# Experimental shock

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SEVERE VENTILATION-PERFUSION MISMATCH CAUSED BY BACTERIAL EXOTOXINS IN PERFUSED LUNGS

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The multiple inert gas elimination technique was applied to bloodfree perfused isolated rabbit lungs. Commonly accepted criteria for reliability of the method were found to be fulfilled in this model. Ventilation-perfusion ($V_A/Q$) distributions in isolated control lungs corresponded to those repeatedly detected under physiological conditions. In particular, a narrow unimodal dispersion of perfusate flow was observed, and perfusion of low-$V_A/Q$ areas as well as true shunt flow ranged below 1 % each upon use of 1 cm $H_2O$ PEEP. Gas-flow was characterized by narrow dispersion in the midrange $V_A/Q$ areas.

Intravascular application of the bacterial exotoxins staphylococcal alpha-toxin and E. coli hemolysin resulted in acute pulmonary hypertension, followed by delayed onset pulmonary edema formation. This vasoconstrictor response was paralleled by severe $V_A/Q$ mismatch, characterized by the appearance of low and very low $V_A/Q$ areas, shunt, and bimodal distribution of ventilation and perfusion. Studies with specific inhibitors suggested that this mismatch was predominantly caused by thromboxane-mediated redistribution of perfusate flow in this model. The gas exchange disturbances were prevented by thromboxane synthetase inhibitors and by thromboxane receptor antagonists. Moreover, when applied subsequent to the exotoxin challenge, thromboxane receptor antagonists acutely reversed the $V_A/Q$ mismatch. Exotoxin-induced true shunt flow in this model was not only dependent on the amount of edema formation, but was markedly influenced by the pulmonary artery pressure height and the kinetics of pressure increase.

We conclude that mimicry of septic lung failure by bacterial exotoxin application in perfused lungs causes severe $V_A/Q$ mismatch related to endogenous vasoactive mediator generation.

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**EFFECTS OF SODIUM BICARBONATE ($HCO_3Na$) ON CELL METABOLISM IN EXPERIMENTAL ENDOTOXINIC LACTIC ACIDOSIS.**

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Although deleterious effects of severe lactic acidosis in shock states are not doubtful, alkali therapy remains controversial. Potential adverse effects of $HCO_3Na$, the most widely used buffer agent, include increase in $CO_2$ production, worsening hemodynamic status and paradoxical intracellular acidification. We investigated the effects of $HCO_3Na$ load on acid-base balance and intracellular bioenergetics in an experimental model of endotoxinic shock.

ANIMALS AND METHODS: 16 anesthetized, mechanically ventilated (adjusted to achieve normocapnia) and paralyzed rats were given at T0 an IV bolus of E. Coli LPS (15 mg/kg). At T+30min (T30) they were randomly assigned either to an ALK group (n=8) receiving $HCO_3Na$ intravenously (2 mmol/kg in 2 min) or to a SAL group (n=8) receiving an equimolar saline injection. Mean arterial pressure (MAP), arterial pH (pHa), $PaCO_2$ and lactates were measured at TO, T30, T35, T60, as well as intracellular pH (pHi) and phosphocreatine/inorganic phosphate ratio (Pcr/Pi) on the hindlimb using $^{31}P$ NMR spectroscopy.

RESULTS (mean±SE): LPS induced at T30 a significant decrease in MAP (58±6 vs 120±8 mmHg), pHe (7.20±0.03 vs 7.35±0.01), pHi (6.86± 0.04 vs 7.08±0.01) , a marked hyperlactatemia (7±3 vs 1.2±0.2 mmol/l) and a drop in Pcr/Pi. In ALK group, MAP further decreased at T35 ($p<0.05$) and T60 ($p<0.001$), compared to T30 whereas it remained unchanged in SAL group. $HCO_3Na$ increased pHe and $PaCO_2$ transiently (T35:$p<0.001$; T60:NS). In SAL group pHe decreased and $PCO_2$ remained stable. pHi and Pcr/Pi had a similar evolution in both groups.

CONCLUSION: On this model of severe septic metabolic acidosis, partial correction of pHe using $HCO_3Na$ did not improve metabolic cellular injury. Furthermore, hemodynamic tolerance was better in SAL group, suggesting a possible deleterious effect of $HCO_3Na$.

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EFFECTS OF ISOVOLEMIC HEMODILUTION ON JEJUNAL OXYGENATION

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During isovolemic hemodilution enhanced blood flow is the primary mechanism for compensation of reduced oxygen content. There are few studies on the redistribution of blood flow to different organs and none has dealt with the effects on tissue oxygenation of intestinal mucosa. The aim of our study was to investigate the influence of isovolemic hemodilution on mucosa and serosa oxygen tension and oxygen saturation.

5 domestic pigs (43,6±2,3kg) were anesthetized, paralysed (Sufentanyl, Midazolam, Vecuronium) and normoventilated. Systemic hemodynamic was monitored with an arterial and a pulmonary artery catheter. A small segment of the jejunum was isolated and perfused with constant pressure using a non pulsatile pump supplied by the right femoral artery. An area of the jejunal mucosa and serosa was exposed by an antimesenteric incision. A venous catheter was inserted into the segment's draining vein. Two modified Clark-type multiwire oxygen electrodes (MDO) were placed on the surface of the exposed mucosa (pO2muc) and serosa (pO2ser). An "Erlanger Microlightguide Spectrophotometer" (EMPHO II), based on the principles of remission spectrophotometry, was used for determination of intracapillary hemoglobin oxygenation (Hbsat).

Isovolemic hemodilution was performed using a 6% solution of hydroxyethylstarch (Leopold, Graz; Austria). Hematocrit was lowered from a control value (Hct-c) in four steps to a final value of 7,2%, each step lasting 30 minutes. Measurements of pO2muc, pO2ser, Hbsat, jejunal oxygen delivery (DO2j) and consumption (VO2j) and corresponding systemic parameters (DO2sys, VO2sys) were obtained within the last 5 minutes of each dilution step.

**Results:** Baseline values: DO2sys 13,8 ± 2,4 ml/kg*min; VO2sys 5,8 ± 0,5 ml/kg*min; Hct-c 29,2 ± 1,1; DO2j 6,4 ± 1,4 ml/100g*min; VO2j 1,4 ± 0,2 ml/100g*min. Baseline tracings of PO2muc (24,9 ± 8,2mmHg) and Hbsat (48,4 ± 18,3%) showed regular oscillations with a frequency of 4,3 to 4,6 per minute. PO2ser (56,4 ± 7,0mmHg) exhibited no oscillations.

VO2sys and VO2j remained constant until Hct 9,0%. VO2j dropped by 20% at final step. PO2muc and Hbsat declined to a lesser degree than pO2ser with hemodilution. At Hct 9,0% PO2muc was 14,9 ± 5,3 mmHg, Hbsat 35,9 ± 9,8% and PO2ser 31,4 ± 16,1mmHg. At a Hct below 10% loss of the pO2muc and Hbsat oscillations was observed.

**Conclusions:** Jejunal mucosal oxygenation is well preserved until a Hct of 9%. There is some evidence that mucosal layers are preferentially perfused within the jejunum during extreme isovolemic hemodilution.

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INCREASED HEPATIC BLOOD FLOW DOES NOT PROTECT HEPATIC ULTRASTRUCTURE IN SEPSIS.

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We have developed a pig peritonitis model of multi system organ failure where low cardiac output (CO) and reduced liver blood flow (HBF) is associated with liver ultrastructural damage. We hypothesised that maintaining or increasing CO and HBF should afford hepatic protection when compared to sham or low flow animals. 20 pigs (25-30kg) were anaesthetised and divided into 4 groups: low (L), medium (M) and high flows (H) and sham operated (S). Arterial lines, pulmonary artery termodilution catheters and CVP infusion lines were inserted. A laparotomy was performed and flow probes placed around the portal vein and hepatic artery. Haemo-dynamics were measured and peritonitis induced in the 3 treatment groups. L received 200ml colloid per/hr, M had baseline CO maintained, and H was given sufficient to increase CO 30%. Sham group was uninfected. After 8 hrs hepatic tissue was removed and the animals culled. Tissue was processed for microscopy and the tissue elements randomised and digitised. The area of tissue, sinusoids, endothelium (E), occlusion of sinusoids by leukocytes (L) and the patent area of the sinusoids (PS) were measured, and expressed as % of total sinusoidal area (TS). The 3 elements were expressed as % of total sinusoidal area.

| Group | E/TS | L/TS | PS/TS | HBF | CO |
|---|---|---|---|---|---|
| Low | 54.7±2.4 | 27.3±1.2 | 17.9±2.2 | 300±32 | 1.43±0.2 |
| Med | 53.3±6.6 | 12.6±2.1 | 33.1±6.8 | 1088±97 | 3.88±0.4 |
| High | 51.4±6.7 | 14.7±1.3 | 33.8±6.9 | 1450±133 | 5.81±0.3 |
| Sham | 18.3±4.1 | 5.1±0.5 | 76.6±4.5 | 980±79 | 3.98±0.5 |

Although CO and HBF was increased in the H Group, endothelial swelling and leukostasis in the 3 treatments were similar and significantly higher than the sham group whilst sinusoidal patency was significantly lower.

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### THE PROTEASE INHIBITOR, APROTININ, REVERSES ACUTE HEMODYNAMIC CHANGES IN EXPERIMENTAL SEPTIC SHOCK (SS)

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The plasma kallikrein-kinin system is activated by endotoxin. In SS, kinins could be mediators of hypotension, systemic vasodilatation, and capillary leak. In high doses, aprotinin (Trasylol, Bayer) inhibits plasma kallikrein. In ovine experimental SS due to peritonitis, we found beneficial effects of aprotinin infused from 30 minutes after surgery[1]. We report here the effect of aprotinin given late in SS.

Ovine surgical peritonitis was induced as previously described[2] (n=5). Once volume-resistant hypotensive SS developed, (fall in mean arterial pressure >40 mm Hg, mean 8.5±1.3 hours post-surgery), aprotinin $10^6$ KIU was given as an intravenous bolus, followed by $10^6$ KIU/hour.

| | Change in MAP from baseline (mm Hg) | Change in SVR from baseline (dyne/sec/cm$^{-5}$) |
|---|---|---|
| **Pre-aprotinin** | - 53.8 ± 4.6 | - 714 ± 75 |
| **Aprotinin** | - 12.6 ± 5.0 * | - 281 ± 36 * |
| **Post-aprotinin** | - 49.8 ± 10.8 ** | - 636 ± 180 ** |

* p <0.01 vs pre-aprotinin ** p<0.01 vs aprotinin

Aprotinin produced a rapid increase in MAP and systemic vascular resistance, with no change in cardiac output. This did not persist after infusion was stopped, suggesting that high plasma levels are necessary. Urine output, sodium excretion, and creatinine clearance also improved during aprotinin infusion. If reproduced clinically, these effects of aprotinin could prove useful in SS.

1. Cumming AD, Nimmo GR. Crit Care Med, in press.
2. Cumming AD et al. Crit Care Med, 1988; 16: 1132.

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### INCREASED CARDIAC OUTPUT AND RENAL BLOOD FLOW AFTER VOLUME LOADING DOES NOT PREVENT RENAL ULTRASTRUCTURAL DAMAGE IN AN ANIMAL MODEL OF SEPSIS

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This study was undertaken to document the possible protective effect on renal ultrastructure of maintaining high cardiac output(CO) and renal blood flow(RBF) in a pig peritonitis model. In 9 anaesthetised animals routine haemodynamic measurements were made. In addition renal blood flow was measured using a thermodilution catheter placed in the left renal vein. There were 4 animals in the placebo(P) and 5 in the high volume(H) group. P were given hetastarch to maintain CO at baseline levels, H to increase CO by 30%. RBF increased by 57% and MABP by 36% in H compared to P. Renal tissue was acquired at 8 hrs and the animals were then culled. Tissue was processed for histological examination, photographed and the pictures randomised. Individual structures were independently scored blind by 3 people (0 =normal,10=grossly abnormal). In the P group the proximal nephron(PT) showed considerable vacuolation(PTv) and mitochondrial damage(PTm) with little loss of microvilli(PTmc) but marked loss of patency of the tubular lumen(PTlp). In the glomeruli(GL) there was leukostasis(GLlk) with capillary lumen occlusion(GLvo)with reduction of the urinary space(GLus). Statistical significance (*) was tested by ANOVA.

| | PTlp | PTv | PTm | PTmc |
|---|---|---|---|---|
| Placebo | 4.9±0.3 | 5.3±0.2 | 5.0±0.3 | 2.8±0.2 |
| High | 7.1±0.3* | 5.9±0.2 | 5.5±0.2 | 3.0±0.2 |

| | GLus | GLlk | GLvo |
|---|---|---|---|
| Placebo | 2.2±0.5 | 3.6±0.5 | 4.0±0.5 |
| High | 3.8±0.5* | 4.8±0.4 | 5.2±0.3* |

In the H group there was no improvement, in fact glomerular and tubular luminal occlusion was significantly worse. We conclude that increasing renal perfusion offers no protection from structural damage as seen with electron microscopy.

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# Pediatrics I. Respiratory

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### COMPARISON OF RESPIRATORY MECHANICS MEASUREMENTS DURING VOLUME AND PRESSURE CONTROLLED VENTILATION IN NEONATES

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It has recently been demonstrated that respiratory mechanics of infants could be evaluated during volume controlled ventilation either by the "pulse" method or the interrupter method (Pediatr Pulmonol. 12; 203-212, 1992); however, these methods cannot be used during pressure controlled ventilation that is the subject of a new interest. The aim of the study was to measure compliance and resistances during pressure controlled ventilation (part I) and to compare the results with those obtained by the interrupter technique during volume controlled ventilation (part II). Flow, volume, and pressure were measured at airway opening in 16 neonates (age 12,4 +/- 16,75 days; B.W. 2400 +/- 720 g) mechanically ventilated with a Servo-ventilator 900C; flow/volume, flow/pressure, and volume/pressure were displayed on a X/Y table. In the part I, the method is based on the statement that, when applying constant inspiratory pressure (Pao) during passive inflation, the equation of motion of the respiratory system is : $V(t) = (Pao-PEEPrs,infl) \times Crs,infl-(Rrs,infl \times Crs,infl) \times \dot{V}(t)$, where 1/Crs,infl is the total elastance of the respiratory system, V(t) the volume, Rrs,infl. the resistance, PEEPrs,infl the total end-expiratory pressure. Pao being constant, the relationship between inspiratory volume and flow is then a linear function of the type $Y = a + bX$, in which the slope (b) defines the time constant (T) of the respiratory system.When flow is equal to zero, at the end of inflation, equation is : Crs,infl.=tidal volume/(Pao-PEEPrs,infl). We verified in each test that inspiratory flow was equal to zero at the end of inflation on the P /$\dot{V}$ loops. Rrs,infl. is then defined by T/Crs,infl. In the part II, Compliance (Crs,occl) and resistances (Rrs,occl) were also measured by the occlusion technique during volume controlled mode (Kochi et al. J Appl Physiol. 64: 441-450, 1988). We found a strong correlation between Crs,infl. and Crs,occl. ($r=0.86$; $p<0.001$) and between Rrs,infl and Rrs,occl ($r=0.84$; $p<0.002$). Intrinsic PEEP calculated during the two modes of ventilation by using end-expiratory occlusion were comparable ($r=0,92$; $p<0.001$). We concluded that pulmonary mechanics can be simply estimated in infants during pressure controlled ventilation .

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### SEQUENTIAL RESPIRATORY MECHANICS IN TERM INTUBATED NEONATES RECEIVING MUSCLE RELAXANTS

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Term neonates in severe respiratory failure often receive muscle relaxants in an attempt to optimize mechanical ventilation. An increase in pulmonary resistance has been reported with pancuronium. Measurements of pulmonary mechanics in term neonates receiving vecuronium (Norcuron) are not available. We evaluated the cumulative effects of Norcuron on pulmonary mechanics in 10 infants (BW 2680-4285g, GA 38-41 wks, age 0.5-2 days); 8 patients had meconium aspiration and 2 pneumonia. The initial dose of Norcuron was 0.2 mg/Kg IV, followed by 0.1 mg/Kg as needed. Respiratory mechanics and 1-hr monitoring of computerized pulse oximetry were obtained 1-hr prior to and 1-hr after the initial dose of Norcuron, and at 24-hr intervals for the duration of the paralysis (72 hours). At comparable mean airway pressure and FIO2, we monitored airway pressure, flow and tidal volume (VT) and only mechanical breaths were analyzed. Respiratory resistance (Rrs) and compliance (Crs) were calculated (PeDS). Oxygen saturation (SaO2) was measured with the Nellcor N-200 monitor and a computer operating an oximetry software.

| | Crs | Rrs | SaO2<90% | <85% |
|---|---|---|---|---|
| | ml/cmH2O/Kg | cmH2O/L/sec | % OF TIME | |
| 1 HR BEFORE | 0.35 | 59 | 1.6 | 0.7 |
| 1 HR AFTER * | 0.39 | 70 | 0.7 | 0.4 |

* p > 0.05

In addition, there were no significant changes in Crs, Rrs, oxygenation, heart rate or blood pressure, measured daily during Norcuron therapy (ANOVA). Our findings indicate that Norcuron does not significantly affect Rrs and Crs in term neonates. Norcuron appears to be well tolerated in infants who require muscle relaxants.

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