesia, underwent right-sided carotid artery and jugular vein dissection. These vessels were each cannulated with Millar conductance based PVL catheters, which were introduced into the LV and RV sequentially. Initially, Aortic arch pressure was recorded and used to represent systemic blood pressure. Biventricular PV loops were first acquired at baseline and then the inferior vena cave was occluded to assess the end systolic and end diastolic PV relationships. PVL data was analyzed with the most current ADI Chart and Millar PVAN software.

RESULTS: In all subjects, RV systolic pressures were 26 ±3% the peak LV pressure, while RV stroke volume (SV) was nearly identical to LV SV at 95 ± 9%, when averaged over a minimum of 5 PV loops. Additionally, RV dP/dTmax and dP/dTmin were 30 ± 2% and 33 ±9% of LV values. Based upon this finding, it was possible to reconstruct the systolic LV PV relationship based solely on the RV PVL data combined with the Aortic arch pressure. Predicted end arterial elastance (EAE) and Cardiac Output (CO) from RV-reconstructed LV PV Loops was also identical (95 ±7%) to actual measurements from the real-time LV PVLs.

CONCLUSION: These findings not only confirm that conductance based catheterization of the RV can yield reliable physiologic measurements, but they may also be used to estimate left ventricular parameters of function.

Making a Good Receptor Even Better: Disrupting the beta2 Adrenergic Receptor PDZ Binding Motif

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INTRODUCTION: b1 and b2 adrenergic receptors (bARs) mediate the primary responses to catecholamines in the mammalian heart. Continuous b1AR stimulation is toxic to the myocardium; prolonged b2AR activation is protective. At doses used clinically b2AR agonists lose their subtype selectivity due to similarities between b1ARs and b2ARs at the agonist binding sites. Understanding the signaling differences between b1ARs and b2ARs might facilitate development of better therapeutic agents (i.e., agents that elicit the inotropic enhancement characteristic of b1AR stimulation and the protective effects of b2AR activation while avoiding b1AR-mediated cardiac toxicity).
We previously reported gene expression differences between wild type (WT) mice, mice with disruption of the b2AR (b2KO), and mice with disruption of only the b2AR PDZ binding motif (b2PDZ). Our data suggested that disruption of the b2AR PDZ binding motif caused the b2AR to lose some of the properties that distinguish it from the b1AR. However, mice with disruption in the b2PDZ binding motif did not up-regulate expression of the mutated b2AR gene, suggesting some retention of b2AR activity in b2PDZ mice.

HYPOTHESIS: We hypothesized that the b2AR PDZ binding motif is essential for b2AR-mediated protection against detrimental cardiac remodeling during continuous b1AR stimulation. We predicted that left ventricle compliance would be less and contractility would be impaired in b2KO and b2PDZ mice relative to WT mice.

METHODS: We evaluated the cardiac function of anesthetized WT, b2KO, and b2PDZ mice using pressure-volume catheters inserted in the animals' carotid arteries and advanced into their left ventricles under pressure waveform guidance. We elicited continuous bAR activation in half the mice studied by infusing isoproterenol for 14 days prior to catheter insertion. Using the WT and knockout mice, we evaluated the impact of continuous b1AR stimulation with or without b2AR activation.

RESULTS: We observed no differences between WT and b2PDZ mice in terms of the left ventricle end diastolic pressure volume relationship. We identified a significant genotype effect ($p=0.01$) when b2KO and b2PDZ mice were compared (the slope of the end diastolic pressure volume relationship was significantly greater in b2KO mice compared to b2PDZ mice). We observed lower cardiac output in b2KO mice relative to WT mice ($p=0.04$) and higher cardiac output in b2PDZ mice relative to WT mice ($p=0.02$). Similar trends were observed when stroke volumes were compared. We observed higher heart rates in b2PDZ animals than in WT mice ($p=0.004$); no difference in heart rate was observed between b2KO and WT animals.
Conclusions: The results of our study suggest that a segment of the b2AR other than the PDZ binding motif is needed for b2AR-mediated protection against remodeling associated with diastolic dysfunction. Our assessments of left ventricle inotropic performance and heart rate indicate that disruption of the b2AR PDZ binding motif causes b2ARs to behave like additional

b1ARs in vivo and allows them to increase contractility and heart rate without eliciting toxic effects.

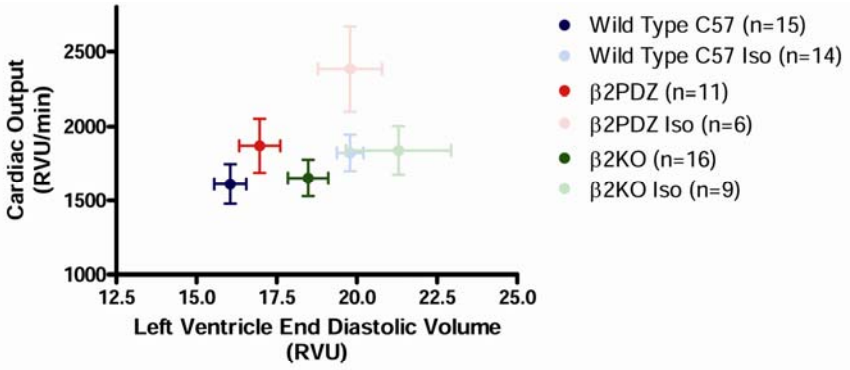

Figure 1. **Starling Plot for Wild Type, β2KO, and β2PDZ Mice.** The Starling Plot indicates that isoproterenol infusion causes left ventricle remodeling in all three genotypes (demonstrated by an increase in Left Ventricle End Diastolic Volume). Only in β2PDZ mice is a significant increase in cardiac output is also observed.

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Risk Factors for Nosocomial Pneumonia in a Neuroscience ICU

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INTRODUCTION: Nosocomial pneumonia is defined as pneumonia occurring more than 48 hours after admission to the hospital. It's the most common infection in the ICU setting. Nosocomial pneumonia can prolong ICU stay by about 10 days.[sup]1[/sup] Maintaining blood glucose at or below 110 mg/dL reduces morbidity and mortality among critically ill patients in the surgical ICU.[sup]2[/sup] The aim of this prospective cohort study was to find the contribution of admission blood glucose level and coma status to the patient's risk of developing nosocomial pneumonia in a specialized neuroscience ICU setting.

METHODS: With IRB approval, we retrospectively collected the data of 236 intensive care patients with pure head trauma or stroke (including hemorrhagic stroke) who needed to stay in the ICU for more than 48 hours between June 2004-February 2005. Pneumonia prevention guidelines (NAP Pathway) of the Infectious Diseases Dept. were practiced throughout.[sup]3[/sup] The end point of the study was pneumonia diagnosis by CPIS criteria[sup]4[/sup] or transfer from the unit. Chi-square analyses, two-tailed unpaired t-tests, and nonparametric equivalents of t-test were used for univariate comparison of the groups. Data are presented as absolute value, mean ± standard deviation, or median (interquartile range).

RESULTS: Sixty patients (~25%) developed 68 cases of nosocomial pneumonia. Time to develop pneumonia was 10 ± 6 days. Most of infections were late-onset pneumonia (onset > 96 h in 64 of 68 cases). The most common pneumonia pathogens were as follows: 12 MRSA, 11 MSSA, 9 Oral Indigenous Flora, 9 Enterobacter spp., 5 Serratia spp., and 5 H. influenza. At ICU admission, 32 of 60 (53%) nosocomial pneumonia patients had GCS ? 9 compared to only 33 of the 176 patients without pneumonia (19%) ($P < 0.001$). Initial blood glucose levels were significantly higher in the patients with nosocomial pneumonia compared to the others (152 ± 73 vs. 134 ± 43 mg/dl, respectively, $P = 0.022$) (Table 1).

CONCLUSIONS: We conclude that, at admission, neurologically sicker patients as well as patients with higher blood glucose levels were more prone to get nosocomial pneumonia during their ICU stay. Possibly, severeness of neurological status causes an increase in stress response, which converts to increased glucose levels. Whether strict glucose control should be considered as a potential incidence-lowering approach for pneumonia is another hypothesis to be tested.

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Oldest Old Patients Admitted To a Post-Surgical Intensive Care Unit Have Low Mortality

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Mark T Keegan, M.D.; Mayo Clinic, Department of Anesthesiology

INTRODUCTION: As the older population increases, admissions to the intensive care unit (ICU) of those patients aged ≥ 85 years (the "oldest old") would be expected to increase. The reported survival in this group is widely variable with some studies reporting in-hospital mortality up to 40%1, 2. We hypothesized that ICU, hospital and 6 month mortality would be high in this population and similar to that commonly reported in previous studies.

METHODS: Following IRB approval, the medical records of all patients ≥ 85 years old admitted to a post-surgical ICU at a tertiary referral hospital between January 2000 and September 2006 were reviewed. Pre-admission morbidities, ICU and hospital events, and survival up to 6 months from ICU admission were determined. The data were analyzed using descriptive statistics appropriate for the data distribution.

RESULTS: 470 patients ≥ 85 years of age were admitted to the study ICU. The median patient age was 88 years (interquartile range 86 to 90 years). 52.1% of patients were females. Major reasons for admission included vascular (44.5%), orthopedic (25.3%) and non-cardiac thoracic (8.3%) procedures. The remaining patients included those undergoing other surgical procedures or medical ICU overflow. 73.8% of patients were admitted directly following surgery, 13.7% were admitted from a regular care floor and 9.3% from the emergency room.

The first ICU day Acute Physiology Score and APACHE III scores (mean ± standard deviation) were 39.2 (± 21.0) and 63.2 (± 20.7), respectively. Median lengths of ICU and hospital stay were 1.6 days (interquartile range 0.9-3.1 days) and 8.1 days (interquartile range 5.6-12.6 days), respectively. The APACHE III-predicted ICU and hospital mortalities on the first ICU day were 7.8% (± 13.5) and 16.0% (±17.7), respectively. 22 patients (4.6%) died in the ICU while an additional 24 died while in the hospital after discharge form the ICU resulting in a 9.7% hospital mortality rate. The standardized mortality ratios for ICU and hospital death were 0.596 (95% CI 0.374-0.903) and 0.608 (95% CI 0.445-0.811), respectively. 38.5% of patients were discharged to home with the remainder discharged to a nursing home or facility with skilled nursing care. Following admission to the ICU, 1-, 3-, and 6-month mortalities were 17.1%, 23.5% and 26.8%, respectively.

CONCLUSION: ICU and hospital mortality in oldest old patients admitted to this surgical ICU is lower than previously reported in this age group by other investigators. The majority of patients are discharged to a nursing home or facility with skilled nursing care. Further work is needed to identify predictors of hospital and post-discharge mortality.

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SUMMARY: ICU and hospital mortality in oldest old patients is lower than previously reported in this age group by other investigators. The majority of patients are discharged to a nursing home or facility with skilled nursing care.

Comparison of Outcome of Self-Extubation and Accidental Extubation in ICU

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INTRODUCTION: To assess and compare the vulnerability and severity of outcomes in ICU patients who suffered self-extubation and accidental extubation during their stay in the ICU.
Design Prospective observational study.
Setting 16-bedded mixed intensive care unit in a tertiary care hospital.

MATERIALS AND METHODS: All adult patients admitted in ICU with either an endotracheal tube or a tracheostomy was included in the study. The time and description of the type of unplanned extubation, the cause and severity of the incident and its impact on the course of the patient's illness, the person who noted the incident first, and how it was detected were noted.

RESULTS: The rate of unplanned extubation was 32 (1.42/100 tube days) in 552 intubated patients (2243 tube days). Of them, 26 patients suffered self-extubation while the rest 6 patients were accidentally extubated. Reintubation was required in 8 patients after self-extubation while it was needed in all the six patients of accidental extubation.Three patients of accidental extubation went on to develop respiratory arrest including one patient who developed cardiac arrest.
Discussion- The rate of unplanned extubations in our study was found to be 1.42/100 tube days which is comparable with studies done by Epstein et al 1 (1.6%), Carrion et al 2 (1.5-2.4%) and Chatterjee et al 3. It is significantly higher in comparison with Moons et al 4 (0.68/ 100 tube-days) and Kapadia et al 5 (0.14%).
In our study, we tried to differentiate between the etiologies behind the incidents of self extubation and accidental extubations. Self extubations occurred in those who were alert or agitated or violent in spite of sedation or mechanical restraints - though no adverse outcomes occurred in them as they were recognized early and might have already been fit to be extubated around that time. These alert or agitated patients easily brought their attention to the doctors on duty or staff nurse before any significant hypoxia could occur. Reintubation 6,7,8 was needed in only 8 patients following self-extubation.
In contrast, when accidental extubations occurred in sedated or obtunded patients, these events led to more adverse incidents due to the late recognition or they were too sick to withstand even short episodes of hypoxia. All the patients who suffered accidental removal of the tubes required to be reintubated to help them combat the subsequent hypoxia. The Glasgow Coma Score was below 8 in all of them and they were unable to maintain airway and ventilation on their own. These obtunded individuals were unable to draw attention to them before significant desaturation occurred. On episode of cardiac arrest took place after accidental extubation. The severity of the outcome in the patients who suffered accidental removal of tube is very poor and needs more aggressive management than the patients with self-extubation due to difference in susceptibility of the patients and time duration of detection of the incident before irreversible sequelae are likely to occur.

CONCLUSION: The outcome of the patients who suffered self-extubation is better than those with accidental extubations.

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Table-1 Self-extubation vs. accidental extubation

	Self-extubation (n=26)	Accidental Extubation(n=6)
Reintubation	8(30.76%)	6(100%)
Midnight Incidents	6(23.07%)	2(33.33%)
Detection by residents	20(76.92%)	4(66.66%)
Detection by nurses	6(23.08%)	2(33.33%)
Catastrophic event	0	1(16.6%)

Table-2 Outcome of unplanned extubations

	Self-extubation (n=26)	Accidental Extubation(n=6)
Transient Desaturations	18	0
Hypoventilation	8	3
Respiratory arrest	0	3
Bradycardia	2	3
Cardiac arrest	0	1
Aspiration pneumonia	0	1

The Use of Methylene Blue for Vasodilatory Shock

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We report the use of methylene blue (MB) in a non-septic vasoplegic patient who happens to belong to two groups of patients in which the use of MB has not been widely studied: pediatric patients and lung transplant patients. The patient was a 14-year-old girl who had received a bilateral lung transplant secondary to cystic fibrosis. She had significant vasodilatory shock with extremely high vasopressor medication requirements beginning in the operating room and continuing to escalate on post-operative day 1. Vasopressor agents were titrated to maintain a mean arterial blood pressure (MAP) greater than 65 mmHg. On post-operative day 1, she was receiving: norepinephrine 30mcg/min, vasopressin 6 units/hour, phenylephrine 45 mcg/min and epinephrine 2 mcg/min. Her physical exam was significant for warm legs and feet and a transesophageal echocardiogram showed a hyperkinetic heart without signs of hypovolemia. Methylene blue (MB) was administerd as an adjunct for vasoconstriction. Notably, she was simultaneously receiving inhaled nitric oxide (NO) at 20 ppm. Methylene blue 2 mg/kg IV was administered over 10 minutes and remarkable recovery of vascular tone was noted. Before the 10-minute infusion had finished, her vasopressor requirements had decreased to: norepinephrine to off, vasopressin to 1 unit/hour, phenylephrine to off, and epinephrine to 1 mcg/minute. Although, her pulmonary pressures were not being monitored, there was no change in her CVP with MB administration.

The mechanism of widespread vasodilation involves the activation of the enzyme guanylate cyclase (GC) by NO [1]. Nitric oxide is produced by the enzyme nitric oxide synthase (NOS). Of the three types of NOS, inducible NOS (iNOS) appears to be activated by the influence of endotoxins and cytokines, which may play a key role in vasodilatory shock in septic and post-operative patients.

MB is a chemical dye that selectively inhibits iNOS and GC in vascular smooth muscle cells [2]. It is likely that inhaled NO may off-set any potential increases in PVR that may be associated with MB [3]. Unlike non-selective NOS inhibitors, such as as N-nitro-L-arginine methyl ester (L-NAME) and N-monomethyl-L-arginine (L-NMMA), MB has had favorable outcomes in vasoplegic patients. MB may also have other beneficial effects such as improved myocardial performance by depressing effects of molecules such as TNF-alpha. MB also inhibits superoxide radical formation by competing with oxygen for the transfer of electrons by xanthine oxidase [4].

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Development of a Hospital-Wide System for The Deployment of Ultrasound Guidance in All ICUs for The Placement of Central Venous Catheters

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Earlier studies have documented that ultrasound (US) guidance can improve the safety of and shorten the time needed for the placement of central venous catheters (1,2). Despite of this evidence and the recommendation of AHRQ (2) this practice has not been broadly implemented. As we attempted to deploy this strategy in an academic teaching (tertiary care) facility we found the following obstacles for the effective implementation: 1. no evidence (guide) on how extensive of a training is necessary for the users of the US to obtain the benefits of US use; 2. no guide (not even recommendation) exist for the development of quality control mechanisms; 3. the US examination of the target vessels was not standardized. Therefore, we designed a three-phase study (incorporating these elements) to evaluate the efficacy of a classroom-based US competency course versus and a more extensive program based on a web-accessible self-directed learning method and hands-on training with phantoms created for the simulator-based teaching of US guidance. The goal of the study is to establish the level of training necessary for the safe implementation of routine US use for central venous catheter placement as well as to develop a cost effective method for the training.

Here we report our experience from the observational phase of our study from 238 patients. The rate of overall complications was 19.5%, the rate of pneumothorax was 9.5%, both higher than expected and above the published national average. Two third of both of these complications occurred in patients requiring attempts at more than one sites, a population that is most likely to benefit from the use of US guidance. Sixty five percent of our patients had more than two risk factors present for difficult line placement and only 8.5% of the patients had none.

Univariate analysis of the relationship of risk factors and complications indicated possible correlation with 4 risk factors (mechanical ventilation, short neck, history of line infection and difficult placement), while our multivariate analysis concluded that our sample size was not sufficient to confirm the independent contribution of any of these factors. Further data collection is in progress to help us arrive to a definitive conclusion.

Additionally, we followed the incidence of blood stream infection in our patients: 26 of the 235 patients (11 %) we followed for the development of line-related infections had blood cultures that were positive following the placement of central venous catheters, but we only consider 13 of these patients (5.5 %) to have developed line-related infections based on an algorhythm assessing the type and timing of positive blood cultures in relation to the placement of the catheters. Thrombosis maybe short or long term complications of the presence of central venous catheters: 83 of our 238 patients (34.9 %) we followed had upper extremity ultrasound exam performed based on the clinical suspicion of possible DVT, but only 32 of these patients (13.5) had US-confirmed DVTs following the placement of central venous catheters.

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The Ultimate Goal

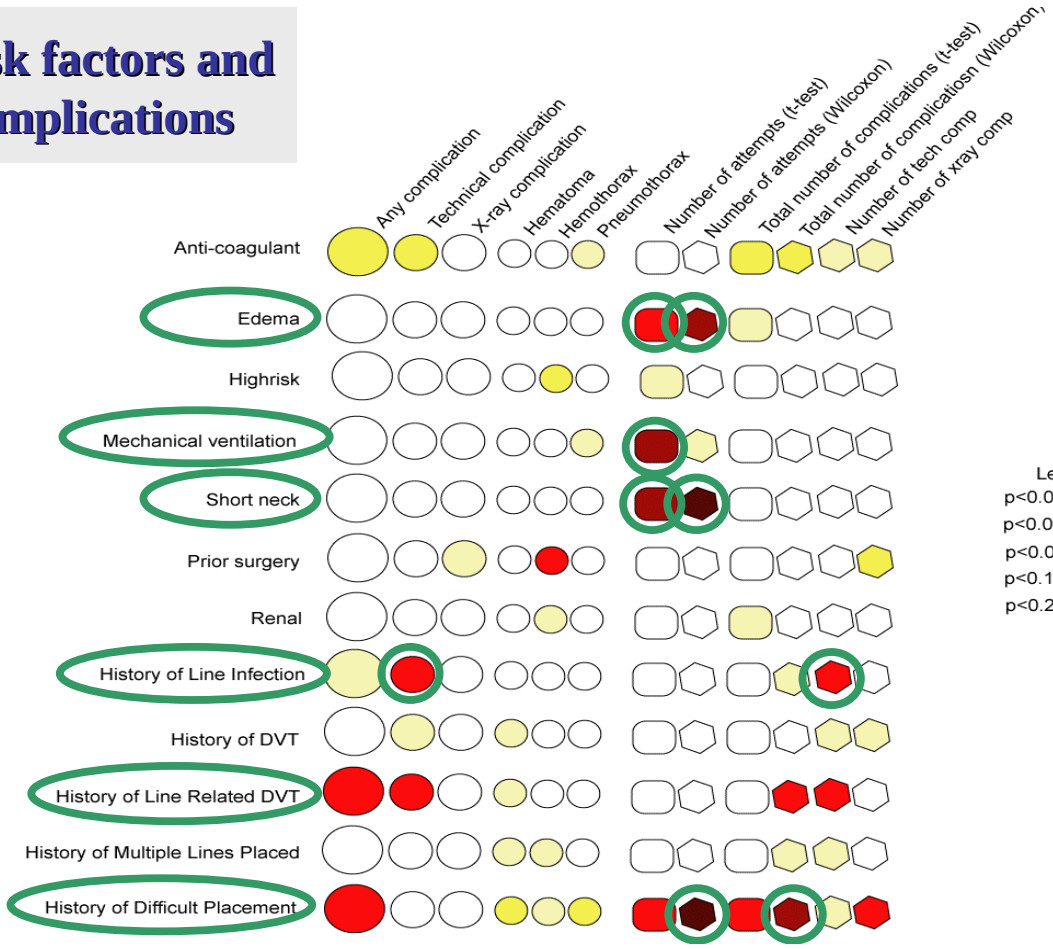
Improve Patient Safety in All BWH ICUs by Providing

Bedside US for routine use in all BWH ICUs

By **creating a quality control (QC) mechanism** for professional reads of bedside US recordings, and for QC review and ongoing training

A structured training program to assure competence of all ICU staff and fellows in the use of bedside US

Risk factors and Complications



Perioperative Coagulation Management in a Patient with Afibrinogenemia Undergoing Liver Transplantation

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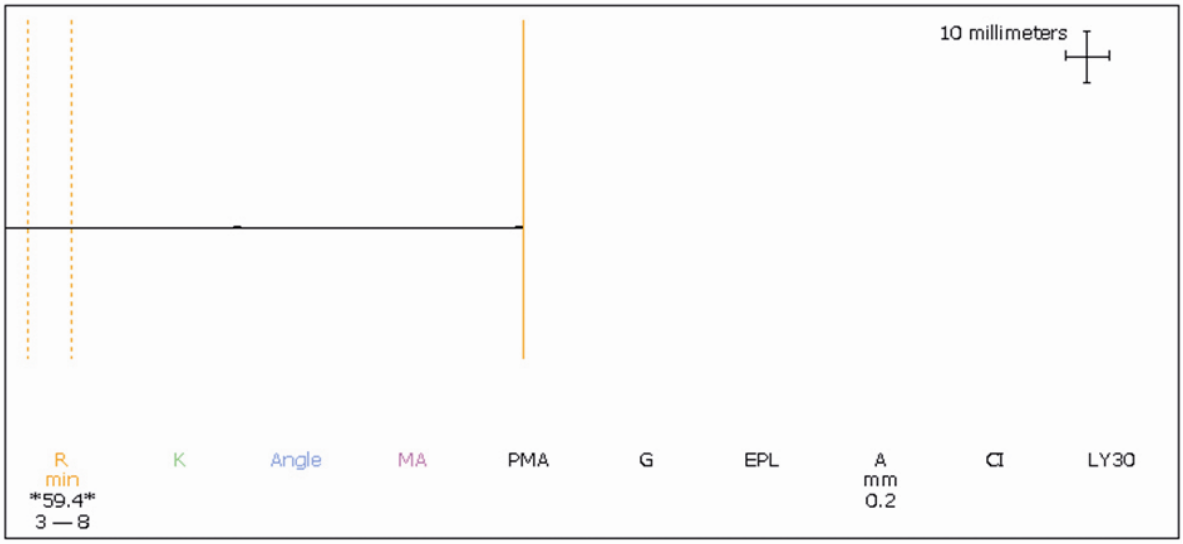
Johns Hopkins University

CLINICAL BACKGROUND: Afibrinogenemia is a rare hereditary coagulation disorder characterized by a propensity toward bleeding. The severity of bleeding varies from patient to patient but tends to be more frequent and severe in association with trauma and surgical procedures. Although fibrinogen replacement therapy is the standard for management in these patients, such treatment is also one of the risk factors for thrombosis.

CASE REPORT: A 21-year-old Hispanic woman with afibrinogenemia developed ascites, a distended abdomen, an enlarged liver, scleral icterus, and umbilical vein and abdominal wall vein distension. Computed tomography (CT) scan showed occlusion of the hepatic veins and the infrahepatic vena cava consistent with Budd-Chiari syndrome. Because of her afibrinogenemia and Budd-Chiari syndrome, the patient was at high risk for early death related to such complications of portal hypertension as esophageal varices bleeding. These developments led to her evaluation for, and placement on, the liver transplantation waiting list. The patient's unmeasurable international normalized ratio (INR) artifactually increased her Model for End-Stage Liver Disease (MELD) score to 40. Immediately before transplant surgery, an initial thrombelastogram (TEG) showed a flat line, indicating a complete lack of fibrin clot formation. Preoperatively, 20 units of cryoprecipitate were infused. The first intraoperative TEG demonstrated a tracing consistent with normal clot formation. Coagulation studies normalized with the newly functioning liver. In this patient who had a severe fibrinogen deficiency, no evidence of clot formation could be achieved with TEG before surgery (Fig. 1). With adequate intraoperative fibrinogen replacement and postoperative intrinsic production from the transplanted liver, a normal TEG tracing could be recorded (Fig. 2,3).

SIGNIFICANCE: We desribe the perioperative coagulation management of the first reported patient with congenital afibrinogenemia, complicated by Budd-Chiari syndrome, to undergo liver transplantation. The liver transplantation appears to have corrected the fibrinogen deficiency, presumably limiting the chance of recurrent Budd-Chiari syndrome. This case report discusses the essential role of fibrinogen in the coagulation cascade, as visualized by thrombelastography, and exposes the interplay between plasma fibrinogen and thrombin levels, which determine coagulation or fibrinolysis.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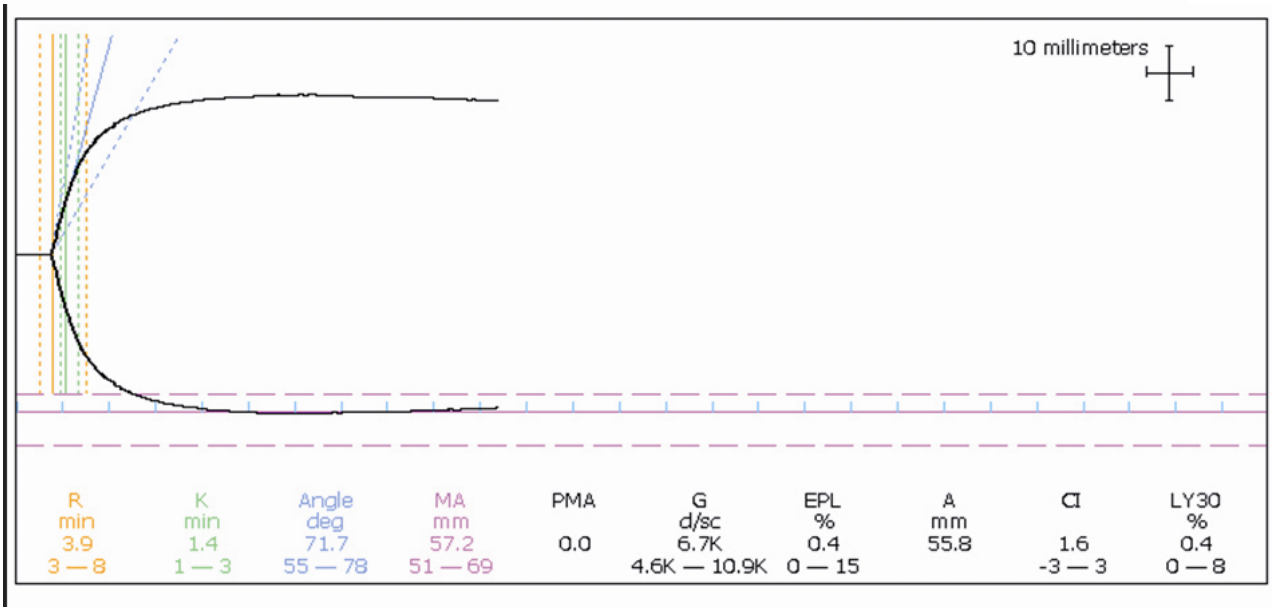
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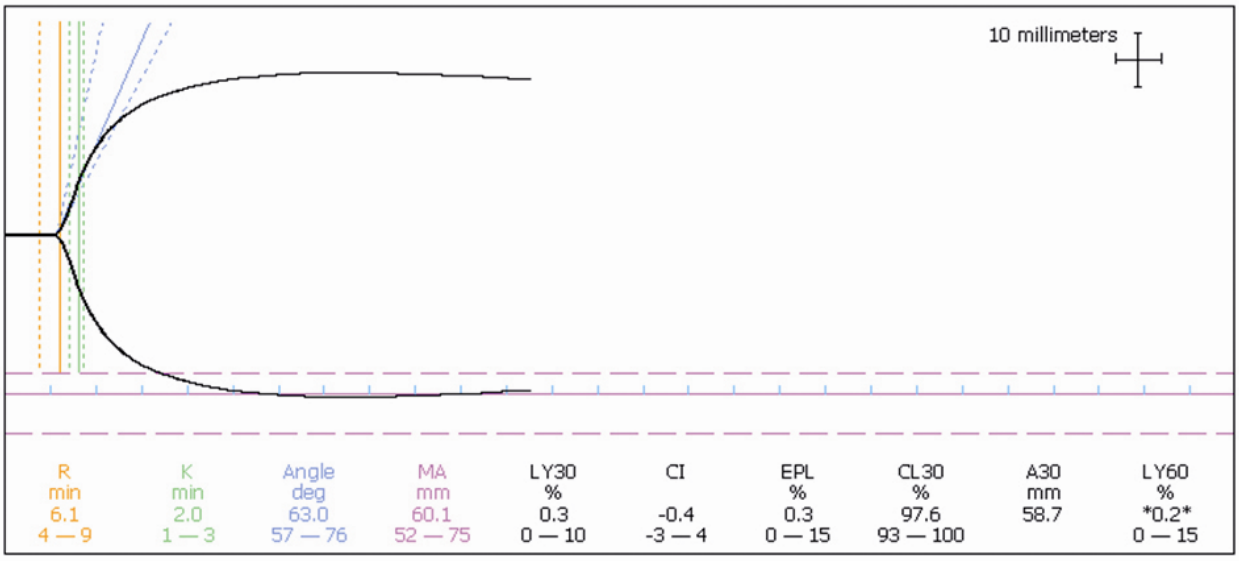
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Is Intraabdominal Hypertension an Independent Predictor of ICU Survival?

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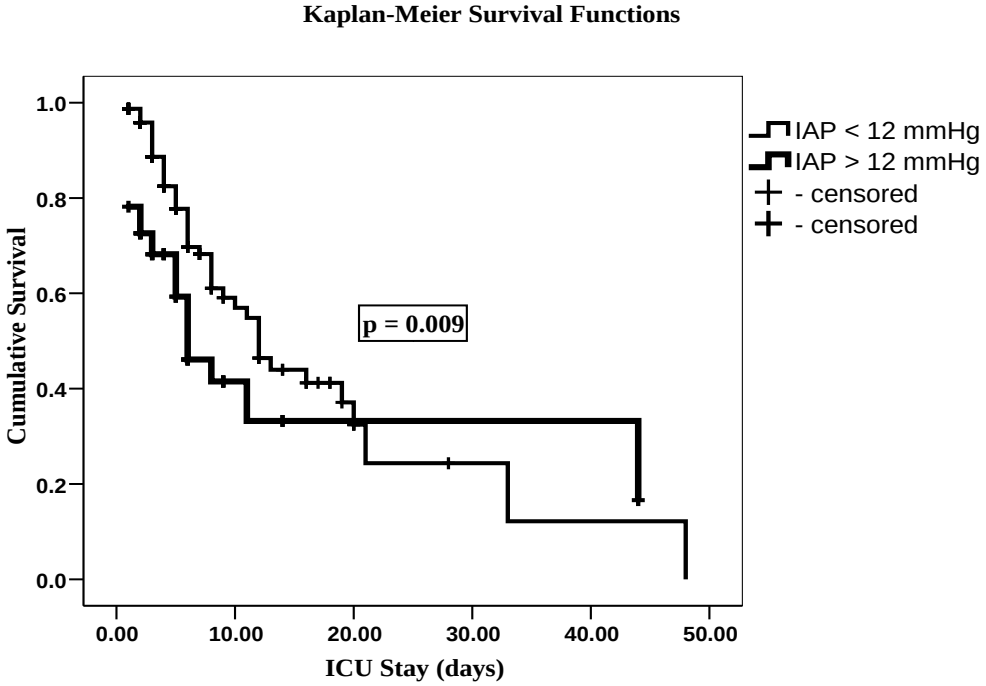
INTRODUCTION: Although deleterious effects of intra-abdominal hypertension (IAH) on various organ systems are widely investigated, its impact on overall surgical ICU survival is not well established.

METHODS: In a prospective observational study, we have studied 211 critically ill surgical ICU patients. Patients were allocated in 2 groups according to mean intra-abdominal pressure (IAP) values during their ICU stay: group 1. – IAP < 12mmHg, n = 56 (IAH absent) and group 2. – IAP > 12mmHg, n = 155 (IAH present). IAP was measured transvesically in accordance with World Society of Abdominal Compartment Syndrome guidelines. Abdominal perfusion pressure (APP = MAP - IAP) and filtration gradient (FG = MAP - 2×IAP) were calculated for each IAP measurement. All investigated continuous variables were summarized by calculation of areas under the curves using trapezoidal integration of all values obtained for each patient during the whole ICU stay. The Kaplan-Meier method was used to estimate survival function for groups. Cox regression further determined explanatory variables for observed differences in survival. Investigation protocol was not influencing on treatment, and all patients received standard treatment according to established guidelines. Statistical analysis carried out with SPSS 15. 0 for Windows (SPSS, Chicago, IL, USA).

RESULTS: Groups were uniform in demographics and co-morbidities. Median survival time in group 1. was 12 (1.484) vs. 6 (1.375) in group 2, expressed as median (SEM). Log-rank test revealed significant differences between survival curves for 2 groups (p = 0.009).

CONCLUSION: Sustained IAH is an independent predictor of overall mortality in surgical ICU.



Final stepwise optimized Cox regression model showed that IAP > 12mmHg is independently associated with survival. More specifically patients with sustained IAH had 2.208 times higher probability of overall ICU death then patients without IAH.

Cox regression Summary

	B	SE	Wald	p value	EXP(B)
UO	-0.001	0.000	4.473	0.034	0.999
MAP	0.167	0.080	4.342	0.037	1.182
IAP	0.792	0.259	9.374	0.002	2.208
APP	-0.983	0.286	11.813	0.001	0.374
FG	0.827	0.244	11.451	0.001	2.286
P_aCO_2	-0.100	0.051	3.921	0.048	0.905
$P_{alv}O_2$	0.258	0.104	6.114	0.013	1.295
$D_{A-a}O_2$	-0.266	0.105	6.431	0.011	0.766
P_aO_2	-0.240	0.103	5.391	0.020	0.787
Glasgow coma score	-0.358	0.182	3.885	0.049	0.699

UO – daily urine output
MAP – mean arterial pressure
P_aCO_2 – carbon dioxide tension in arterial blood
$P_{alv}O_2$ – alveolar partial pressure of oxygen
$D_{A-a}O_2$ – alveolar-arterial difference of oxygen
P_aO_2 – oxygen tension in arterial blood

Does a Unit Dedicated to Hospital Transfer Make "Cents"?

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INTRODUCTION: Patient transfers from community hospitals to tertiary care centers are increasing. This increasing demand in the setting of limited supply of tertiary care beds has negative outcomes for the patient, community hospital and referral center. Effects include lower patient satisfaction, delay in care, increased morbidity, increased length of stay (LOS) and cost for the tertiary center, lost revenue for the referral center and bed congestion at the community hospital. We present an operational and financial analysis of a novel approach for transferring patients to our tertiary care facility: The Hospital Transfer Unit (HTU).

UNIT DESIGN: A 12 bed HTU dedicated to incoming transfers was constructed. Each bed in the unit is equipped and staffed to provide care for either regular nursing floor (RNF) or intensive care unit (ICU) patients. Patients accepted in the HTU receive the same level of care given in the hospital until a bed becomes available. The HTU provides a means of patient triage where physician evaluation can move a patient from RNF status to ICU or vice versa. As beds become available, the patient is transferred in and the HTU bed is made available for other patients needing transfer.

METHODS: Hospital transfer data from the nine month period before and after the HTU opened was compared. The total number of patients transferred into the hospital and the number of patients waiting greater than 8 hours for transfer were studied. An estimated contribution margin (CM) was calculated from recent historical data for the CM of ICU and RNF patients and the relative mix of these patients. Likewise, an average LOS of 9.8 days, derived from recent census data, was used for financial estimates.

RESULTS

	Nine month period prior to HTU	Nine months of HTU operation	Difference
Total Hospital Admissions	7205	8125	920 (12.8 % increase)
# of Transfers waiting > 8 hours for a bed	1645	2197	552 (33.6% increase)
Estimated CM by transfer pts.	$108,734,087	$122,622,500	$ 13,888,413

CONCLUSIONS: A dedicated hospital transfer unit substantially facilitates the ability of a tertiary care center to accept transfer patients. The ability of the HTU to triage patients allows for fewer "inappropriately" placed patients that prevent other transfers. Increased waiting times suggest that bed availability may not be the bottleneck in hospital transfer. Further study is needed to elucidate this. Regardless, a dedicated hospital transfer unit appears to be a financially sound approach to facilitating hospital transfer.

Quality of Basic Life Support Skills among EMS-Certified Physicians in Austria

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INTRODUCTION: The recent 2005 consensus guidelines on cardiopulmonary resuscitation (CPR) have reiterated the importance of basic life support (BLS) skills for survival after cardiac arrest. BLS is commonly administered by lay persons and emergency medical technicians, whereas advanced life support (ALS) is performed by paramedics. Outside the U.S., many countries have implemented a tiered system with physician-staffed ALS units, many of which are staffed by anesthesiologists. A large number of licensed physicians in Austria obtain additional certification for prehospital emergency care by attending a 2-weeklong course although only a small fraction actually work as EMS (emergency medical services) physicians. The goal of our study was to test the quality of the BLS skills of physicians with EMS certificate in Austria.

METHODS: During mandatory biannual 2-day recertification seminars for physicians with an EMS certificate in Austria, we invited all attending physicians to voluntarily and anonymously participate in this study. The simulated standard scenario was single-rescuer BLS for an adult cardiac arrest victim without the use of an automated external defibrillator (AED) and bag-mask-valve ventilation. BLS quality according to the published guidelines was assessed by the same group of experienced BLS instructors during all seminars. We used the Resusci® Anne manikin (Laerdal Medical AS, Norway) without skill-reporting for all tests. We recorded the quality of the initial check, the correct call for help/assistance, mouth-to-mouth ventilations and chest compressions.

RESULTS: We included 167 physicians into our study, of whom only a small fraction actually works in the prehospital setting. The overall quality of BLS was poor: initial check and mouth-to-mouth ventilations were performed correctly by 49 of 167 (29%) and chest compressions by 35 of 167 physicians (21%). Overall, only 14 physicians (8%) made no mistake during BLS; 86 physicians (51%) made at least one major mistake and would have failed a formal BLS skills test. The remaining 98 physicians (59%) made some minor errors that -judged by BLS instructors-could have been easily corrected (e.g. rate of chest compressions per min too high or low).

CONCLUSIONS: Our study shows a sobering picture of the quality of BLS among EMS certified physicians in Austria. Only 1 out of 12 physicians performed BLS at the published standard and half of all attending physicians would have failed a formal BLS test. Based on our results and the recognized importance of BLS for survival after cardiac arrest, physicians should practice BLS more regularly and frequently -in particular if they consider working in the prehospital setting.

SUMMARY: Our study tested the quality of basic life support (BLS) skills among 167 physicians with EMS certificate in Austria and showed that half of the tested physicians would have failed a formal BLS skills test.

Failure to Detect Early Signs of Deterioration Despite Implementation of a Rapid Response Team

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Dartmouth Medical School

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Dartmouth Hitchcock Medical Center, Department of Critical Care Medicine

INTRODUCTION: Rapid response teams are specifically designed to address failure to rescue, which is typically related to 1. failure to recognize a problem; 2. failure to plan for the problem; or 3. failure to communicate regarding the problem. We hypothesized that after the implementation of a hospital-wide rapid response team, no patients admitted to the intensive care unit (ICU) from inpatient wards should demonstrate early signs of deterioration for a prolonged period of time.

METHODS: All patients admitted to the combined medical-surgical ICU from all inpatient surgical, medical, step-down, and special care wards were prospectively identified during the time period from Jan 30, 2006 to December 31, 2006. In early 2007, a retrospective chart review to abstract early signs of deterioration in the 24 hours preceding ICU admission was conducted. Early signs of deterioration were defined as the presence of hemodynamic, respiratory, and/or mental status abnormalities. In addition, the time from the first onset of these abnormalities to the time of ICU admission was collected.

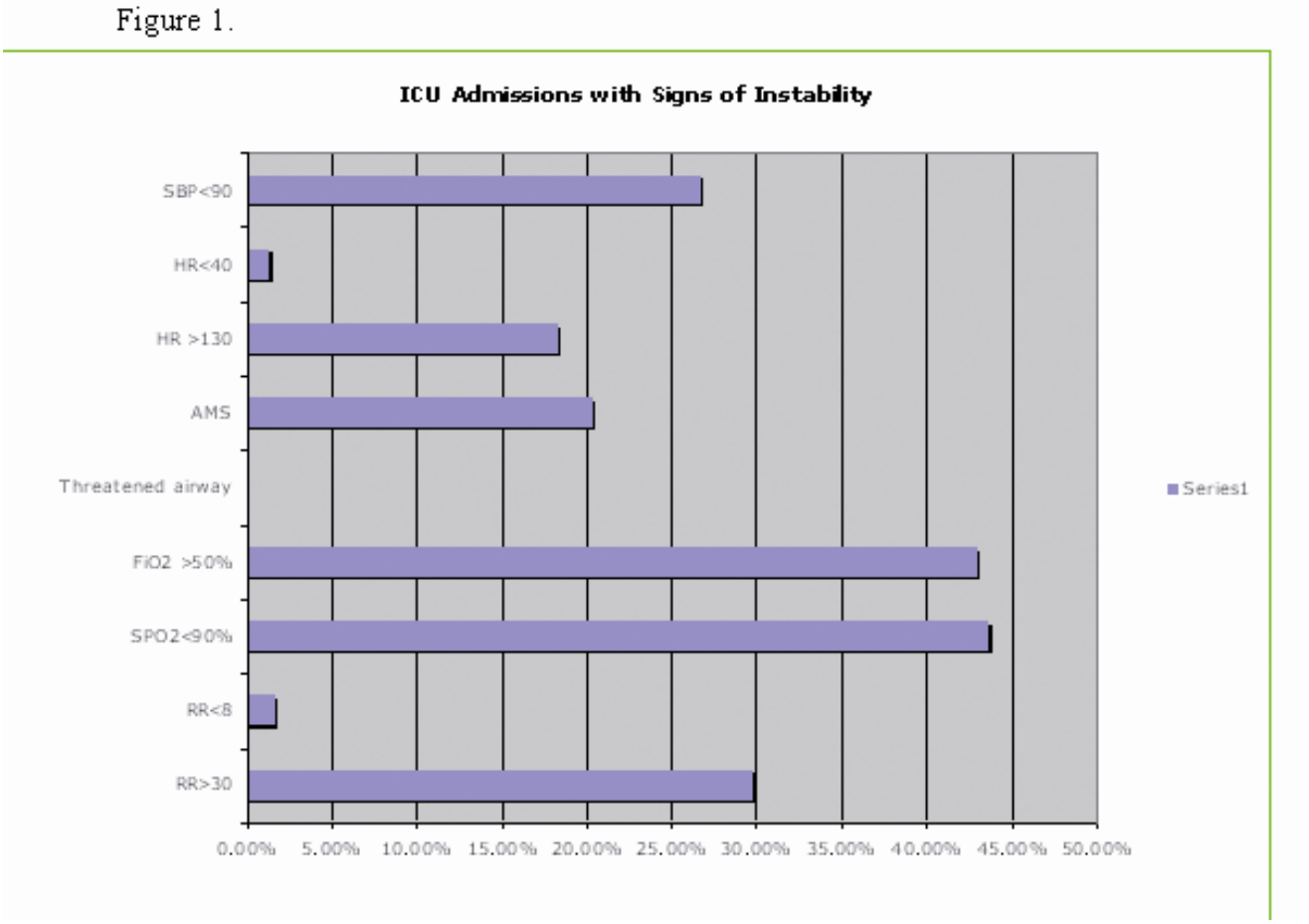
RESULTS: There were 301 admissions to the ICU from the wards during this time period. The frequency of signs of early deterioration is presented in Figure 1. The most frequent abnormalities were respiratory (Oxygen Fi02 >50% or respiratory rate > 30, or Sp02 < 90%).

One half of these admissions had onset of early signs of deterioration within 2 hours prior to admission to the ICU (n=152; 50%). There were a large number of patients that had early signs of deterioration for longer than 10 hours (25%, n=75).

The rapid response team was activated for 113 total calls during the time period and 46 of these activations (41%) occurred on patients that were subsequently admitted to the ICU. Sixteen of these 46 activations (35%) occurred among patients that had early signs of deterioration for less than 2 hours prior to ICU admission. The remaining 30 activations (65%) were for patients with early signs of deterioration for longer periods of time.

CONCLUSIONS: Despite the implementation of a rapid response team, we continue to see patients with early signs of deterioration remaining on hospital wards for long periods of time. Further education of teams caring for patients on hospital wards regarding 1) emphasizing early detection of clinical signs of deterioration and 2) the utility of early activation of rapid response teams may help reduce the time to implementation of intensive care and of early goal directed therapies.

Figure 1.


ICU Admissions with Signs of Instability
SBP<90
HR<40
HR >130
AMS
Threatened airway
FiO2 >50%
SPO2<90%
RR<8
RR>30
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
40.00%
45.00%
50.00%
Series1

Tracheostomy Tube Malposition in Patients Admitted to a Mechanical Ventilation Weaning Unit

Ulrich Schmidt, M.D., Ph.D.
Massachusetts General Hospital, Department of Anesthesia & Critical Care

J. Kwo, M.D., D. Hess RT, Ph.D., E. Gettings, M.S., S. Lagambina, B.S., F. Khandwala, M.S., L. Bigatello, M.D., H.T. Stelfox, M.D., Ph.D.
Massachusetts General Hospital, Department of Anesthesia & Critical Care, University of Calgary, Department of Critical Care

RATIONALE: Tracheostomy is probably the most common surgical procedure performed in intensive care units and anecdotal reports suggest that tracheostomy tube malposition may be an important barrier to successful weaning from mechanical ventilation. We sought to determine the incidence and risk factors associated with tracheostomy tube malposition.

METHODS: We identified consecutive adults admitted to an acute care unit specializing in weaning from mechanical ventilation between July 1, 2003 and January 1, 2005 who received tracheostomies during their hospitalization. Bronchoscopy reports were reviewed for each patient to look for evidence of documented tracheostomy tube malposition (>50% obstruction). Demographic, clinical and surgical factors were examined using multivariable analyses by means of backward stepwise regression ($p<0.10$).

RESULTS: Thirty-eight out of 404 patients (9%, 95% confidence interval [CI]; 7%-13%) were found to have malpositioned tracheostomy tubes. The single factor associated with tracheostomy tube malposition was the subspecialty of the surgical service that performed the tracheostomy ($P=0.006$). Compared to general surgeons, thoracic surgeons were equally likely (odds ratio 1.23, 95% CI; 0.50-3.01, $P=0.650$) while other subspecialty surgeons were more likely (odds ratio 4.20, 95% CI; 1.70 -10.00, $P=0.001$) to have their patients diagnosed with a malpositioned tracheostomy tube. Tracheostomy tube malposition was not associated with etiology of respiratory failure ($p=0.113$), APACHE II score ($p=0.876$), type of tracheostomy procedure ($p=0.999$) or type of tracheostomy tube ($p=0.122$). Malposition of tracheostomy tubes was associated with significant prolongation of mechanical ventilation post tracheostomy (median, 25 d vs. 15 d, $p =0.009$) , but not an increased risk of in hospital mortality (37% vs. 30% $p = 0.28$)

CONCLUSIONS: Tracheostomy tube malposition appears to be relatively common in patients weaning from mechanical ventilation. Surgical expertise may be a significant risk factor for this important complication. Tracheostomy tube malposition is associated with prolonged mechanical ventilation.

Cost Savings of an Anesthesiology Directed Tracheostomy Service

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University of Miami

INTRODUCTION: Tracheostomy is a well established procedure for the patient who is expected to need long term ventilation. While there is vast opinion as to timing most opinion concludes that for patient comfort, safety and hygiene tracheostomy is optimal to leaving an endotracheal tube in place for a protracted amount of time.
There are several operative services that perform surgical open tracheostomy at our institution. ICU practitioners would occasionally perform bedside tracheostomy (open or percutaneous) in selected patients. In developing our anesthesia airway rotation we incorporated a formal tracheostomy service for the hospital. With rapid acceptance and efficiency along with involvement of house staff in this service we decided to look at the financial aspects of open surgical tracheostomy in the operating room versus bedside percutaneous tracheostomy.

METHOD: When approaching hospital financial analysis there are two major aspects to consider and that is the billings for a procedure versus the cost. In any hospital there are multiple payers and thus multiple formulas for reimbursement. While it is nearly impossible to compare everyone's bill and perhaps even more difficult to compare what is eventually paid; the costs are obtainable. For those patients who are without funding we felt costs were worth considering

We reviewed our last 50 percutaneous tracheostomies. We made a detailed list of supplies, medications and equipment used. In addition we made a list of all equipment, charges and costs for an operative tracheostomy (averaging O.R. and hospital anesthesia charges for 10 procedures). There were several items we did not capture as their variability seemed too broad. These include ICU nursing time away from the unit, time for respiratory therapy to accompany the patient to the O.R., time that the O.R. was not utilized because they were awaiting an intubated patient. Additionally, we did not include the time for respiratory therapy to assist in the percutaneous tracheostomy and decided that time for the attending anesthesiologist and two house officers would be financially null for both procedures.

We then calculated average non-discounted full price charges. Patient charges are however not reflective of costs. This is a far more elusive item. To estimate hospital costs we took 5 items with known costs from each procedure and compared them to charges and applied this factor to gross charges.

RESULTS: It was found the average billed costs of an open procedure in the operating room were $9557 versus $1334 for the bedside percutaneous tracheostomy. In addition the cost of an attending general, ENT or oral surgeon was saved.

Using our method or related known hospital costs to hospital charges, we obtained an extrapolated hospital cost of $3323 for the open operative tracheostomy versus $465 for the bedside percutaneous tracheostomy.

DISCUSSION: For patients that have funding the difference in billings ($9557 v. $1334) may be considered lost revenue for an institution. However in a busy institution where O.R. time is in short supply the hospital may actually benefit financially. Patients referred to the Anesthesia/Critical Care Medicine-Tracheostomy Service are done within 24 hours allowing other operative cases to proceed and in enhancing patient progress through the ICU. For those cases where funding is absent the difference in cost ($2858) is a direct savings to the institution. In our institution 270 tracheostomies were performed last year. Extrapolating from a one month review 7% were part of the primary surgery, usually ENT. Of the remaining procedures, 11% were not appropriate for percutaneous procedure (children, body habitus or high vent support); this leaves approximately 230 or conceivably $657,000 in potential savings for the institution. Lastly and perhaps equally important, the Anesthesia Tracheostomy Service permits Anesthesiology residents, fellows and Pulmonary Critical Care fellows the opportunity to participate in invaluable experience in invasive airway management. The ASA algorithm describes three limbs where emergency invasive airway access is recommended1. It would seem unimaginable to find the first time attempting this in a life and death emergency.

Effect of Anesthesia Management Interventions to Prevent Intraoperative Hypotension and Death Following Severe Traumatic Brain Injury

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BACKGROUND: Hypotension is a primary risk factor for poor outcome after traumatic brain injury (TBI).(1,2) Hemodynamic evaluation using heart rate and blood pressure can be unreliable indicators of intravascular volume status as systemic hypertension secondary to Cushing's reflex is commonly observed in TBI.(3) High sympathetic tone from circulating catecholamines and diuresis following mannitol infusion further confound the clinical assessment of intravascular volume and the risk of intraoperative hypotension (IH).(4) A sudden reduction in sympathetic tone following brain decompression (reversal of Cushing's response) is often associated with a drop in blood pressure. Anesthetic agents that cause systemic vasodilation or myocardial depression may exacerbate hemodynamic instability. Anesthesia management interventions that improve hemodynamic assessment capabilities, reduce the use of anesthetics that cause cardiovascular depression, and anticipation of potential hemodynamic instability upon opening of the dura may reduce the incidence of IH and influence outcome in patients with severe TBI.(5)

METHODS: A retrospective review of severe TBI cases between 1996 and 2003 with isolated head trauma and a GCS of ≤ 8 needing emergent craniotomy was conducted at a university affiliated level 1 trauma center. In November 2003 anesthesia staff implemented a modified practice change for intraoperative management of TBI patients consisting of mandatory central venous pressure (CVP) monitoring, limited use of anesthetic agents in severe TBI patients, and more aggressive fluid management (target central venous pressure of 10-15 mmHg). A comparison of intraoperative hemodynamic parameters, use of anesthetic agents, fluid resuscitation volume, and the incidence of IH and death pre and post practice change was conducted. The study was approved by the institution's IRB.

RESULTS: Between 1996 and 2003, there were 20 intraoperative deaths associated with profound hypotension after opening of the dura (Group A). These 20 cases were compared to 21 consecutive TBI patients with similar severity of injury and hemodynamic profiles admitted after implementation of the intraoperative management changes (Group B). Mannitol was administered for signs of elevated intracranial pressure to all patients in both groups. In comparison to Group A, there was a 53% reduction in the dose of inhaled anesthetics ($p = 0.03$), a 52% increase in fluid volume resuscitation ($p = 0.02$), and a CVP of 14.9 ± 5.9 mmHg in Group B, versus no CVP monitoring in Group A. There was an attenuation of hypotensive episodes (mean arterial pressure < 90 mm Hg) in Group B (see figure) and no intraoperative deaths.

CONCLUSION: Improved hemodynamic monitoring, limited use of anesthetic agents, liberal fluid management, and anticipation of hemodynamic instability reduces the incidence of IH and death in patients with severe TBI requiring emergent craniotomy.

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