# Oral Presentations
# Critical care of the heart – 462-466

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**CARDIOGENIC SHOCK COMPLICATING ACUTE MYOCARDIAL INFARCTION. THE IBERICA STUDY.**

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**INTRODUCTION.** The appearance of cardiogenic shock (CS) during the acute phase of myocardial infarction (AMI) is a relatively frequent complication associated with a worse prognosis.

**METHODS.** During the 1996-1998 period, all the AMI of the 7 participating areas of the IBERICA study in Spain were registered. The cases were detected through an active record in the Coronary Care Unit, and also from the hospital discharge reports and from the sanitary transport system reports. The occurrence of CS at admission and during hospital stay, clinical and demographic variables were collected. The 28 day case-fatality was determined

**RESULTS.** 8963 AMI were registered, and 929 (10.3%) were complicated with CS.
In the multivariable regression analysis, the variables associated with the appearance of CS were age and female gender (RR 1.5; CI 1.2-1.8), diabetes (RR 1.4; CI 1.1-1.6), previous AMI (RR 1.6; CI 1.3-1.9), typical symptoms (RR 0.3; CI 0.2-0.3), mechanical complications (RR 11.2; CI 8.0-15.8), anterior AMI (RR 1.5; CI 1.2-1.8) or no valuable electrocardiogram (ECG) (RR 3.6; CI 2.5-5.1). In this subgroup of patients, 28-day case fatality was 77.5%. The variables related to 28-day case-fatality were the age (RR 1.03; CI 1.01-1.05), diabetes (RR 1.6; CI CI 1.1-2.4) and mechanical complications (RR 1.9; CI 1.0-3.5). The patients complicated with CS who survived, received more reperfusion treatments: thrombolysis (41% vs 26%; p<0.001); angioplasty (33% vs 7%; p<0.001); cardiac surgery (14% vs 3%; p<0.001)

**CONCLUSION.** The proportion of AMI patients presenting CS is 10%. These patients have a very high 28-day case-fatality (77.5%). The patients who survived received more reperfusion treatments. These results suggest that the reperfusion strategies should be optimized in these patients.

Grant. Fondo de Investigación Sanitaria 1997

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**PLASMA GLUCOSE LEVEL ON HOSPITAL ADMISSION: PREDICTOR FOR OUTCOME IN PATIENTS WITH HEART ATTACKS**

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**INTRODUCTION.** Preliminary data suggest that plasma glucose levels on admission have a predictive value in patients with acute myocardial infarction for short-term and long-term follow up, even without known history of diabetes mellitus (DM).
**METHODS.** We evaluated in a systematic follow up study the relationship between plasma glucose levels on admission and the short- and long-term outcomes in all patients (pts), admitted with an acute myocardial infarction to our institution from 1.1.95-1.12.99 (n=425). Plasma glucose concentrations were determined in all pts upon admission. Pts were stratified to three groups according to an oral glucose tolerance test for normal (I, <7.8 mmol/l), borderline elevated (II, 7.8-11 mmol/l), and elevated stress-glucose values (III, >11mmol/l). Mortality and recurrent ischemic events were analysed accordingly in the three groups during hospitalisation and follow up.
**RESULTS.** There was a strong correlation between plasma glucose levels on admission with age, anterior myocardial infarction and cardiogenic shock (group III>II>I). Only 49% of the pts in group III with elevated glucose levels had a previously established diagnosis of DM. The extent of myocardial infarction and in-hospital mortality correlated significantly with the degree of hyperglycaemia on admission, even in pts without a history of DM (Tab 1). In-hospital survivors with elevated plasma glucose levels on admission showed a trend to higher mortality during a median follow-up of 30 (6-66) months. However, the number of recurrent myocardial infarction and recurrent interventions (Re-PCI, CABG) was similar in all groups (Tab 2).

| | group I (n=121) | group II (n=155) | group III (n=135) | p value |
|---|---|---|---|---|
| plasma glucose on admission | 6.5 ± 0.8 | 9.0 ± 1.0 | 15 ± 7.0 | 0.0001 |
| diabetes mellitus (%) | 4 | 11 | 49 | 0.0001 |
| Age (years) | 56 ± 13 | 59 ± 11 | 64 ± 12 | 0.0002 |
| anterior infarction (%) | 33 | 41 | 56 | 0.01 |
| peak CK-MB (U/l) | 208 ± 221 | 254 ± 264 | 327 ± 295 | 0.02 |
| prior cardiogenic shock (%) | 6 | 11 | 33 | 0.0001 |
| in hospital mortality (%) | 0 | 5 | 16 | 0.0001 |

base line characteristics

| | group II (n=148) | group III (n=113) | p value | |
|---|---|---|---|---|
| follow-up mortality (%) | 3.3 | 5.4 | 8.0 | 0.1 |
| recurrent infarction (%) | 6.2 | 6.5 | 4.1 | 0.7 |
| recurrent PCI (%) | 20 | 20 | 20 | 0.8 |

follow-up

**CONCLUSION.** Elevated plasma glucose levels on admission were predictive of increased mortality in patients admitted for acute myocardial infarction independently of a previously established diagnosis of diabetes mellitus.

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**INTRACORONARY BETA-2 RECEPTOR ACTIVATION INDUCES DYNAMIC LOCAL T-PA RELEASE.**

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**INTRODUCTION.** Tissue-type plasminogen activator, t-PA, regulates endogenous intravascular fibrinolysis. This function depends on the amount of t-PA locally released rather than on circulating basal levels of t-PA. With increasing knowledge of the relation between hemostasis and sympathetic activation, a further clarification of the role of adrenergic control of regional release of fibrinolytic factors is warranted. This study aimed to identify possible beta-adrenergic dependent mechanisms for the acute release of t-PA and plasminogen activator inhibitor type-1 (PAI-1) in the coronary vascular bed.

**METHODS.** In healthy pigs (n=10) under general anaesthesia, regional coronary fluxes of t-PA and PAI-1 were studied before and during the administration of isoprenaline (IPR) into the left main coronary artery. Arterial-venous concentration gradients of t-PA and PAI-1 were obtained across the coronary vascular bed together with coronary blood flows (retrograde termodilution). Coronary net fluxes of total t-PA antigen (ELISA, detecting both complex bound and free fraction) and active t-PA (functional assay detecting biological free fraction) were determined at baseline and at 3, 5, 7 and 10 minutes of IPR infusion.

**RESULTS.** During IPR, net release of total t-PA increased in a biphasic pattern with transiently high levels at 3 (+440 %) and 7 minutes (+620%) and a return towards base-line at 10 minutes. Net coronary release of active t-PA increased with maximum levels at 3 minutes (+50%). Baseline coronary net flux of total PAI–1 showed a decrease which was most pronounced at 10 minutes.

**CONCLUSION.** In summary, a fast and dynamic beta-2 agonist-mediated local release of t-PA into the coronary vasculature was demonstrated. For total t-PA this response was characterised by a biphasic profile. Findings suggest that local adrenergic mechanisms in the heart are involved in the regulated release of t-PA in the coronary circulation.
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Grant. Swedish Heart-Lung Fondation

## 465

**FACTORS INFLUENCING CARDIAC TROPONIN I IN SEPTIC PATIENTS WITH MYOCARDIAL DYSFUNCTION**

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**INTRODUCTION.** Elevation of Cardiac Troponin I ( cTni ) can be associated with myocardial dysfunction and determines secondary cardiac injury in septic patients. We would like to find firstly if the presence of acute renal failure (ARF) and usual coronary risk factors can influence the incidence of cTni, and secondly, if the patients' heart patterns are more relevant in influencing mortality than cTni itself.

**METHODS.** Over a period of 16 months, 155 patients who had severe sepsis (SS) and septic shock (SSH), but without any associated acute cardiac affection, were included in this study. After haemodynamic stabilisation, plasma cTni was measured at admission and daily for three consecutive days. It was considered elevated if the value was more than 0,4mg/L. Echocardiography (Echo) was performed during the first 24 hours and determined three different cardiac patterns: congestive dilated heart (CH), hyper dynamic (HDH) and hypertrophy heart (HH) in every patient.Student t test and chi-square test were used for statistical analysis.

**RESULTS.** 104 patients had elevated cTni after three days (Group I) and 51 had not (Group II). There was no significant HD change observed, except left ventrICUlar stroke work index was lower in Group I (p<0.05). Patients of Group I had significantly more systemic Hypertension (AHT) than Group II, but no difference in the previous incidence of Diabetes or Coronary Disease existed between the two groups. The incidence of Atrial Arrythmias, Shock, Multiple Organ Failure (MOF), and death were significantly higher in Group I compared with Group II (p<0.05). ARF was also higher in Group I (p<0.05) according to the incidence of MOF, but there was no correlation between the evolution of cTni and the serum Creatinin. Cardiac dysfunction was detected in 67/104 patients of Group I by Echo, but the mortality and MOF was similar between patients who had HDH or CH and HH. However, the HDH pattern was more often observed in Group II than Group I .In both groups 95% of all patients in whom CH had been detected died.

**CONCLUSION.** cTni was significantly elevated in septic patients who had AHT and developed ARF, which was correlated with the higher incidence of MOF present. Mortality was not influenced by different cardiac patterns at admission, in those patients. However, the mortality became very high when Congestive Dilated Heart had been detected, whether or not the patients had elevated cTni.

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**RELEVANCE OF TROPONIN-I FOR DETECTION OF EARLY GRAFT OCCLUSION AFTER CORONARY ARTERY BYPASS GRAFTING**

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**INTRODUCTION.** The detection of early graft occlusion following coronary artery bypass grafting (CABG) enables immediate reintervention and may prevent or limit myocardial damage, thus potentially improving prognosis. To date usual indicators of early graft occlusion are still of uncertain diagnostic value.

**METHODS.** We investigated a diagnostic discrimination limit of troponin-I for detection of early graft occlusion. In a prospective study patients following elective CABG with troponin-I level above 20 ng/ml with or without hemodynamic and ECG changes underwent re-angiography. Patients with (group 1) and without (group 2) graft occlusion were correlated with troponin-I, concomitant myoglobin and creatine kinase levels, hemodynamic and ECG changes.

**RESULTS.** From Jan/2001 to Mar/2002 36/1510 (2.4 %) patients underwent re-angiography. 24/36 patients were detected with early graft occlusion (group 1), whereas 12/36 did not show any graft failure (group 2). Maximum troponin-I and concomitant myoglobin and creatine kinase levels leading to repeat angiography were significantly increased in group 1 compared to group 2. Hemodynamic changes were not different between the groups. New Q-waves were present in 5/24 in group 1 and did not occure in group 2. In group 1 4/24 underwent coronary artery stenting and 11/24 redo CABG. Hospital mortality in group 1 was 2/24 patients and 2/12 in group 2.

| | group 1 | group 2 |
|---|---|---|
| troponin-I (ng/ml) | 54.0 ± 20.8 | 33.4 ± 20.6 * |
| myoglobin (ng/ml) | 1066 ± 768 | 325 ± 233 * |
| creatine kinase (U/l) | 922 ± 648 | 632 ± 312 |

*p<0.05; (mean ± SD)

**CONCLUSION.** The diagnostic discrimination limit of troponin-I for detecting early graft occlusion seems to be above 30 ng/ml. Therefore, patients with a troponin-I level above 30 ng/ml have to undergo re-angiography to decide wether or not reintervention is indicated.

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**SLEEP AND ADVERSE ENVIRONMENTAL FACTORS IN PAEDIATRIC INTENSIVE CARE PATIENTS**

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**INTRODUCTION.** Sleep deprivation and abnormal sleep patterns are well documented in adult ICU. Few studies have described a similar decrease in sleep time in the paediatric ICU (PICU). However, there is no information available on sleep architecture in the sedated mechanically ventilated PICU patients. This study was designed to describe sleep pattern in this population using polysomnography (PSG) and to determine the influence of environmental factors (noise, light and contact with care giver) and severity of illness on the quantity and quality of sleep.

**METHODS.** Thirteen critically ill (PIM median 9%, range 4-100%) paediatric patients (age median 15 months, range 2-84 months, 8 females and 5 males) were included. Sleep PSG, staff interventions, noise and light levels were continuously monitored over a 24-hour period. All patients were on conventional mechanical ventilation and sedated with midazolam and/or morphine infusion.

**RESULTS.** There were severe alterations to sleep architecture throughout the 24 hours, with no significant difference between day and night. Rapid eye movement (REM) sleep was virtually absent (2.7±4%) of total sleep time (TST) with increase in nonrapid eye movement (NREM) 3 and 4 (52±22%) and decrease in NREM 2 (27±18). Although the total wake time was only 12±9% of TST, there was severe sleep fragmentation as reflected by the high number of arousals per hour of sleep (12±6). Light and noise levels showed diurnal variation, but noise levels were persistently above 56 dB (A) with peak reaching 100 dB (A) at night. Staff interventions were frequent (34±7) with no significant day/night difference.

**CONCLUSION.** The above findings suggested a significant electrophysiological abnormality of sleep in the PICU patients with increased environmental adverse conditions. However, this study was limited by a small sample size and a wide age variation. Future investigations with a larger sample size are needed to identify the variation between different age groups and clinical conditions.

# Oral Presentations
# Paediatrics (III) – 467-471

## 467

**ENDOTHELIN-1 IN NEONATES WITH HYPOPLASTIC LEFT HEART SYNDROME IN PERIOPERATIVE PERIOD**

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**INTRODUCTION.** Hypoxia, acidosis, shear stress, congestive heart failure, deep hypothermia and circulatory arrest, ischemia and reperfusion are the conditions that stimulate the production of endothelin-1 (Et-1), the most potent vasoconstrictor, that could affect pulmonary, systemic and coronary circulation. All the above factors are present in neonates with hypoplastic left heart syndrome (HLHS). We have investigated plasma endothelin-l concentration in neonates with HLHS after the Norwood procedure and compared the results with findings observed in neonates with transposition of great arteries (TGA) after anatomical correction performed in deep hypothermia and circulatory arrest.

**METHODS.** Plasma Et-1 concentration was assessed in 30 neonates (mean weight 3.37 kg, mean age 17 days) with HLHS operated employing the Norwood procedure; the control group consisted of 15 TGA neonates (weight 3.32,mean age 6.06 days) after anatomical correction. The early mortality rate was 16% in HLHS group. There was no death in TGA group. Blood samples for Et-1 assessment were obtained from the radial artery before operation, twice during extracorporeal circulation and 2, 4, 6, 8, 12, 20 hours postoperatively and analyzed by radioimmunoassay. Hemodynamic and biochemical parameters were assayed simultaneously.

**RESULTS.** Preoperative plasma Et-1 did not differ in the HLHS and TGA group, but was significantly higher 4, 6,8, 12 and 20 hours postoperatively (p<0.05) in the HLHS group. The maximal plasma level of Et-1 was observed 8 hours after operation in both groups. The increase rate between 2 and 8 hours post operation was 142% in HLHS infants, and 28% in the TGA group. In non-survivals with HLHS, Et-1 level was significantly higher 6 hr postoperatively (90.00∂5.78 versus 44.42∂31.22; p<0.007), shortly before death. In HLHS neonates hypercarbic gas mixture administered postoperatively resulted in significantly higher Et-1 plasma levels 4 and 6 hours (p<0.003;p<0.007) after operation. In TGA neonates after anatomical correction, 20 hours postoperatively Et-1 plasma levels were lower than in the preoperative period (25.30∂10.91 versus 37.02∂13.54, p<0.05).

**CONCLUSION.** Et-1 plasma levels increase significantly in HLHS and TGA neonates in the postoperative period, but are significantly higher in HLHS group. Maximal Et-1 plasma levels are observed 8 hours after operation both in HLHS and TGA group. The administration of carbon dioxide in inspired gas mixture can significantly influence plasma Et-1 levels. The univentrICUlar circulation system facilitates high Et-1 levels. Et-1 affects the pulmonary, systemic and coronary bed resistance and may cause a discrepancy between the myocardial oxygen demand and supply and influence the early survival rates.

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**DAILY ENERGY EXPENDITURE AND ENERGY BALANCE IN CRITICALLY ILL CHILDREN**

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**INTRODUCTION.** Evolution of energy expenditure (EE) in critically ill children necessitating mechanical ventilation is poorly documented, so is their energy balance during the PICU stay. Thus clear recommendations for nutritional support (NS) in PICU patients are still missing. Our aim was to evaluate daily by indirect calorimetry EE in artificially ventilated critically ill children; to compare the measured EE to the actual NS and Recommended Dietary Allowances (RDA) for age and to evaluate the cumulative energy balance for each patient during the ICU stay.

**METHODS.** After bench validation of our ventilator and parental consent, EE was measured (Deltatrac II, Datex) for 60 minutes in ventilated children under analgesia and sedation, at 24 hours and then each day until extubation. Were included only children ventilated for more than 72 hours.

**RESULTS.** 75 indirect calorimetric measurements were performed in 11 critically ill children (after cardio-thoracic surgery or burns), mean age: 20 ± 23 (SD) months, (median 8 mo): Bwt 8.8 ± 6.0 Kg; PRISM score 12.4 ± 4.7. Table 1 shows (mean ± SEM): EE, NS in Kcal / Kg Bwt, the daily energy balance (EnBal=(NS-EE)/EE) for the first 9 days. EnBal balance was negative (p<0.02) at day 1 and positive (p<0.05) at day 9. By contrast, the cumulative EnBal remained negative until day 7. Finally, EE values represented 53% of RDA for days 1-4 and 60% at day 7-9.

| | D1 | D2 | D3 | D4 | D5 | D7 | D9 |
|---|---|---|---|---|---|---|---|
| n | 11 | 11 | 11 | 11 | 8 | 5 | 3 |
| EE (Kcal./kg) | 55±4 | 54±3 | 54±4 | 53±4 | 57±6 | 61±6 | 70±3 |
| NS (Kcal./kg) | 34±5 | 48±5 | 54±6 | 57±7 | 56±7 | 75±11 | 86±6 |
| EnBal (%) | -35±10 | -7±12 | + 6±15 | +12±15 | +3±12 | +32±21 | + 22±4 |
| EE/RDA % | 54 | 52 | 53 | 52 | 56 | 59 | 66 |

**CONCLUSION.** Energy expenditure is stable during the first 9 days of PICU stay in ventilated critically ill children. EE represents about 55-65% of RDA during that period. Using early enteral feeding, the constituted caloric deficit during the first days can be cancelled at day 7 for most patients. Surprisingly, no hypermetabolic state (Ebb phase) was observed in this group of critically ill children.

## 470

**PLASMA LEVELS OF INTERLEUKINE-6 AND INTERLEUKINE-10 IN PRETERM NEONATES WITH SEPSIS**

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**INTRODUCTION.** Weak immune system predisposes preterm infants to infection, which is a major cause of neonatal morbidity and mortality (1). Endotoxine activate monocytes, macrophages, lymphocytes, fibroblasts and endothelial cells can produce pro-and anti-inflammatory cytokines. Production of interleukine-6 (IL6) is stimulated by tumor necrosis factor alfa, and interleukine-1. IL-6 is the main stimulant of synthesis of C-reactive proteine(CRP) and fibrinogen during the acute phase response. Interleukine -10 (IL-10) is produced in monocytes, B-cells and has anti-inflammatory properties such as supression of synthesis of pro-inflammatory cytokines. The role of IL-6 and Il-10 in neonatal sepsis is still unclear and we know only a little about relationship between plasma levels of these cytokines in premature infants with infection(2). The aim of this study was to evaluate plasma IL-6 and IL-10 and analyse the interaction between these interleukine and CRP in low birth weight neonates suspected for sepsis.

**METHODS.** In a prospective study we measured IL-6 and IL-10 levels by enzyme linked immunoabsorbent assay in 43 neonates with symptoms of sepsis at 0 and 24 hour later. CRP levels were measured at the same time. The study was carried out in a period from November 1999 to august 2000. Mean gestation age was 30,1 weeks (26-33), mean postnatal age was 8,3 dawys (5-16), mean birth weight -1175grams (730-1950). Plasma CRP, IL-6, Il-10 levels were evaluated when neonates showed the following symptoms: respiratory status deterioration, tachycardia, por peripheral perfusion, arterial hypotension, lethargy, feeding intolerance, temperature instability, hyperglycaemia, metabolic acidosis.

**RESULTS.** In a study group sepsis was confirmed by positive blood cultures in 27 neonates. Sixteen of them had Gram positive infection and eleven Gram -negative sepsis. The mean CRP level at 0 hour was rather low (12mg/L, range 2-25mg/L) and was significantly higher at 24 hour - 54 mg/L (range 8-185mg/L). IL-6 levels were high from the start of examination: 890pg/ml (range: 230-2400pg/ml) at 0 hour nad 720pg/ml (range: 165-2600pg/ml) at 24 hour. IL levels were: 156 pg/ml (range: 37-340pg/ml) at 0 hour and 228pg/ml (range: 125-607pg/ml) at 24 hour. Very high levels of IL-10 were found in non-survivors and those neonates who developed multi organ failure durin the sepsis treatment. High levels of IL-6 and Il-10 significantly correleted with CRp level at 24 hour.

**CONCLUSION.** Preterm infants with sepsis showed increased IL-6 IL-10 and CRP levels. Only high concentration of IL-10 was associated with multi organ failure and high mortality rate among neonates with severe sepsis

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2. Romagnoli C. et al. Plasma levels of interleukione-6 and interleukine-10 in preterm neonates evaluated for sepsis. Eur J Pediatr 160: 345-350

## 471

**COMPUTERIZED SWITCH OF VENTILATION MODE DURING WEANING**

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**INTRODUCTION.** Ventilatory strategies in newborn infants with RDS vary widely among units. Sophisticated technology allows patient to trigger and volume guarantee ventilation. However several new ventilation technologies have not been tested thoroughly in neonatal and pediatric clinical trials. In this study we compared a computerized weaning method with a manual mode operated by the physician.

**METHODS.** 20 infants ventilated by PRVC (Pressure Regulated Volume Controlled) ventilation in a pediatric intensive care unit (PICU) were randomized in two groups; Group A (Automode) : PRVC with computerized switch to Volume Supported ventilation (VS), and Group B: PRVC manually switched to VS ventilation. In both groups there was an automatic switchback to PRVC in the case of apnea. Randomization took place when in the next 24 hours spontaneous breathing efforts could be expected. The ventilator used was a Siemens Servo 300 with automode. Eighteen patients completed the study. Both groups were comparable in terms of age and pulmonary disease.

**RESULTS.**

| | Group A Computerized switch | Group B Manual switch |
|---|---|---|
| Number | 9 | 9 |
| Mechanical ventilation (days) | 4.5(±1.9) | 4.2(±3.4) |
| Randomization time to extubation (hours) | 14.6(±11.5) | 18.7(±12.7) |
| Randomization time to switch (hours) * | 5.6(±8.2) | 11.3(±9.8) |
| Comfort score at extubation * | 15(±2.3) | 21.8(±3.9) |

*p< 0.05

**CONCLUSION.** Automode ventilation with computerized automatic switch from controlled to supportive ventilation is a safe mode of weaning in pediatric patients. It is associated with shorter delay times and better comfort scoring at extubation compared to the physician's decision to wean the patient. Newborns and pediatric patients with RDS might benefit from computerized weaning methods in order to shorten the latency time between weaning decision and switch to a supportive mode and increase the comfort score at extubation.

# Oral Presentations
# Recruitment of the lungs – 472-477

## 472

**THE EFFECTS OF PEEP AND RECRUITMENT MANEUVER ON LUNG VOLUME AND OXYGENATION AFTER CARDIAC SURGERY**

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**INTRODUCTION.** In patients ventilated after heart surgery performed in cardiopulmonary bypass (CPB), oxygenation is commonly impaired. This could be counteracted by a lung recruitment maneuver (LRM) followed by PEEP (1). However, PEEP (up to 10 $cmH_2O$) has not been found to be effective in itself (2). Hypothesis: 1) PEEP, as an expiratory phenomenon, may only overdistend already open parts of the lungs but not recruit collapsed lung regions. This will produce an increase in the end-expiratory lung volume (EELV) without any improvement in oxygenation. 2) After a LRM PEEP is needed to keep the newly recruited lung regions open.
**METHODS.** Following coronary artery bypass graft surgery (CABG), 30 circulatory stable patients (55-79 yr) were at arrival to the ICU randomised to receive LRM and PEEP 12 $cmH_2O$ (LRM+PEEP group), PEEP of 12 $cmH_2O$ (PEEP group) or LRM and zero PEEP (LRM group) and studied while still sedated and mechanically ventilated (volume control, Vt 5-6 ml/kg, $FiO_2$ 0,5). The LRM consisted of four inflations to a $P_{aw}$ 45 $cmH_2O$ for 10 s with an interval of 20 s in between. After baseline measurements of EELV (SF6 washout), hemodynamics and blood gases, the patients received one of the three interventions followed by frequent measurements of EELV, Cardiac Index and blood gases. After 75 min of ventilation PEEP was discontinued. Additional samples of blood gases were made at 90 min. Statistics: ANOVA with PLSD ($p<0.05$).
**RESULTS.** After LRM+PEEP both $PaO_2$ and EELV (1075 (102) to 1915 (208) ml (mean (SEM)) $p<0.01$) increased and were maintained during the 60 min intervention. After LRM $PaO_2$ increased transiently but a significant change in EELV could not be detected. In the PEEP group EELV increased (1262 (121) to 1910 (139) ml, $p<0.01$) and was maintained without significant change in $PaO_2$. At 90 min $PaO_2$ was equal to baseline values. No hemodynamic changes was found.

| | Baseline | 0 min | 5 min | 15 min | 30 min | 60 min | 90 min |
|---|---|---|---|---|---|---|---|
| LRM+PEEP | 13.4 (1.15) | 27.8 (2.3)[2] | 23.6 (2.1)[3] | 23.0 (1.9)[3] | 23.6 (2.1)[3] | 23.9 (2.2)[4] | 15 (1.5) |
| LRM | 14.6 (1.3) | 26.2 (1.7)[2] | 15.9 (1.3) | 16.7 (1.6) | 17.5 (1.3) | 17.8 (1.0) | 18.3 (1.1) |
| PEEP | 18.4 (2.1)[1] | 17.5 (2.0) | 17.6 (1.9) | 18.7 (1.8) | 19.2 (1.8) | 20.3 (1.9) | 21.2 (1.7)[5] |

$PaO_2$ (kPa) at baseline and after the intervention. Mean (SEM). 1: $p<0.05$ vs LRM+PEEP; 2: $p<0.01$ vs PEEP; 3: $p<0.05$ vs LRM and PEEP groups; 4: $p<0.01$ vs LRM group; 5: $p<0.05$ vs LRM+PEEP group

**CONCLUSION.** In patients in the recovery phase after a CABG with CPB ventilated with $FiO_2$ 0.5, 1) PEEP (12 $cmH_20$) in itself increased lung volume but not oxygenation, indicating overdistension. 2) a lung recruitment maneuver was essential to improve oxygenation even when high level of PEEP was used and LRM without subsequent PEEP was not effective.
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**IMPROVEMENT OF SURVIVAL AFTER LONGTERM MECHANICAL VENTILATION IN THE PRONE POSITION**

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**INTRODUCTION.** Mechanical ventilation in the prone position is commonly accepted as a strategy to improve oxygenation in severe hypoxaemic patients. Despite the fact that oxygenation improves in about 60 to 70 percent, it has not been shown to improve survival. However, in most studies the duration of prone position was relatively short. The aim of our retrospective study was to determine the effect of prone position on oxygenation and survival in patients being kept for a longer time in prone position. Factors that could predict a positive response or survival benefit were also studied.
**METHODS.** All patients who were ventilated in the prone position since the introduction of this strategy in our hospital were included. A murray-score of >2.5 was the only inclusion criterium. Sex, age, BMI, APACHE-II and Murray-score, complications, haemodynamic parameters and the $PaO_2/FiO_2$-ratio were extracted from the medical records and analyzed. The $PaO_2/FiO_2$-ratio was determined just before (T0), and after 2, 12 and 24 hours in prone position. A patient was defined a responder (R) if the $PaO_2/FiO_2$-ratio rised >2.67 kPa on at least 2 of the above mentioned timepoints compared with T0
**RESULTS.** 51 patients were included: 30 R (59%) and 21 NR (41%). The median duration of ventilation before prone postion was 3.0 days, without statistically significant difference between R and NR. The mean APACHE-II score was 23.1, the median Murray-score was 3.30 (range 2.7-4.0). The median duration of prone position was 32.0 hours (range 1-113.25). If oxygenation or haemodynamic parameters declined the patient was immediately returned to the supine position. We found no statistical significant difference between R and NR for sex, APACHE-II, Murray-score, type of bed, duration of length of stay on the ICU before prone postion or ventilation prior to prone position. However, younger patients and patients with a lower BMI responded more often to prone position (NS). Haemodynamic parameters were stable for all patients during prone position.
Survival analyses (K-M curves) determined at two moments revealed that there was no statistically significant difference in mortality rate at discharge from the ICU. However, at discharge from the hospital 13 of the 30 responders (43.3%) survived, compared with 3 of the 21 non-responders (14.3%) (Log-Rank P=0.002)
**CONCLUSION.** On the ICU of this hospital patients are turned to prone position relatively late, though the percentage responders, 59%, meets the percentage in literature. (1) The mortality rate for responders at discharge from the hospital is 57%, which is significant lower than the mortality rate for non-responders (86%). It seems that responders to prone position on this ICU have a significant higher chance of survival. Possible explanations for this finding are the longer period a patient is kept prone and the adjustment of ventilator-settings during the prone position which can prevent adjustive ventilator-induced lungdamage.
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## 474

### IMPACT OF PEEP LEVEL ON THE DEFINITION OF ARDS

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**INTRODUCTION.** The American European Consensus Conference (AECC) definition of ARDS takes into account the timing of onset, the degree of hypoxemia and the presence of pulmonary infiltrates on chest X-ray. Hypoxemia criteria rest on a $PaO_2/FiO_2$ relationship < or equal to 200. However, $PaO_2/FiO_2$ might be markedly modified by therapeutic measures already present in the moment of ARDS diagnosis but not considered in AECC definition, such as cardiovascular resuscitation, recruiting maneuvers and, especially, the level of PEEP. There have been claims to consider PEEP level to best assess severity of hypoxemia. Our hypothesis was that optimization of respiratory variables in the first hours after ARDS diagnosis might induce a change in $PaO_2/FiO_2$ that could mask the fulfillment of AECC criteria.

**METHODS.** We studied consecutive patients that met AECC criteria of ARDS at the moment of diagnosis on a PEEP level < or equal to 5 cm $H_2O$. Risk factors, severity scores and outcomes were recorded. $PaO_2/FiO_2$ was obtained after 6, 12 and 24 hs. with PEEP levels indicated by attending physicians. Lung injury score (LIS) was also calculated, on admission and at 24 hs. Data (mean ± SD) were analyzed with ANOVA.

**RESULTS.** 42 patients were included. Age was 43±15 years. APACHE II and SOFA scores were 24±8 and 9±3 points, respectively. Mortality was 60%. 23 patients had a pulmonary cause of ARDS. There were no differences in the behavior of $PaO_2/FiO_2$, PEEP and LIS between ARDS of pulmonary versus extrapulmonary cause, and between survivors and non-survivors. After 24 hours of ARDS diagnosis, only 16 patients (38%) still had $PaO_2/FiO_2$ < or equal to 200. Their mortality was not different from the rest of the patients (60 vs. 62 %).

| | 0 hs. | 6 hs. | 12 hs. | 24 hs. |
|---|---|---|---|---|
| $PaO_2/FiO_2$ | 125±45 | 206±90* | 218±81* | 232±89* |
| PEEP (cm $H_2O$) | 1±2 | 11±4* | 12±4* | 13±4* |
| LIS | 2.3± 0.5 | | | 2.4±0.6 |

* p < 0.0001 vs. basal

**CONCLUSION.** The use of PEEP resulted in improved oxygenation, so after 24 hs. most patients did not fulfill AECC hypoxemia criteria of ARDS. LIS remained stable. These results suggest that PEEP level should be taken into account for the diagnosis of ARDS. Pattern of $PaO_2/FiO_2$ response to PEEP did not identify a population with a worse outcome.

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### PEEP INCREASES FRC AT ZEEP IN ARDS PATIENTS

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**INTRODUCTION.** Alveolar recruitment is commonly computed by measuring the difference in volume at a given pressure between different pressure-volume (P-V) curves. For this purpose the expired volume from positive end expiratory pressure (PEEP) to zero end expiratory pressure (ZEEP) (PEEP related lung volume) is used as reference of the P-V curves on the volume axis. This method assumes that the absolute lung volume at ZEEP does not change with PEEP or recruitment maneuvers, even in presence of recruitment. However, this assumption has been proved only in postcardiac-surgery patients[1]. We hypothesized that in ALI/ARDS patients part of the PEEP recruited lung remains open at ZEEP. Aim of the study was to investigate this assumption in ARDS patients.

**METHODS.** We studied five sedated and paralyzed ARDS patients (4 males, age 59±14, $PaO_2/FiO_2$ 90 ± 12), ventilated in CPPV (PEEP 11 ± 4 $cmH_2O$, $FiO_2$ 0.63±0.16). All patients were monitored with an arterial pressure catheter and a Swan-Ganz catheter. We recorded airflow, airway and esophageal pressures. In all patients we randomly applied three different level of PEEP (5,10 and 15 $cmH_2O$), while maintaining the same ventilatory setting. At each PEEP level, after 30 minutes, we performed a P-V curve using the slow inflation method from PEEP to 50 $cmH_2O$. PEEP related lung volume was measured recording the volume exhaled after disconnecting the patients from the ventilator during an end-expiratory occlusion maneuver. After waiting at least 5 seconds for complete exhalation we measured FRC by means of an helium dilution technique. $PaO_2$ and shunt was also measured in all patients.

**RESULTS.** The increasing levels of PEEP resulted in a significant improvement in $PaO_2$ and shunt. Values of PEEP related lung volumes were 192±63 ml, 552±118 ml and 974±251 ml respectively at 5, 10 and 15 PEEP levels ($p<0.01$). For the same levels of PEEP the values of the FRC at ZEEP were 384±170 ml, 484 ± 207 ml and 555±190 ml respectively ($p<0.01$).

**CONCLUSION.** In ARDS patients ventilation at different levels of PEEP may result in different absolute lung volumes at ZEEP. Assuming the same lung volumes at ZEEP would have resulted in underestimation of recruited volume of 100±65 ml between PEEP 5 and 10 $cmH_2O$ and of 70±39 ml between 10 and 15 $cmH_2O$. these results imply that closing pressure of a portion of the recruited lung are lower than ZEEP. We suggest that FRC at ZEEP should be measured when computing alveolar recruitment.

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Grant. Miur

## 476

### STATIC V-P CURVES OF RESPIRATORY SYSTEM AND GAS EXCHANGE IN EARLY AND LATE ARDS

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**INTRODUCTION.** In earlier studies based on assessment of static volume-pressure (V-P) curves of the respiratory system (Chest 86; 58-66, 1984) and histological examination (N Engl J Med 342; 134-149, 2000), it has been suggested that by the 7th day of mechanical ventilation the lungs of ARDS patients evolve into an essentially fibrotic stage characterized by reduced compliance. However, in the early studies relatively large tidal volumes (VT) were used (10-15 ml/kg). Since then lower tidal volumes have been recommended.

**METHODS.** In the present study in 8 mechanically ventilated ARDS patients in whom baseline VT of 7 ml/kg (range: 5-8.5) was used, static inspiratory V-P curves of the respiratory system were assessed on ZEEP at an early (2-3 days) and a later stage (9-11 days)of mechanical ventilation.

**RESULTS.** In only two patients there was a distinct shift to the right of the V-P curves, consistent with pulmonary fibrosis. In the other six patients, the V-P curves essentially did not change (2 patients) or were shifted to the left consistent with an improvement of the compliance. On baseline ventilation on ZEEP, in the 4 patients with a shift to the left of V-P curve, $PaO_2/FiO_2$ increased from the early to late stage (81+21 to 172+82), the change being close to significance ($p=0.06$). In contrast, in the 4 patients in whom the V-P curve did not change or shifted to the right, the $PaO_2/FiO_2$ did not change ($p=0.44$).

**CONCLUSION.** In conclusion in ARDS patients ventilated with VT of 5-8.5 ml/kg "fibrotic" changes in V-P curve present in a minority of cases (2 out of 8 patients) and the $PaO_2/FiO_2$ does not improve.

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### AWAKE PRONE POSITION FOR SPONTANEOUSLY BREATHING, HYPOXIC PATIENTS WITH PNEUMONIA

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**INTRODUCTION.** Prone position have been used and applied on mechanically ventilated ARDS patients since 1975 with an 69 % reported response rate on $PaO_2$. Theoretically the same results should be achieved with spontaneously breathing patients in prone position, and thereby avoiding intubation and the complications related to mechanical ventilation. The objective of this study is to examine awake prone position (APP) in spontaneously breathing, hypoxic patients. Can patients in respiratory distress accept prone position ? Is it possibel to raise $PaO_2$ in hypoxic spontaneously breathing patients with pneumonia by turning them into prone position ? Can APP contribute to avoid intubation ?

**METHODS.** Pilot study with four consecutive patients with radiological verified pneumonia and hypoxia in spite of maximal oxygen delivery where placed in prone position. The hips, shoulders, legs and knees were protected against pressure by positioning the patients on Tempur® cushions. With regard to the face, different cushions were used, depending on what was optimal for the individual patient. The change in $PaO_2$ and the oxygenfraction in the delivering device (nasal catheter) ($FIO_2$) before and after APP was compared. Values presented as mean and range.

**RESULTS.** The mean age of the patients was 52 years (18-75 years). All had radiological verified pneumonia. The patients were in prone position for 121 min (50-300 min). Patients were turned supine when APP was no longer needed or when the patient felt uncomfortable. The mean $PaO_2$ before APP was 7.4 KPa (5.5-9.3 KPa) with a oxygen fraction in the nasalcatheter (flow 15 L/min.) of 0.75 (0.6-1.0). After APP the values were $PaO_2$: 9.6 KPa (7.9-11.7 KPa), $FIO_2$: 0.5 (0.3-1.0). All patients had a rise in $PaO_2/FIO_2$ after APP. No side effects were observed. Intubation was avoided and prone position was well tolerated.

**CONCLUSION.** In the present study APP was well tolerated and the expected positive change in oxygenation ability was observed in all the patients. No patients needed intubation afterwards. Patient compliance is of major importance in relation to APP, exact information and close observation by a trained intensive care nurse is necessary. The present study indicate that APP might be a way to avoid intubation in hypoxic patients with pneumonia. But the results are preliminary and further studies are needed.

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# Oral Presentations
# Experimental trials for treatment of sepsis – 478-483

## 478

**ENHANCED SURVIVAL TO CECAL LIGATION AND PUNCTURE IN MICE, INDUCED BY ORAL PREADMINISTRATION OF LPS**

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**INTRODUCTION.** Lipopolysaccharides (LPS) induce the characteristic changes observed in septic shock (SSh). Protection against lethal doses of LPS have been achieved with pre-administration of sublethal doses by intraperitoneal (IP) or intravenous (IV) routes, however this strategy had been useless in the cecal ligation and puncture (CLP) model. Since oral administration of antigens has been demonstrated to protect against some proinflammatory diseases such as experimental autoimmune encephalomyelitis, we fed LPS to mice previous to the CLP procedure to determine its protective capacity compared to other routes of administration.

**METHODS.** 8-12 wk old (23-25 g) Balb/c mice were treated with 50 micrograms of LPS in 100 microliters of RPMI every four days for a total of 5 doses, either by IP, subcutaneous (Sc), oral (O) or IP+Sc routes. One week later, under sterile conditions, a 1 to 2 cm midline incision was made and the cecum was exposed. With a 4-0 silk suture, the cecum was tightly ligated at its base without causing bowel obstruction, the cecum was then punctured twice with a 21 gauge diameter needle. We evaluated survival, cytokines expression in liver and lung and antibody anti-LPS production.

**RESULTS.** Pretreatment with LPS by the O and Ip+Sc routes significantly ($p<0.05$) raised survival from 50% in control animals to 88 and 91% respectively. In liver, pretreatment with O LPS induced the expression of TNF-alpha later (4 h) and in a lesser proportion (12 %) than in C mice (1.5 hrs, 22%). IL-10 was expressed in a greater proportion in the O group than in the C group (34 vs 15%). In lung, TNF-alpha was also expressed later (24h) and in a lesser proportion (7%) in the O than in the C group (1.5 hrs, 27%). In the Ip+Sc group TNF-alpha was expressed only until 48h after the procedure. Both protective pretreatments (O and Ip+Sc) induced a significant increase ($p<0.005$) in IgM antibodies.

**CONCLUSION.** These results suggest that protection induced by pretreatment by the O and Ip+Sc routes could be related both with a delayed and decreased inflammatory response at target organs and with the induction of anti-LPS antibodies of IgM isotype. Furthermore, oral LPS could represent an innocuous potential alternative in preventing target organ damage in septic shock that should be further studied.

Grant. CONACYT 31102-M

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**EFFECT OF PPAR-ALPHA AGONIST ON ENDOTHELIUM FUNCTION IN RABBIT ENDOTOXIN SHOCK**

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**INTRODUCTION.** In vivo LPS and TNF-alpha infusion are associated with prolonged alteration of endothelium function which remains present at least until day 5 (D5). In in vitro models, it has been demonstrated that peroxisome proliferator-activated receptor alpha (PPAR-alpha) decreases NF-kB and related TNF-alpha expression.

**METHODS.** We therefore investigated at D5 after LPS (0.5 mg/kg iv) the effect of a 2-week pretreatment with a diet containing 0.5% fenofibrate (LPS-FENO group) on endothelium-dependent (ED) and independent (EI, sodium nitroprussiate or SNP, $10^{-9}$ to $3.10^{-5}$ $mol^{-1}$) relaxation. This response was compared between LPS alone (LPS group), FENO alone (FENO group), LPS-FENO group and control animals (CTRL). The calcium ionophore A23187 ($10^{-9}$ to $3.10^{-6}$ $mol^{-1}$) and acetylcholine (Ach, $10^{-9}$ to $3.10^{-5}$ $mol^{-1}$) were used to discriminate ED receptor-dependent (Ach) and ED receptor-independent (A23187) response.

**RESULTS.** Contraction to phenylephrine (PHE, $10^{-9}$ to $3.10^{-5}$ $mol^{-1}$) was similar in all groups. Relaxation to ACh was reduced in vascular rings taken from LPS animals when compared to CTRL or FENO animals. In contrast, in LPS-FENO animals ED receptor-dependent was preserved. Relaxation to A23187 or sodium nitroprusside (SNP) was not changed in all groups (table, mean±ESM, ANOVA, * : p<.0005 vs CTRL; ** : p<0.005 vs LPS).

| | CTRL (n=9) | FENO (n=6) | LPS (n=8) | LPS-FENO (n=4) |
|---|---|---|---|---|
| Max PHE contraction (%) | 209±16 | 199±13 | 208±10 | 224±8 |
| Max Ach relaxation (%) | 71±5 | 64±6 | 43±2* | 69±5** |
| Max A23187 relaxation (%) | 81±4 | 79±3 | 73±5 | 82±8 |
| Max SNP relaxation (%) | 84±4 | 87±4 | 88±6 | 96±4 |

mean±ESM, ANOVA, * : p<.0005 vs CTRL; ** : p<0.005 vs LPS

**CONCLUSION.** Our results demonstrate that 2-week pretreatment with fenofibrate (0.5%) prevents endothelium dysfunction resulting from LPS injection. This study deserve further investigations aiming at understanding the inflammatory cascade responsible of this endothelium function improvement.

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**ENDOTHELIN RECEPTOR ANTAGONIST TEZOSENTAN ATTENUATES ACUTE LUNG INJURY IN ENDOTOXEMIC SHEEP**

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**INTRODUCTION.** During endotoxemia, the release of endothelin (ET), a potent endothelial-derived vasoconstrictor peptide, contributes to pulmonary hypertension, increased capillary permeability, and lung edema, thus, promoting acute lung injury (ALI)(1). Several studies including short-term administration of ET receptor antagonists in experimental sepsis have revealed beneficial effects with improvements of hemodynamic and metabolic parameters (1, 2). However, most of the presently available ET receptor antagonists have a prolonged half-life and have been administered orally only. Recently, a potent water-soluble, ET receptor antagonist, tezosentan, has been designed for parenteral use (3). The aim of the present work was to evaluate the effects of continuous infusion of tezosentan on hemodynamics, extravascular lung water (EVLW) accumulation, and gas exchange in endotoxemic sheep.
**METHODS.** Seventeen sheep were anesthetized and instrumented with vascular catheters. After a one-week recovery, the animals were subjected to intravenous (IV) infusion of Ringer lactate 3 mL/kg/h for 24 h. Sheep were randomly assigned to three groups: 1) the sham-operated group (n=3) received only Ringer lactate; 2) the LPS group (n=7) in addition received an IV infusion of E.coli lipopolysacharide (LPS) 15 ng/kg/min; 3) the tezosentan group (n=7) received Ringer lactate, LPS, and, after 4 h of endotoxemia, tezosentan (Actelion Ltd., Allschwil, Switzerland) 3 mg/kg as an IV injection over 30 min, followed by continuous infusion of 1 mg/kg/h for the remainder of the experiment. Hemodynamics, EVLW assessed by a double indicator technique (Cold Z-021; Pulsion Medical Systems, Germany), and blood gases were determined every 4 h. Data were assessed by two-factor ANOVA for repeated measurements. Scheffe's test was used for post hoc analysis when appropriate.
**RESULTS.** In the sham-operated group, all variables remained unchanged. LPS caused pulmonary hypertension, increased EVLW, and led to arterial hypoxemia. During the first 12 h of administration, tezosentan reduced the increments in pulmonary arterial pressure, vascular resistance index, and capillary pressure by 40-50%, as compared to the LPS group ($p<0.05$). In parallel, tezosentan prevented EVLW from rising, further increased cardiac index, and reduced the mean arterial pressure and the systemic vascular resistance index ($p<0.05$). From 8 to 12 h, tezosentan attenuated the decline in $PaO_2$ and decreased venous admixture, returning these variables almost completely to baseline.
**CONCLUSION.** In endotoxin-induced ALI, continuous infusion of the novel ET receptor antagonist tezosentan ameliorates pulmonary hypertension, lung edema, and arterial hypoxemia.
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**ACTIVATED PROTEIN C APPLICATION DURING ENDOTOXEMIA – MICROHEMODYNAMIC AND CELLULAR MECHANISMS**

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**INTRODUCTION.** Activated protein C (APC) reduced pro-inflammatory mediator release in a recent prospective randomised sepsis trial. Decreased inflammatory response was associated with less sepsis mortality in APC- patients. In vitro studies suggest potential anti-inflammatory APC effects on a cellular level. However, APC has not been in vivo characterised in terms of leukocyte-endothelial cell interaction and capillary perfusion failure. This study for the first time investigates APC actions on circulating leukocytes and capillary perfusion by intra vital fluorescence microscopy in vivo.

**METHODS.** In skin fold preparations of Syrian hamsters, normotensive endotoxemia was induced by i.v. administration of 2 mg/kg endotoxin (LPS, E. coli, 2mg/kg). Intravital video fluorescence microscopy allowed determination of venular leukocyte adherence (VLA) and functional capillary density (FCD), which served as a measure for capillary perfusion. APC (APC group, n=8, activated plasma Protein C (24 mg/kg i.v.) was substituted during 8h after LPS administration. Controls were saline-treated animals receiving LPS.

**RESULTS.** LPS induced a massive increase in VLA with a maximum at 8h. Simultaneously, capillary perfusion decreased to about 50% of baseline after 24h of endotoxemia (FCD24h: 57 ± 10 cm-1 vs. FCDbaseline: 137 ± 14; $p<0.01$ vs. baseline), whereas APC-treated animals showed only minor changes (FCD24h: 100 ± 15 vs. FCDbaseline: 120 ± 10, $p>0.05$).

**CONCLUSION.** APC reduced LPS-mediated capillary perfusion failure and decreased venular leukocyte adherence. Since in this model LPS did not induce macrohemodynamic disturbances, APC is likely to exert its microcirculatory effects by direct interaction with either leukocytes or the endothelium.

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**HEMODYNAMIC EFFECTS OF LEVOSIMENDAN AFTER SURGERY IN "LPS PRETREATED" RABBITS: PRELIMINARY RESULTS**

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**INTRODUCTION.** Sepsis induces myocardial dysfunction and vascular hypocontractility. Recent data suggest that phosphorylation of myocardial contractile proteins decreases myofilament sensitivity to calcium and may contribute to myocardial depression (1). Levosimendan (LS), a new calcium sensitizing drug and $K_{ATP}$ channel opener is used in human heart failure (2). Aim: to evaluate LS effect on heart function, vascular tone and renal microcirculation in rabbit without LPS (LPS-) and 36 hrs after LPS administration (LPS+).
**METHODS.** Heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure (mmHg), systolic (sAoV), mean aortic (mAoV) blood flow velocities (20 MHz pulsed Doppler, $cm.sec^{-1}$), ejection time (Dt) and renal cortical (Cort) and medullary (Med) flows (laser Doppler, tissue perfusion units) were measured in anesthetized and ventilated rabbits. Heart inotropic quality was estimated by maximal acceleration (gmax, $cm.sec^{-2}$) and sAoV. Pulse pressure (pp) was calculated as SAP – DAP. In LPS+ group, LPS (600 mg/kg) was injected 36 hrs before experiment. Data were collected in both LPS+ (n = 4) and LPS- (n = 3) groups every 15 min during a 4hrs LS infusion (200 mg/kg/h).
**RESULTS.** Data in Mean(SD). All parameters were gaussian. 36 hrs after LPS administration, rabbits weight was lower (-9%, p=0.03, paired *t*-test) and temperature greater (+1.1(0.7)°C, p=0.04) compared to pre-LPS administration. In addition, at baseline (before LS administration), LPS+ had a lower pp than LPS- (29(4) and 39(5) mmHg respectively, p=0.03, unpaired *t*-test). In addition, HR increased and DAP decreased during LS infusion, in both groups (p<0.01). Although LS increases both sAoV and gmax, it did not change mAoV (table 1). This was likely related to the decrease in Dt during LS infusion in both groups (p<0.01). Interestingly, LS seemed to better improve cardiac systolic function and renal cortical flow in LPS+ group than in LPS-.

| | Baseline LPS+ | Baseline LPS- | LS 2hrs LPS+ | LS 2hrs LPS- | LS 4hrs LPS+ | LS 4hrs LPS- |
|---|---|---|---|---|---|---|
| SAP | 95(16) | 102(16) | 90(18) | 72(11) | 86(20) | 70(15) # |
| gmax | 4222(812) | 4034(801) | 5257(965) | 4490(1384) | 5460(287) # | 5092(934) # |
| sAoV | 68(12) | 65(6) | 78(10) | 74(5) | 82(6) # | 74(5) # |
| mAoV | 24(5) | 21(5) | 25(5) | 19(2) | 26(5) | 19(3) |
| Cort | 37(12) | 27(9) | 43(15) | 21(10) | 42(21) | 18(9) # |
| Med | 18(10) | 17(5) | 16(9) | 12(3) | 18(14) | 20(6) |

Hemodynamics at baseline, and during LS infusion at 2 and 4 hrs. # p<0.01 ANOVA for repeated measures.

**CONCLUSION.** These preliminary data show that LS may improve cardiac systolic function in LPS+ animals. Other hemodynamic and renal effects are more complex and need further investigations.
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## 483

**INHIBITION OF LPS-STIMULATED PATHWAYS IN MACROPHAGES BY THE FLAVONOID LUTEOLIN**

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**INTRODUCTION.** We have previously shown that the flavonoid luteolin inhibits the expression of pro-inflammatory molecules induced by LPS and also reduces LPS-induced lethal toxicity. In the present study we tested the ability of luteolin to block signaling pathways implicated in LPS-induced inflammatory gene expression in macrophages.

**METHODS.** All experiments were performed using the RAW 264.7 murine macrophage cel line. TNF-a was determined in the culture supernatants by ELISA. Activation of kinases was assesed indirectly by detecting the phosphorylated forms of the kinases by western blot analysis.

**RESULTS.** Exposure of cells to LPS (1mg/ml) increased phosphorylation of the mitogen-activated protein kinase family members ERK1/2, p38 and JNK1/2 in a time-dependent manner. Pretreatment of RAW 264.7 with luteolin (10mM for 30 min) inhibited the LPS-induced ERK1/2 and p38, but not JNK1/2, phosphorylation, and blocked the LPS-induced TNF-a release. To investigate which of these pathways contribute to the inhibitory effects of luteolin on TNF-a release, cells were pretreated with pharmacological inhibitors of these pathways; PD98059 and SB203580 when used alone failed to inhibit TNF-a release, whereas pretreatment with both agents attenuated TNF-a release. We have previously shown that luteolin blocks Akt phosphorylation in response to LPS in RAW 264.7 macrophages. To determine the role of Akt in TNF-a release, cells were transiently transfected with a dominant negative form of Akt (K179M). Overexpression of K179M Akt did not alter LPS-induced TNF-a release, suggesting that inhibition of this kinase does not mediate the inhibitory action of luteolin. In addition, DRB (a pharmacological inhibitor of CK2) blocked TNF-a release in a concentration-dependent manner, whereas co-treatment of cells with luteolin and DRB did not have an additive effect.

**CONCLUSION.** We conclude that luteolin interferes with LPS signaling by reducing the activation of several MAPK family members and that its inhibitory action on TNF-a release correlates with inhibition of ERK, p38 and CK2 activation.

Grant. Thorax Foundation

# Oral Presentations
# Regional perfusion – 484-489

## 484

**INTESTINAL ISCHAEMIA AND RECOVERY: MICRODIALYSIS OF LACTATE AND GLYCEROL**

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**INTRODUCTION.** The aim of this study was to evaluate lactate and glycerol as markers of intestinal ischaemia and recovery.

**METHODS.** In 18 pigs (19-27 kg), the superior mesenteric artery was clamped for 60 (n=12) or 120 (n=6) min, respectively. Blood flow was monitored in the superior mesenteric artery and the portal vein using ultrasonic flowprobes and in intestinal tissue using the microsphere technique. Microdialysis catheters were introduced in the subclavian artery and into the lumen and mucosa of the jejunum. Intraperitoneally the catheter was attached to the serosal surface of the intestine in 6 of the animals (60 min clamp). Microdialysate samples (1mL/min) were collected in 30 minutes fractions.

**RESULTS.** Blood flow in the superior mesenteric artery, the portal vein and in intestinal tissue returned to baseline levels immediately after declamping. Arterial lactate and glycerol remained unchanged in both groups. Sixty minutes arterial clamping produced a marked increase of lactate and glycerol. After 120 minutes reperfusion, lactate and glycerol decreased to about half of ischaemia level in the lumen, and to baseline level at the serosal side. Clamping for 120 min produced a marked increase in luminal and mucosal lactate and glycerol , but was not associated with decreased levels either in lumen or mucosa within 120 minutes of reperfusion.

| | Baseline | Ischaemia | 30 min | Reperfusion 120 min | 240 min |
|---|---|---|---|---|---|
| Clamp 60 min | | | | | |
| Luminal lactate | 0.1(0.02) | 4.1(0.6)[a] | 5.8(0.5)[a] | 2.3(0.4)[a,b] | 1.2(0.3)[a,b] |
| Peritoneal lactate | 2.4(0.3) | 7.4(1.1)[a] | 5.0(0.9)[a] | 1.8(0.4)[b] | 1.5(0.4)[b] |
| Luminal glycerol | 34(9) | 430(65)[a] | 408(71)[a] | 275(60)[a] | 144(50)[b] |
| Peritoneal glycerol | 18(5) | 88(12)[a] | 45(13)[b] | 8(1)[b] | 13(5)[b] |
| Clamp 120 min | | | | | |
| Luminal lactate | 0.1(0.03) | 4.5(0.8)[a] | 5.9(0.9)[a] | 4.9(0.6)[a] | |
| Luminal glycerol | 16(5) | 1014(28)[a] | 1099(193)[a] | 951(176)[a] | |

Mean values (SEM). Lactate (mmol/L). Glycerol (mmol/L). a significant difference from baseline, b significant difference from ischaemia.

**CONCLUSION.** Peritoneal microdialysis detects intestinal ischaemia and subsequent recovery. Monitoring luminal or peritoneal lactate and glycerol might help differentiate between transient cellular hypoxia and cellular damage in the intestine.

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**DOPAMINE UNDER ALPHA-1 BLOCKADE, BUT NOT FENOLDOPAM, INCREASES GASTROMUCOSAL OXYGENATION DURING PEEP**

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**INTRODUCTION.** Ventilation with positive end-expiratory pressure (PEEP) decreases microvascular oxygenation of gastric mucosa ($mHbO_2$), e.g. by reduction of systemic $O_2$-delivery ($DO_2$). This PEEP-induced reduction of $mHbO_2$ may not be restored by dopamine (DOP) (1). We tested, whether the alpha-1 agonism of DOP (a mixed DA1, DA2, alpha-1 and beta agonist) hereby masks possible positive DOP-effects on $mHbO_2$. The selective DA1-agonist fenoldopam (FEN) increases -under physiological conditions- $mHbO_2$ (2). We tested therefore, whether FEN also restores the PEEP-induced reduction of $mHbO_2$. Since the respective effects may depend on the level of $DO_2$, we performed these interventions either under PEEP alone – i.e. at a reduced $DO_2$ – and also after restoration of the $DO_2$ to pre-PEEP-levels by volume expansion.

**METHODS.** Anaesthetised, chronically instrumented dogs (n=8, flowprobes for cardiac output measurement) were repeatedly studied for $mHbO_2$ (spectrophotometry, EMPHO-II (3)) and $DO_2$. Interventions: DOP (2.5 / 5.0 mg/kg/min) alone and after alpha-1-blockade (prazosin), FEN (0.1 / 1.0 mg/kg/min) and saline (control). All interventions were performed under PEEP (15 $cmH_2O$) alone and after volume expansion (HES-infusion), which restored $DO_2$ back to baseline before PEEP. Statistics: Analysis of variance for repeated measurements, p<0.05. The results are presented as mean ± sem.

**RESULTS.** Ventilation with PEEP significantly reduced $mHbO_2$ from 57±2 to 37±3% and $DO_2$ from 19.0±1.4 to 11.7±1.2 ml/kg/min. Although HES-infusion restored $DO_2$ to baseline, $mHbO_2$ remained significantly reduced. DOP significantly increased $DO_2$ under both conditions (PEEP and PEEP+HES), however $mHbO_2$ was unaffected. In contrast under alpha-1-blockade DOP increased $mHbO_2$ under PEEP (from 37 ± 1 to 42±1%, p<0.05) and under PEEP+HES (from 49±2 to 55±1%, p<0.05). FEN had no significant effect on $mHbO_2$ or $DO_2$ under both conditions, likewise saline.

**CONCLUSION.** Only after alpha-1 blockade DOP increased the PEEP-reduced $mHbO_2$, whereas DOP alone – despite similar increase of $DO_2$ – was without effect on $mHbO_2$. Thus, an alpha-1-mediated vasoconstriction appears to prevent an increase in gastric mucosal oxygenation by DOP alone. In contrast to physiological conditions (2), selective DA1-stimulation (FEN) does not increase $mHbO_2$ under PEEP and PEEP + HES, indicating a less potent role of this receptor-system under compromised haemodynamic conditions.

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## THE EFFECT OF TRANSFUSION OF REJUVENATED STORED ERYTHROCYTES ON INTESTINAL MICROVASCULAR OXYGENATION

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**INTRODUCTION.** Although it is known that transfusion of stored red blood cells (RBCs) does not always improve tissue $O_2$ consumption under conditions of limited tissue oxygenation, the effect of transfusion of rejuvenated stored RBCs on microvascular oxygenation has not been determined.

**METHODS.** Hemorrhagic shock (MAP below 55 mmHg) was induced in 18 anesthetized and ventilated male Wistar rats. The effect of resuscitation on intestinal microvascular $PO_2$ was investigated for fresh (n=6), 28 days stored (n=6) and stored and subsequently rejuvenated RBCs (n=6). All RBCs were stored in SAG-M; fresh RBCs were immediately transfused whereas the old RBCs were rejuvenated with an adenine containing RBC processing solution (Rejuvesol; enCyte Systems Inc) prior to transfusion. Systemic hemodynamic and intestinal oxygenation parameters were monitored until 60 minutes after resuscitation. Intestinal microvascular $PO_2$ ($mPO_2$) was determined with the $O_2$ dependent quenching of Pd-porphyrin phosphorescence. Statistics: ANOVA for repeated measurement

**RESULTS.** MAP, mesenteric blood flow, [Hb], and intestinal $mPO_2$ and $O_2$ consumption ($VO_2$) were significantly decreased during hemorrhagic shock. In all groups, [Hb] increased following RBC transfusion, although not to baseline values. Intestinal blood flow returned to baseline values after the fresh and rejuvenated, but not the stored RBC transfusion. $VO_2$ and mesenteric venous $PO_2$ were restored with transfusion of all RBCs as well. However, the intestinal $mPO_2$ returned to baseline values only after transfusion of fresh RBCs.

**CONCLUSION.** In contrast to fresh RBCs, transfusion of the stored and the rejuvenated RBCs did not restore the microcirculatory oxygenation, possibly due to impaired $O_2$ unloading. These storaged-induced changes were only partially reversed by rejuvenation, resulting in a better mesenteric blood flow after transfusion, but were not enough to impair intestinal $VO_2$ and mesenteric venous $PO_2$.

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## INTRAMUCOSAL-ARTERIAL $PCO_2$ GAP FAILS TO REFLECT INTESTINAL DYSOXIA IN ANEMIC HYPOXIA.

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**INTRODUCTION.** An increase in intramucosal-arterial $PCO_2$ gap ($DPCO_2$) could be determined by tissue hypoxia or by reduced blood flow. Our hypothesis was that in anemic hypoxia with preserved blood flow,$DPCO_2$ should not be altered.

**METHODS.** In eighteen anesthetized, mechanically ventilated sheep, oxygen delivery was stepwise reduced by hemorrhage (ischemic hypoxia, IH, n=9) or by hemorrhage with simultaneous dextran infusion (anemic hypoxia, AH, n=9). We measured cardiac output, superior mesenteric blood flow (gut blood flow), gases, hemoglobin and oxygen saturations in arterial, mixed venous and mesenteric venous blood, and ileal intramucosal $PCO_2$ by tonometry. Data (mean±SD) were analyzed with two-way ANOVA.

**RESULTS.** Both IH and AH caused similar reductions in systemic and gut oxygen delivery and consumption ($DO_2$ and $VO_2$). However, intramucosal, mixed venous and gut venous $PCO_2$ gradients were significantly greater in IH than AH.

| | Gut blood flow (ml/min/kg) | Gut $DO_2$ (ml/min/kg) | Gut $VO_2$ (ml/min/kg) | $DPCO_2$ (mm Hg) |
|---|---|---|---|---|
| AH basal | 625 ± 112 | 78.4 ± 22.5 | 25.7 ± 4.6 | 9 ± 9 |
| AH final | 958 ± 341* | 24.6 ± 10.1* | 15.9 ± 5.8* | 14 ± 9 |
| IH basal | 610 ± 203 | 69.6 ± 24.5 | 27.8 ± 9.1 | 14 ± 9 |
| IH final | 222 ± 85*§ | 20.5 ± 6.9* | 15.8 ± 4.9* | 41 ± 18*§ |

* $p < 0.01$ vs. basal. § $p < 0.01$ vs. AH.

**CONCLUSION.** $DPCO_2$ failed to reflect intestinal dysoxia during anemia-induced supply dependency. Blood flow seemed to be the main determinant of $DPCO_2$. Tonometry appeared as a useful method for the monitoring of perfusion, with limited value to detect anaerobic metabolism when blood flow was kept preserved.

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## DOPEXAMINE PROTECTS COLONIC, BUT NOT GASTRIC MUCOSAL EPITHELIUM IN LETHAL ENDOTOXIN SHOCK

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**INTRODUCTION.** Even though dopexamine increases splanchnic blood flow in postoperative[1] and septic patients[2], the effects on gastric mucosal perfusion are conflicting suggesting perfusion heterogeneity in splanchnic region [2,3]. We hypothesised that dopexamine alters blood flow distribution and metabolism within splanchnic region.
**METHODS.** In an experiment with normovolemic, normoventilated and normoglycemic pigs under anesthesia, 21 animals were randomised into three groups: 1) prolonged lethal endotoxin shock for 14 hours induced by *E. Coli* endotoxin (0111:B4) infusion (ETX, n=7 at baseline), 2) endotoxin shock with dopexamine infusion (DOPE, n=7) or 3) controls (n=7). Microdialysis capillaries were introduced into the lumen of stomach, jejunum and mid-colon. Regional blood flows were recorded and intestinal luminal microdialysate was collected in 30-minute fractions. Results are presented as median (interquartile range). We used non-parametric test for repeated measurements (Friedman) for within group comparison.
**RESULTS.** Endotoxin produced primary hypodynamic shock followed by hyperdynamic, hypotensive phase. Controls and dopexamine-treated animals survived the experiment, while three animals died in ETX group. Despite increased CI in DOPE group, the proportional celiac trunk flow (Trunk/CO) was barely maintained, while fractional superior mesenteric arterial flow (SMA/CO) increased. Proportional splanchnic blood flow (Qsplanc/CO) decreased during hypodynamic state but recovered to baseline in hyperdynamic phase (Table). Endotoxin induced intestinal luminal lactate release from under detection limit to 0.8 (0.5-1.0) mM in colon ($p<0.001$) and from 0.1(0.0-0.2) mM to 1.5(0.6-2.3) mM in stomach ($p=0.001$). In DOPE group, there was no luminal lactate release in colon ($p=0.24$), whereas in stomach luminal lactate increased gradually from 0.1(0.0-0.1) mM to 0.9(0.3-1.5) mM ($p=0.002$). Jejunal luminal lactate remained low in both groups. Control animals remained stable.

| | | Baseline | 4h | 12h | 14h | p-value |
|---|---|---|---|---|---|---|
| CI(ml kg-1min-1) | ETX | 111(107-118) | 79(68-83) | 132(121-196) | 151(140-156) | 0.02 |
| | DOPE | 99(85-103) | 142(113-162) | 122(114-181) | 131(104-174) | 0.03 |
| Qsplanc/CO(%) | ETX | 23(22-27) | 22(21-24) | 25(20-29) | 23(19-27) | 0.9 |
| | DOPE | 31(27-31) | 19(17-23) | 32(26-36) | 30(26-35) | 0.01 |
| SMA/CO(%) | ETX | 11(9-13) | 10(9-13) | 16(12-19) | 17(13-19) | 0.05 |
| | DOPE | 12(12-14) | 10(9-13) | 19(15-21) | 20(16-21) | 0.001 |
| Trunk/CO(%) | ETX | 15(12-17) | 12(8-15) | 8(7-10 | 8(7-10) | 0.1 |
| | DOPE | 11(9-14) | 7(6-8) | 7(7-9) | 7(5-9) | 0.1 |

**CONCLUSION.** Dopexamine protects colonic, but not gastric mucosal epithelium. The difference between the regions may be related to redistribution of blood flow within splanchnic circulation. Further studies on organ-specific effects of vasoactive drugs are warranted.
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Grant. The Finnish Medical Foundation

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## CVVH-INDUCED TEMPERATURE CHANGES: EFFECTS ON SPLANCHNIC OXYGEN AND ENERGY BALANCE IN SEPTIC PATIENTS

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**INTRODUCTION.** The current practise during continuous venovenous hemofiltration (CVVH) is to warm replacement fluids (RF) and/or "returned blood" (RB) to avoid hypothermia. However, the optimal core temperature target is unknown. Temperature changes (i.e. cooling) during CVVH may affect hemodynamics (increased peripheral vascular tone) and metabolism (decreased oxygen consumption), but the impact of temperature manipulation on hepatosplanchnic region remains to be determined. Therefore, we studied the effects of temperature changes during CVVH on hepatosplanchnic oxygen kinetics and energy balance in critically ill septic patients.
**METHODS.** As a pilot of a larger ongoing study, 6 stable medical ICU patients with severe sepsis or septic shock were studied. Five patients required norepinephrine (0.17 ± 0.20 ug/kg/min, no change during the study). CVVH was performed on Hygiea (Kimal) machine using polysulphone hemofilter (Ultraflux AV 600S). Blood flow was 150 ± 15 ml/min. RF was given in predilution mode (2400 ± 400 ml/h). Baseline data (=HOT 1) were collected when both RF and RB were warmed (to 37°C). The second data set (=COLD) was obtained after 120 min of "cooling" (RF 20°C, RB without warming) and third data set (=HOT 2) after 120 min of "warming" (the same setting as during HOT 1). In addition to systemic hemodynamics (arterial and PA catheters), arterial and hepatic venous blood gases, lactate (L) and pyruvate (P) levels were measured. Gastric mucosal $PCO_2$ ($PgCO_2$) was determined using air tonometry (Tonocap) and $PCO_2$ gap ($PgCO_2$-$PaCO_2$) was calculated. Global oxygen consumption ($VO_2$) and carbon dioxide production ($VCO_2$) were measured with indirect calorimetry (Deltatrac).
**RESULTS.** Data are median and 25th and 75th percentiles (RM-ANOVA) *vs. HOT1.

| | HOT 1 | COLD | HOT 2 |
|---|---|---|---|
| core temperature (°C) | 38.1 (37.9;38.4) | 36.9 (36.8;37.3)* | 37.9 (37.5;38.1) |
| MAP (mmHg) | 85 (84;88) | 93 (87;102)* | 86 (85;99) |
| cardiac index (l/min/m2) | 4.4 (3.9;4.8) | 4.1 (3.5;4.2)* | 4.5 (3.6;4.7) |
| SVR (dyn*s/cm5*m2) | 1302 (1160;1340) | 1795 (1482;1870)* | 1413 (1311;1820) |
| $VO_2$ (ml/min/m2) | 193 (143;199) | 170 (133;184)* | 188 (134;204) |
| hepatic venous $O_2$ saturation (%) | 49 (41;58) | 51 (39;57) | 52 (40;64) |
| hepatic venous L/P ratio | 10 (9;15) | 13 (9;16) | 13 (11;18) |
| $PCO_2$ gap (kPa) | 1.3 (0.8;1.6) | 1.5 (1.3;2.0) | 1.2 (0.6;1.9) |

**CONCLUSION.** Our preliminary results suggest that mild core cooling during CVVH may not affect hepatosplanchnic oxygen and energy balance in critically ill septic patients.

Grant: IGA MZ NB 6728-3

# Oral Presentations
# Long-term outcomes – 490-495

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**COMPARISON OF A SPECIFIC AND GENERIC QUALITY OF LIFE INSTRUMENT IN CRITICALLY ILL MEDICAL PATIENTS**

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**INTRODUCTION.** To compare the measurement properties of an intensive care specific and a generic health-related quality of life (HRQOL) instrument.

**METHODS.** Between June 1998 and May 1999, all consecutively admitted adult non-coronary patients who spent at least 24 hours in our medical intensive care unit (ICU) were eligible. The Fernandez Quality of Life questionnaire (FQOL) and the generic Medical Outcomes Study Short Form (SF)-36 Health Survey were simultaneously employed in 318 admissions. Both questionnaires were administered within the first 24 hours of ICU admission and at six month follow-up. Score distribution, test-retest and internal reliability, and construct validity of baseline data were investigated. Responsiveness was measured using effect sizes (difference between patient baseline and follow-up mean score, divided by baseline standard deviation).

**RESULTS.** The 318 study patients had a mean age of 57 ±17 years, 58% were male, mean APACHE II score after 24 hours was 19 ±10, mean SOFA total maximum score (TMS) was 7.7 ±5.6, mean Charlson comorbidity index (CCI) was 2.2 ±2.1, mean ICU length of stay was 11 ±19 days. Cumulative mortality was 25% in the ICU, 33% in the hospital, and 40% at six month follow-up. Using the intraclass correlation coefficient, test-retest reliability (n=35) was shown to be 0.87-0.96 in all SF-36 scales and 0.82-0.94 in the 3 FQOL scales. The distribution of the SF-36 scale scores showed substantial (>15%) floor/ceiling effects in 2/4 of 8 scales. All 3 FQOL scales had ceiling effects >18%, but no floor effects. Internal reliability as indicated by Cronbach´s alpha was 0.83-0.86 in all 8 SF-36 scales and 0.62-0.83 in the 3 FQOL scales and the aggregate global score. Analysis of construct validity of the baseline scores showed a significant decline of scores with increasing age (ANOVA, SF-36: p<0.0005-0.03; FQOL: p<0.0005-0.001) and burden of chronic illness (CCI= 0, 1-2, and >2 points, SF-36: p<0.0005-0.01; FQOL: p<0.0005-0.002). Women reported lower scores than men in 6 of 8 SF-36 scales (p=0.006-0.04) and in the FQOL subscale normal daily activities (p=0.006). Analyzing responsiveness, survivors of multiple organ dysfunction (MOD; SOFA TMS >5) had significantly reduced Z-scores compared to non-MOD survivors in all SF-36 scales measuring physical health (p=0.001-0.02), whereas the FQOL subscale normal daily activities was only slightly lower in MOD patients (p=0.046).

**CONCLUSION.** Both instruments demonstrated robust test-retest reliability and construct validity. The SF-36 scale items had a higher internal consistency compared to the FQOL scales. The responsiveness of both instruments might be compromised by ceiling effects. Using MOD as an external criterion for judging clinical change, the SF-36 demonstrated a higher responsiveness than the FQOL.

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**LONG TERM QUALITY OF LIFE IN ICU PATIENTS**

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**INTRODUCTION.** Assessment of long term outcome (death and quality of life (QOL) is necessary to evaluate the effectiveness and efficiency of our Intensive Care Units. Analysis of outcome and QOL after ICU discharge, and assessment of associated factors.

**METHODS.** Review of all adult patients admitted consecutively to a multidisciplinary ICU in July and August 2000, except those admitted for uncomplicated postoperative surveillance. Demographic data, past history, admission diagnoses, APACHE II, SOFA score (at admission, maximal and at discharge), hospital and ICU stay (LOS), and ICU and hospital mortality were collected. A telephone or mail interview was carried out to determine the survival status 18 months after discharge from ICU, the working status, and the QOL as assessed by the EuroQOL Instrument. Chi square test was used for qualitative variables and Kruskall-Wallis test for numerical variables.

**RESULTS.** Of the 202 patients studied, 34 (16.8%) died in the ICU and 23 (11.4%) died in the hospital after ICU discharge. Of the 145 patients discharged alive, 21 could not be contacted and 1 patient refused to respond. Of 123 remaining patients, 27 (13.4%) had died after hospital discharge and 96 (47.5%) answered the questionnaire. The responding patients were 56.8±18.9 years old; 63.5% were men. They had an APACHE II score of 9.8±5.1, SOFA at admission 3.3±2.8, SOFA discharge 2.0±1.5, SOFA maximal 3.8±3.1, mean ICU LOS 6.0±13.3 days, mean hospital LOS 34.2±31.1 days. Thirty-eight percent had a worse QOL than prior to their ICU admission, but only 8.3% were severely discapacitated. Twenty-three patients (24%) had reduced mobility (associated factors: prolonged hospital LOS p<0.02), 15 (15.6%) had limited autonomy (associated factors: previous limited autonomy p<0.01; prolonged hospital LOS p<0.01; past history of renal disease p<0.01, diagnosis of cardiopulmonary arrest p<0.03, ICU readmission p<0.03), 24 (25%) had alteration in usual daily activities (associated factors: previous reduced daily activity p<0.0001; high APACHE II p<0.01; age p<0.005; diagnosis of cardiopulmonary arrest p<0.02), 29 (30.2%) expressed more anxiety/depression (associated factors: previous anxiety/depression p<0.001; APACHE II p<0.03; SOFAmax p<0.04; gender F>M p<0.02), 42 (44%) had more discomfort or pain (associated factors: previous discomfort/pain p<0.03; diagnosis of polytrauma p<0.01). Seventeen patients (37.8% of the patients who worked previously) had not returned to work.

**CONCLUSION.** QOL is often impaired more than one year after ICU discharge, but very few patients remain dependent on other people. The most common QOL domains to be affected were those of pain/discomfort and anxiety/depression. Factors commonly associated with a change in QOL were previous reduced QOL, prolonged hospital LOS, and greater disease severity at admission. The degree of organ dysfunction during the ICU stay was associated with an increased incidence of anxiety/depression.

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**HEALTH-RELATED QUALITY OF LIFE 6 MONTHS AND 2 YEARS AFTER DISCHARGE FROM INTENSIVE CARE**

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**INTRODUCTION.** The Short Form 36 (SF 36) questionnaire is considered to be a suitable tool for measuring quality of life (QOL) in former ICU patients (1). From 2 years on after ICU discharge, the further survival is equal to population survival (2). The aim of this study was to investigate possible changes in QOL with time by comparing former ICU patients at 6 months and 2 years after ICU discharge.

**METHODS.** In a 10-bed mixed (predominantly surgical ) ICU in a tertiary referral hospital, all adult (>18 years) ICU survivors discharged between July 1st 1999 and April 15th 2000 and with an ICU stay >24 hours were included. Six months after ICU discharge they were sent the SF 36. The responders were sent the SF 36 again two years after ICU discharge. The data were scored automatically by using previously published equations. An age- and gender adjusted reference group was created from validated population SF 36 scores.

**RESULTS.** Six months after ICU discharge 130 patients were still alive, and 90 (69.2%) answered the SF 36. Of these 90, 73 (81.1%) answered after 2 years. The responders were 38 males and 35 females, with a mean age of 51.2 years. Their mean SAPS II score was 36.5 and mean length of ICU stay was 5.7 days. (GH general health, PF physical functioning, RP role physical, SF social functioning, BP bodily pain, VT vitality, MH mental health. 0 = worst score, 100 = best score).

| | GH | PF | RP | SF | BP | VT | MH |
|---|---|---|---|---|---|---|---|
| 6 months | 53.0 | 54.4 | 30.5 | 58.6 | 57.5 | 46.6 | 71.5 |
| 2 years | 56.7 | 61.0 | 41.8 | 69.7 | 61.9 | 50.9 | 72.0 |
| Difference | +3.7 | +6.6 | +11.3 | +11.1 | +4.4 | +4.3 | +0.5 |
| 95% CI diff. | -4.4 to 11.8 | -4.6 to 17.8 | -1.8 to 24.4 | 1.2 to 21.0 | -5.8 to 14.6 | -2.8 to 11.4 | -5.7 to 6.7 |
| Population | 74.3 | 85.0 | 74.2 | 85.6 | 73.5 | 60.7 | 79.3 |

**CONCLUSION.** From 6 months to 2 years after intensive care, the SF 36 answers in this cohort improved in all dimensions, but significantly only for social functioning. All patient scores were significantly lower than population scores. The low number of patients (n=73) may limit the interpretation.

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**IMPAIRED EXECUTIVE FUNCTION IN PATIENTS SURVIVING CRITICAL ILLNESS**

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**INTRODUCTION.** Critical illness can damage cognitive function, notably memory and attention, thus impairing quality of life among survivors and delaying their return to work. Published studies are largely confined to patients with recent ARDS or cardiac surgery, in whom hypoxia or cardiopulmonary bypass might directly injure the brain. We have therefore studied several aspects of cognitive function in patients discharged from a general intensive care unit (ICU).

**METHODS.** Physical health and cognitive function were tested in 24 patients (12 men, 12 women) of mean age 53 yr (range 26-73 yr) who had spent a minimum of 3 days (median 9 days, range 3-49 days) in a general ICU following major surgical operation (n = 18) or critical nonsurgical illness (n = 6). Mean APACHE II score was 13.7 (range 6-24) on admission to ICU. Between 3-4 months after ICU discharge, physical status was assessed by a simple symptom score (from 0-18), Short Form 36 questionnaire (SF-36) and the EuroQol 'thermometer' (from 0-100), a subjective measure of overall health. Memory was assessed by the List Learning Test, eductive ability (clear thinking) by Raven's Standard Progressive Matrices and executive processes (e.g. problem solving, planning) by the Hayling Sentence Completion Test and the Modified Six Elements Test.

**RESULTS.** The mean symptom score of 4.5 (range 1-11) and EuroQol of 65 (30-95) indicated that the patients still had some impairment of physical health but not severely so. All eight domains of the SF-36 were lower than the normative data from the general population. Percentage reductions were greater for physical functioning (27%) and restricted physical activity (63%) than for mental health (5.6%) and energy/vitality (15.8%). The List Learning scores were superior to the normative values for patients aged 45-60 yr (mean 56.6 vs. 51.4), while the Raven Score (mean 41.3) lay close to the 15th percentile for normal British subjects of that approximate age. The mean scores for the Six Elements Test (2.8) and the Hayling Test (4.0) were well below the national average. Scores were rated as poor in 11 and 9 patients respectively, and there was a close correlation between tests (r = 0.62, p=0.001).

**CONCLUSION.** Physical recovery was very incomplete at a mean 16 weeks after discharge from intensive care. Short-term memory was generally well preserved and eductive ability was reasonable. By contrast, executive function was markedly impaired in this group of general ICU survivors; poor scores were commonly found (37% and 45% of patients) using two standard tests for this organisational activity of the brain.

Grant. Thrombosis Research Institute and Clinical Research Committe

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### HEALTH RELATED QUALITY OF LIFE IN SEVERE SEPSIS

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**INTRODUCTION.** Quality of life (QOL) is a relevant, but poorly studied, outcome variable in critical care (1). As severe sepsis remains a prominent cause of mortality, morbidity and costs we studied the impact of severe sepsis on QOL.
**METHODS.** From September 2000-December 2001, patients admitted to the ICU for >48 hours were eligible for inclusion. QOL was measured on admission (by use of proxies) at discharge and 3 and 6 months following hospital discharge by use of the SF-36 questionnaire. Severe sepsis was defined by the presence or highly likely suspicion of infection, two or more SIRS criteria and one or more dysfunctioning organ systems. Severity of disease was measured by APACHE II.
**RESULTS.** 116 patients, of whom 30 met the criteria for severe sepsis, were included in the study. Patients with severe sepsis (age 65±13) stayed in the ICU longer (15.4±21.4 vs. 6.9±5.2, p<.01).than patients without sepsis (age 66±13). No differences were found in APACHE II scores of sepsis and non-sepsis patients (18.7±7 vs. 16.7±6 respectively). On admission mean QOL in all 8 dimensions of the SF-36 were similar in patients with or without severe sepsis. At hospital discharge no differences in the mental health dimension were found between patients with or without severe sepsis.

| | ICU admission n=30 vs 86 | Hospital discharge n=30 vs 86 | 3 months n=21 vs 52 | 6 months n=15 vs 40 |
|---|---|---|---|---|
| Physical functioning | 22.2±6.1 vs 22.3±6.9 | 15.8±3.9 vs 17.1±5.9 | 18.5±6.3 vs 19.8±6.3 | 19.2±6.2 vs 20.0±16.3 |
| Role-physical | 5.9±1.8 vs 6.1±1.9 | 5.0±1.5 vs 5.3±1.7 | 5.4±1.6 vs 5.5±1.8 | 5.6±1.5 vs 5.7±1.7 |
| Bodily pain | 8.9±3.1 vs 10.0±2.7 | 11.0±1.5 vs 10.7±2.2 | 10.1±2.1 vs 10.4±2.7 | 9.8±2.9 vs 10.0±2.7 |
| General health | 15.4±5.5 vs 16.5±5.6 | 15.1±3.3 vs 16.1±4.8 | 15.6±5.6 vs 16.4±4.2 | 14.1±5.3 vs 14.5±5.5 |
| Vitality | 14.2±5.1 vs 15.1±4.8 | 12.6±4.0 vs 12.9±4.5 | 14.0±4.3 vs 14.7±4.3 | 14.2±4.0 vs 14.9±4.8 |
| Social functioning | 8.7±1.6 vs 8.5±1,8 | 8.8 ±1.6 vs 8.6±1.6 | 8.0±2.1 vs 8.3±2.1 | 8.4±1.6 vs 8.6±1.8 |
| Role-emotional | 5.3±1.1 vs 5.2±1.2 | 5.1 ±0.8 vs 5.6±1.2 | 5.1±1.2 vs 5.2±1.2 | 5.1±1.2 vs 5.2±1.1 |
| Mental health | 22.7±3.4 vs 22.9±4.2 | 23.1±3.8 vs 22.4±3.7 | 22.6±4.6 vs 23.0±4.1 | 22.2±4.1 vs 22.6±3.7 |

Table: QQL dimensions in patients with or without severe sepsis

**CONCLUSION.** Patients with sepsis demonstrated more deterioration in areas of physical health than non-sepsis patients, whereas domains of mental health did not differ between the two groups.
**REFERENCES.** 1.Crit Care Med 2000;11:3599-3605.

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### EUROQOL QUALITY OF LIFE INDEX CHANGES OVER TIME IN SURVIVORS OF MECHANICAL VENTILATION

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**INTRODUCTION.** Health related Quality Of Life (QOL) in survivors from intensive care is influenced by the time span between ICU discharge. In an earlier study using the EuroQol instrument (EQ-5D), with only one interview 15 months after surviving mechanical ventilation, we found a mean TTO index of 0.63. The aim of this study was to detect EQ-5D changes over time by repeating the post-ICU interviews in two similar cohorts of patients.
**METHODS.** The EQ-5D instrument consists of five domains of self-rated function. It also includes an index for transformation of the overall result, where 0 is worst possible health status and 1 equals perfect health. Inclusion criteria were: Consecutive adult mixed ICU patients treated with CPAP or mechanical ventilation for more than 48 hours. Survivors in the first cohort was interviewed by telephone one month and fourteen months after ICU discharge. Survivors in the second cohort was interviewed by an ICU nurse while still in the hospital within one week after ICU discharge, then again by telephone after six months. The sign test was used to detect statistically significant ($p<0.05$) differences over time within the groups.
**RESULTS.** ICU mortality was 10% in both groups. Drop outs after ICU discharge were due to death, persisting weakness, transfer to other hospitals and lost track of patient after hospital discharge. Of 56 patients included in the first group, 24 could complete two interviews adequately. They scored a mean (∂SD) EQ-5D TTO index of 0.66 (∂0.29) after one month and 0.71 (∂0.32) after fourteen months. Nor this, nor any differences in specific domains were statistically significant. Of 75 patients included in the second group, 34 could complete two interviews. There was a significant difference between their EQ-5D index of 0.38 (∂0.26) within the first week after ICU discharge and 0.68 (∂0.31) six months later. There were also significant improvements in the domains mobility, hygiene and activity (tables and figures will be displayed on poster). Both groups scored indices below the 0.83 expected for an age adjusted normal population.
**CONCLUSION.** When applied in two groups of mixed ICU patients within fourteen months after their survival of mechanical ventilation, EuroQol seems to detect clear QOL changes over time only during the first month. To detect whether the observed difference compared to the normal population will remain chronic requires longer observation than the commonly anticipated rehabilitation of six to twelve months after critical illness.
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# Oral Presentations
# Respiratory monitoring – 496-501

## 496

### EARLY DETECTION OF PARTIAL ENDOTRACHEAL TUBE OBSTRUCTION BY USING EXPIRATORY FLOW SIGNAL

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**INTRODUCTION.** The inspiratory pressures may remain unchanged in spite of partial endotracheal tube (ETT) obstruction. Depending on the flow pattern an increase in inspiratory pressures is a late indicator of endotracheal tube (ETT) obstruction. Partial ETT obstruction may, therefore pass unrecognized and will lead to increased work of breathing and diffICUlties in ventilating the patient. The expiratory flow signal allows for early detection of partial ETT obstruction.
**METHODS.** The lungs of 9 piglets were ventilated with volume controlled ventilation ( PEEP of 4 cm H2O). The ETT was stepwise obstructed (three grades) with a graded external clamp. The expiratory flow over volume curve was analyzed as follows: The slope of the flow/volume curve has the dimension of time. For a description and comparison of slope change, the flow/volume curve is divided into 5 slices. The slope of a straight fitted line (least squares fit) to the flow/volume curve within that slice gives the time constant (tauE) of that partICUlar slice. The time constants of the 5 consecutive slices are plotted over the expired volume. Inspiratory pressure for each level of obstruction was measured during an end-inspiratory hold.
**RESULTS.** The time constants (Table) increased in parallel with increasing obstruction, while end-inspiratory pressures did not increase until the obstruction produced an intrinsic PEEP.

| | slice1 | slice2 | slice3 | slice4 | slice5 | Pendin |
|---|---|---|---|---|---|---|
| no obstruction | 554 (470-638) | 566 (504-628) | 513 (449-577) | 428 (346-510) | 389 (315-463) | 10.4 (+-0.8) |
| grade1 | 661 (601-720) | 630 (560-701) | 593 (528- 657) | 476 (406-546) | 360 (237-483) | 11. 5 (+-0.8) |
| grade2 | 877 (771-984) | 930 (756-1001) | 832 (688- 976) | 765 (617- 912) | 521 (321-721) | 11.6 (+-0.5) |
| grade3 | 1563 (1353-1772) | 1666 (1390- 1943) | 1808 (1296-2319) | 1674 (1148-2199) | 1286 (426- 2147) | 12.0 (+-0.2) |

Values are mean (95% confidence interval) for slices and mean (+- SD) for Pendin. N = 9.

**CONCLUSION.** Partial tube obstruction can be detected by the characteristic changes in the pattern of the TauE over expired volume plot making the expiratory flow signal an early and reliable indicator for partial tube obstruction.
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Grant. Laerdal Foundation

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### VOLUMETRIC CAPNOGRAPHY AS A SCREENING TEST FOR PULMONARY EMBOLISM AT THE EMERGENCY DEPARTMENT

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**INTRODUCTION.** Pulmonary Embolism (PE) produces alveolar deadspace that may create a gradient between the arterial and the end-tidal $CO_2$ measured by a time-based capnogram ($PaCO_2$-$EtCO_2$ gradient). The Volumetric Capnography, that is the plot of the expired $CO_2$ partial pressure against the expired volume during a single breath, offers theoretical advantages in calculating deadspace fractions from surfaces ratios and in discriminating PE from obstructive lung diseases. We hypotheses that volumetric capnography will have a better diagnostic performance than the $PaCO_2$-$EtCO_2$ gradient for the clinical suspicion of PE.
**METHODS.** A group of 49 spontaneously breathing outpatient with positive ELISA D-dimers >500 ng/ml was tested. The diagnosis of pulmonary embolism was confirmed in 20 patients using the V/Q lung scan and/or the spiral CT. Curves of volumetric capnography were obtained from a commercially available Datex-Ohmeda compact monitor (CS/3) connected to a computer, allowing the calculation of several variables amongst which the alveolar deadspace fraction (Vdalv/Vtalv), the alveolar to airway deadspace ratio (Vdalv/Vdaw), the slope of phase 3, the late deadspace fraction (fd late) corresponding to the extrapolation of the capnographic curve until a volume of 15% of the total lung capacity.
**RESULTS.** The mean $PaCO_2$-$EtCO_2$ gradient was 5.85 ± 3.62 in the PE positive group and 2.90 ± 3.35 in the PE negative group ($p=0.0053$). The sensitivity and specificity for a 3-mmHg cut-off value of the gradient was 75% (51-91%) and 65% (45-82%) respectively. Four variables from the volumetric capnography shared with the $CO_2$ gradient a statistical difference between the PE positive and the PE negative group: Vdalv/Vtalv 23.8±11.3 % versus 16.5±9.5% ($p=0.019$); Vdalv/Vdaw 84.5±51.3% versus 47.7±29.2% ($p=0.0026$); slope of phase 3 1.23±0.69 %/L versus 1.82±1.15%/L ($p=0.049$); fd late 8.91±13.8% versus-7.06±8.05% ($p=0.0003$). The diagnostic performance expressed with a ROC curve area comparison was 75.5±7.2% for the $PaCO_2$-$EtCO_2$ gradient and 90.1±5.2% for the fd late ($p=0.04$). The correlation coefficient between the $PaCO_2$-$EtCO_2$ gradient and Vdalv/Vtalv, Vdalv/Vdaw, slope of phase 3 and fd late was respectively 89%, 62%, 35%, 81% ($p<0.05$).
**CONCLUSION.** The late deadspace fraction (fd late), a variable from the volumetric capnography, has a statistically better diagnostic performance in the clinical suspicion of PE than the $PaCO_2$-$EtCO_2$ gradient obtained from a time-based capnography. Volumetric capnography is an interesting non-invasive screening tool that applies the pulmonary physiopathology at the bedside of a patient with computerized aid. Future research should define the place of this technique in the diagnostic work-up of PE, especially when the D-dimers are positive.
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Grant. Datex-Ohmeda, Helsinki, Finland

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## THE CONTRIBUTION OF REAL TIME SONOGRAPHY IN DETECTION OF PNEUMOTHORAX IN MECHANICAL VENTILATION

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**INTRODUCTION.** Pneumothorax (PNO) represents one of the most common and dangerous complications of mechanical ventilation and its diagnosis can be extremely diffICUlt in the ICU setting. Although chest x-ray at the bedside remains the main diagnostic modality, thoracic ultrasound has recently gained increased attention for the early identification of PNO (1).

**METHODS.** To evaluate the effect of real time sonography (RTS) on the identification of PNO in mechanically ventilated patients we followed 43 patients to whom clinical suspicion of PNO was raised and confirmed by chest x-ray. 29 of them suffered a serious blunt chest trauma, 6 of them had a clinical picture compatible with PNO after central vein placement, and 8 without apparent reason beside mechanical ventilation. 98 mechanically ventilated patients without PNO underwent RTS, serving as control group. The main sonographic signs examined, were absence of comet tail sign and lung sliding sign.

**RESULTS.** RTS confirmed the presence of PNO in 40/43 cases. In 3 cases subcutaneous emphysema affected the quality of images, resulting in uninterpretable results. Lung sliding sign was evident in 0/40 and absence of comet tail sign was observed in 40/40. No difference was observed in ultrasonographic findings between the different subgroups of PNO patients. 84/98 of the controls demonstrated lung sliding sign and 78/98 presented with comet tail sign. 6/98 of controls demonstrated absence of both lung sliding and comet tail sign. The mean time required to perform RTS was 2 min.

| | Lung sliding | Comet tail sign |
|---|---|---|
| PNO group (n=40) | 0/40 (0%) | 0/40 (0%) |
| Control group (n=98) | 84/98 (86%) | 78/98 (80%) |

**CONCLUSION.** Thoracic ultrasound represents a rapid and noninvasive method for the early diagnosis of pneumothorax in mechanically ventilated patients at the bedside. The concurrent use of ultrasound and radiograph could help rule out problematic cases of PNO.

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# 499

## COMPUTER-AIDED RESPIRATORY PATTERN SELECTION FOR VENTILATION THROUGH SMALL-SIZE E.T. TUBE DURING TLT

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**INTRODUCTION.** Adult ventilation through small-size tubes (e.g. during TLT) is a challenge. The high resistance of the tube involves major air trapping that must be compensated for, by an increase in expiratory time, and/or by a reduction in external PEEP. We have designed an algorithm for computer-aided (CA) calculation of the best ventilator settings, based on constancy of alveolar ventilation and inputs for: a) basal minute ventilation, respiratory pattern, PEEP and tube size; b) patient passive mechanics (resistance, compliance and total PEEP) and ideal body weight; c) safety limit for peak alveolar pressure (Pinsp,stat,max).

**METHODS.** We included 10 patients, passively ventilated (PCV) for a TLT procedure. We studied each patient in two conditions: a) "Basal", before the TLT, with a normal ET tube and ventilation set on clinical basis; b) "Small", during the TLT, with a 4-mm ID ET-tube and ventilation set according to the CA algorithm

**RESULTS.** In the obstructive patients, the CA algorithm suggested a major reduction of frequency and I:E ratio, with increase of tidal volume. In the restrictive patients the algorithm mainly suggested a reduction of PEEP. In all patients, constant $PaCO_2$ confirmed constant alveolar ventilation. Total PEEP was unchanged or moderately increased. In spite of high Ppeak, Pinsp,stat was within the preset limit (25±3 cmH2O) or just moderately higher.

| Data: mean±SD | | Basal | Small |
|---|---|---|---|
| Ve' | l/min | 7.9 ± 1,3 | 7.4±1.2 |
| $PaCO_2$ | mmHg | 41.3±6 | 42.1±3 |
| PEEPext | cmH2O | 6.3±3.9 | 3.5±2.7 |
| PEEPtot | cmH2O | 7.6±3.8 | 9.6±4.1 |
| Ppeak | cmH2O | 24.7± 6.1 | 62.9± 26.3 |
| Pinsp,stat | cmH2O | 20.5±6.3 | 28.3±5.8 |

**CONCLUSION.** Our CA algorithm provides reasonable start-settings for continuing adult ventilation when switching from a normal ET-tube to a 4-mm one.

# 500

## AMBIENT TEMPERATURE EFFECTS ON INSPIRED GAS HUMIDIFICATION DURING NEONATAL MECHANICAL VENTILATION

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**INTRODUCTION.** Humidification of inspired gas is necessary to obtain fluid secretion during neonatal ventilation. It is suggested that high ambient air temperature interfere with humidification quality and may induce endotracheal tube occlusions. The aim of this study was to assess the effect of ambient air temperature on heated humidifier performances.

**METHODS.** We measured on a test bench, the absolute humidity of inspired gas delivered by a continuous flow ventilator (Babylog 8000 – Dräger), with dual heated circuit and a MR730 (Fisher & Paykel) heated humidifier at 3 different settings and 4 ambient air temperatures (24, 27, 30 and 33°C).

**RESULTS.** See table 1. Differences between absolute humidity values at different ambient temperatures were significant ($p<0,05$) for each setting. There was too much condensation in the circuit at 24°C and 27°C with a 40/0 setting and at 24°C with a 40/-3 setting.

| | 37 / -2 | 40 / -3 | 40 / 0 |
|---|---|---|---|
| 24°C | 29.3 | 36.5 | water |
| 27°C | 27 | 33.8 | 41.5 |
| 30°C | 21.5 | 29.1 | 36.7 |
| 33°C | 17.9 | 21.5 | 29.9 |

Table 1 : Absolute humidity (mg H20/l) depending on ambient air temperature (°C) and heated humidifier setting.

**CONCLUSION.** Heated humidifier performances decreased when ambient air temperature increased. On the opposite, condensation occured with low ambient air temperature. Obviously, heated humidifier performances are highly influenced by ambiant air temperature. These results imply the necessity to adapt the heated humidifier settings according to the room temperature.

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## MONITORING OF INTRAPULMONARY SHUNT VOLUME (QS) BY A PARTIAL $CO_2$ REBREATHING TECHNIQUE

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**INTRODUCTION.** Pulmonary capillary blood flow (PCBF) may be calculated from the changes in $CO_2$ elimination ($VCO_2$) during a short $CO_2$ rebreathing period (1). The differential form of the Fick equation for $VCO_2$ permits the elimination of mixed venous $CO_2$ content, thereby allowing the non-invasive measurement of PCBF (2). If this technique works accurately, conventionally determined values of Qs with arterial and mixed venous blood samples must be comparable with the values obtained from subtracting PCBF from total cardiac output (CO).

**METHODS.** After approval by our Ethics Committee 5 critically ill patients aged >18 years and requiring mechanical ventilation were studied. PCBF was measured with the David monitor (MedServ GmbH, Leipzig, Germany). CO was measured by the thermodilution technique with a pulmonary artery catheter (PAC), and arterial and mixed venous blood samples were drawn for measuring arterial ($caO_2$), mixed venous ($cvO_2$), and pulmonary capillary oxygen content ($ccO_2$) with a Co-oximeter (ABL 700, Radiometer, Copenhagen). The proportion of Qs to CO was calculated by the conventional method using the PAC (Qs/CO by PAC): $Qs/CO = (ccO_2\text{-}caO_2)/(ccO_2\text{-}cvO_2)$, and by using PCBF (Qs/CO by David): Qs/CO = (CO-PCBF)/CO. The analysis described by Bland and Altman was used to compare the dataset of the two results with regard to their consistence (2).

**RESULTS.** Mean age, height, weight, and body surface area of the patients was 74.8 (range: 46-88) years, 166.2 (range: 158-190) cm, 95.3 (range: 60-140) kg, and 2.01 (range: 1.64-2.63) m². Mean CO was 6.98 (range: 4.33-13.60) L/min. The table shows the means and ranges of PCBF, CO-Qs (i.e., PCBF by PAC), Qs/CO by PAC, and Qs/CO by David. The Bland-Altman analysis revealed a bias of 0.367 (SD 0.755, 95% CI –0.113-0.847) L/min for PCBF, and 0.027 (SD 0.089, 95% CI –0.030-0.084) for Qs/CO.

| | PCBF by David | PCBF by PAC | Qs/CO by David | Qs/CO by PAC |
|---|---|---|---|---|
| Mean | 5.14 | 5.51 | 0.23 | 0.21 |
| Range | 3.60-7.40 | 3.40-9.28 | 0.09-0.46 | 0.13-0.32 |

**CONCLUSION.** The present study shows that PCBF can accurately be measured by the non-invasive technique of partial $CO_2$ rebreathing in critically ill mechanically ventilated patients. PCBF may therefore be used to guide hemodynamic and respiratory therapeutic interventions in such patients. In combination with a PAC, monitoring of Qs/CO can be performed without drawing blood samples.

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# Oral Presentations
# Very attractive papers on ventilator-associated pneumonia – 502-507

## 502

**CILIARY ABUNDANCE AND ULTRASTRUCTURE OF BRONCHIAL RESPIRATORY EPITHELIUM IN VENTILATED PATIENTS**

Kay R. J.[1], Kirkby J.[1], Macnaughton P. D.[2], Bailey J.[2], Sneyd R. J.[2], Moate R. M.[1], Ingham J.[2], Langton J. A.[2] [1]E.M.Unit, University of Plymouth, [2]Directorate of Anaesthesia and critical care medicine, Derriford Hospital, Plymouth, United Kingdom

**INTRODUCTION.** Impaired respiratory mucus transport is common in patients undergoing mechanical ventilation who often need prolonged tracheal intubation. Ciliary abundance and ultrastructural integrity are key components of effective mucus clearance. A previous study has reported that within the first three days of mechanical ventilation, there is a significant increase in ciliary denudation, but no significant change in the incidence of ciliary ultrastructural abnormalities (1). We have investigated whether more protracted ventilatory support is associated with changes in ciliary abundance and structure.

**METHODS.** Fibreoptic bronchoscopy was performed in a series of orally intubated patients at different time points during their admission to a general medical/surgical intensive care unit. Biopsy samples of bronchial respiratory epithelium were taken and a broncho-alveolar lavage specimen obtained for microbiological culture. Samples were rigorously blinded and prepared for scanning (SEM) and transmission (TEM) electron microscopic examination. The mucosa of biopsies were imaged by SEM, digitally capturing as large an area as possible whilst avoiding any areas of mechanical damage. Standard software were used to quantify ciliary abundance in terms of percentage coverage. TEM was used to quantify the incidence of ultrastructural ciliary abnormalities in at least 500 cilia per patient taken from ten separate areas.

**RESULTS.** The characteristics of the patients studied were 34 male, 23 female; age 62 (18-85) years; length of stay 5 (1-29) days; admission APACHE II score 15 (2-27) [median (range)]. A reduction in ciliary abundance (<70%) and an increase in ciliary abnormalities (>5%) compared to normal values were found in 14/26 and 9/44 patients respectively. There was no clear relationship between these abnormalities and the underlying diagnosis or the presence of infection. However, there was a significant relationship between the incidence of ciliary abnormalities and the length of time patients were ventilated (p= 0.02, R2=11.9%). A stronger relationship was found between the number of days ventilated and ciliary abundance (p= 0.02, R2=-27.1%) with the median value for ciliary abundance for the first 10 days being 88% (range 66%-97%) and for days 11-29 being 50% (range 29%-90%).

**CONCLUSION.** This study confirms that abnormalities of ciliary ultrastructure and abundance are common in patients undergoing mechanical ventilation. These changes are associated with the duration of ventilatory support and they may be an important mechanism contributing to impaired mucous transport. Further studies are required to assess putative factors which may cause these changes.

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## 503

**BRONCHOALVEOLAR LAVAGE ALTERATION IN VENTILATOR ASSOCIATED PNEUMONIA**

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**INTRODUCTION.** Ventilator Associated Pneumonia (VAP) is the most common nosocomial infection of the mechanically ventilated patients. Although bronchoalveolar lavage (BAL) represents one of the main tools for the diagnosis of VAP, BAL alterations that precede and follow VAP have not been elucidated.

**METHODS.** We followed for two weeks 67 conventionally ventilated patients (TV 8-10ml/kg, PEEP: 3-6cm $H_2O$), who initially had normal chest X-ray, satisfactory oxygenation ($PaO_2/FiO_2$>300mmHg), and no sign of cardiopulmonary disease. All patients were subjected to BAL on weekly basis. 13 patients, who during the study developed VAP, were subjected to BAL in the involved bronchopulmonary segment. BAL was repeated at the same segment after VAP's resolution. Proteins, total and classes of phospholipids, differential centrifugation and inflammatory markers (cells, PAF, PAF-AcH) in BAL fluid were measured.

**RESULTS.** VAP caused a significant increase of BAL total protein and albumin. Total phospholipids as well as the percentage phospholipid content in 30.000xg, representing the surfactant fraction with good surface properties, was significantly reduced during VAP and this decrease persisted after VAP's resolution Alterations of individual phospholipid classes were observed, mainly consisting of significantly reduced proportions of PC and PG and increased lysophospholipids. PAF and neutrophils were extremely elevated during VAP and remitted after its resolution. None of the parameters studied before the development of VAP, exhibited a significant difference between VAP patients and patients ventilated for the same period of time, who did not develop VAP.

| | Before VAP | VAP | After VAP |
|---|---|---|---|
| Total cell count (x103) | 188±31 | 426±175 | 210±76 |
| Alveolar macrophage (%) | 72±9 | 56±14 | 77±10 |
| Neutrophils (%) | 20±6 | 42±10 | 21±8 |
| Total protein (ig/mL) | 281±173 | 1425±1288 | 347±81 |
| Albumin (ig/mL) | 81±28 | 424±301 | 91±40 |
| Total phospholipids(PL) (ig P/ml BAL) | 1.6±0.73 | 1.16±0.79 | 1.24±0.49 |
| Phosphatidylcholine (PC), % of total PL | 60±7 | 52±6 | 59±8 |
| Lipids % (Pellet 30000xg) | 66.5±16.2 | 38.3±12.6 | 35.6±11 |
| PAF (pg/9m BAL) | 0 | 272±192 | 6±19 |
| PAF-AcH (nmmol PAF/ml BAL/min) | 0.06±0.03 | 1.79±1.62 | 0.46±0.21 |

**CONCLUSION.** Our results demonstrate high level of BAL protein indicating an increased alveolar-capillary permeability, persisting surfactant abnormalities and strong but reversible local inflammatory reaction during the course of VAP.

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**DIAGNOSIS OF VENTILATOR-ASSOCIATED PNEUMONIA (VAP) USING CLINICAL PULMONARY INFECTION SCORE (CPIS)**

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**INTRODUCTION.** The CPIS proposed by Pugin et al.(1) includes a graded scoring of five readily accessible clinical variables (body temperature, blood leukocytes, tracheal secretions, oxygenation ($PaO_2/FiO_2$), pulmonary radiography) and of culture of tracheal aspirates to determine the likelihood of VAP. A CPIS score >6 is highly suggestive of pneumonia. Recently, a modified CPIS score was proposed by Singh et al.(2), as an operational criteria for decision-making regarding antibiotic therapy. In patients with a clinical suspicion of VAP, a CPIS score remaining <6 at baseline and at 3 days safely allowed to stop antibiotics. However, the diagnostic validity of the CPIS score has yet to be confirmed; besides, its value for initiating empiric therapy would be improved if it took into account direct examination of respiratory tract specimens rather than culture results at 3 days.

**METHODS.** We prospectively studied 79 episodes of clinically suspected VAP, over a 16-month period, in 68 patients having received mechanical ventilation for 11.3 ± 8.2 days. Blinded (single-sheathed protected telescopic catheter, PTC) and directed sampling (bronchoalveolar lavage, BAL) techniques were performed. Pneumonia was confirmed in 40 episodes (VAP+) by a positive BAL fluid culture (>10e4 cfu/ml) of at least one microorganism. The CPIS score at baseline (CPIS B) was calculated from the clinical variables on the day of sampling, or by including in addition the results of gram staining of samples (CPIS G), to which was ascribed a score of 2 when positive or 0 when negative.

**RESULTS.** In the overall population, the mean CPIS B score was 6.24 ± 1.5. In episodes with vs. without pneumonia, the mean P/F ratio was 186 ± 72 vs. 201 ± 71, the leukocytes count 16,865 ± 8,157 vs. 15,126 ± 7,849, and temperature, 38 ± 1°C vs. 38.1 ± 1.1, and the mean CPIS B 6 ± 1.2 vs. 6 ± 1.7, respectively. A CPIS B score >6 was recorded in only 24 of the 40 (60%) VAP+ episodes, and as many as 16 of the 39 (41%) VAP- episodes. The operational characteristics of the CPIS B and CPIS G for predicting pneumonia are shown in the Table:

| | Sensitivity | Specificity | Pos. predictive value | Neg. predictive value |
|---|---|---|---|---|
| CPIS B >6 | 60% (24/40) | 59% (23/39) | 60% | 59% |
| CPIS G(BAL)>6 | 85% (34/40) | 49% (19/39) | 63% | 76% |
| CPIS G(PTC)>6 | 78% (31/40) | 56% (22/39) | 65% | 71% |

**CONCLUSION.** The CPIS score does not accurately identify patients with or without pneumonia. Its operational characteristics are markedly improved by including gram stain of protected specimens in the score, which could be used confidently for decision-making in initiating therapy. Only a few patients having pneumonia would be missed by limiting therapy to those with a CPIS G>6. Therapy can then be adjusted at 24h according to culture results.

**REFERENCES.** (1) AJRCCM 1991; 143:1121; (2) AJRCCM 2000; 162:505

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**VENTILATOR-ASSOCIATED PNEUMONIA RISK FACTORS. A MULTICENTER STUDY**

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**INTRODUCTION.** Ventilator-associated pneumonia (VAP) remains the leading infection of ICU acquisition. Risk factors associated with VAP development have been studied in somes monocenter studies. The objective of this study was define the role of several potential risk factors associated or not previously with VAP.

**METHODS.** Prospective observational and multicenter study in 17 ICUs. Studied risk factors were demographic, severity of illness, underlying disease, therapy and prophylaxis, type of ICU, structural differences. Statistics analysis: means, and X2.

**RESULTS.** During the 12 months study period 1704 patients were admited in the 17 participating ICUs for a mean of 16.5+17.6 days, with 9.1+9.2 days of mechanical ventilation. The mean age was 57.3+18 with 66.5% males. The APACHE II score was 18.2+ 7.6. Overall, 353 patients developed 403 VAP, representing 22.01 VAP episodes for 1000 MV days. Risk factors for VAP are expressed in the table. Length of stay (30.4+24 vs 12.9+13.3 days, p<0.01) and mortality (46.6% vs 38.2%) were higher in patients with VAP.

| | VAP (%) | No VAP (%) | p value |
|---|---|---|---|
| COPD | 25.9 | 20.2 | 0.01 |
| Paralizing agents | 35.6 | 18.9 | <0.01 |
| Sedative agents | 22.8 | 14.1 | <0.01 |
| Previous pneumonia | 26.9 | 20.0 | 0.02 |
| ARDS | 30.2 | 19.4 | <0.01 |
| Aspiration | 33.1 | 19.3 | <0.01 |
| Previous sepsis | 24.7 | 17.4 | <0.01 |
| Previous antibiotic | 19.5 | 27.4 | <0.01 |

**CONCLUSION.** Pulmonary disease of previous or recent acquisition and sedative and paralizing agents increase the risk of VAP. Overall, antibiotic use decreases the rate of VAP.

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### UPPER DIGESTIVE INTOLERANCE AND PNEUMONIA IN EARLY FED MULTIPLE INJURED PATIENTS

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**INTRODUCTION.** Early enteral nutrition (EN) after injury reduces septic complications, above all pneumonia. On the other hand, because of upper digestive tract paralysis post injury, it is believed to meet more intolerance problems, a risk factor for hospital pneumonia, than a delayed one (1, 2). The purpose of our study was therefore to determine, whether early intragastric nutrition in a group of ventilated multiple injured patients present a risk for nosocomial pneumonia in comparison to the patients receiving EN later than 24 hours after admission.

**METHODS.** Multiply injured patients were studied prospectively and randomized into two groups: group A placed on an immediate intragastric EN, group B started on EN later than 24 hours after admission. Before feeding sessions, gastric contents were aspirated. For the diagnosis of nosocomial pneumonia, in addition to the new or changing infiltrates, at least 2 criteria had to be present: purulent tracheal aspirate, a body temperature more than 38.0 0C, and 10.000/mm$^3$ or greater increase or 4.000/mm$^3$ or lower circulating leukocyte levels.

**RESULTS.** Out of 52 multiple injured patients, 27 included for early enteral nutrition started 10.3±3.5 hours and 25 for enteral nutrition started 42.5±13.9 hours after injury. All patients, but one, survived their treatment in ICU. There were no significant differences between the groups regarding their demographic data, the length of mechanical ventilation and ICU stay. More intolerance problems and pneumonia were in group B (Table 1). Patients with pneumonia were older and spent significantly more days on artificial ventilation and in ICU (Table 2).

| | All | Group A | Group B | p-value |
|---|---|---|---|---|
| Volume of EN on day 4 (ml) | 866±645 | 1205±512 | 807±605 | 0,02 |
| Days with upper intestinal intolerance | 1.6±2.1 | 1.0±0.9 | 2.2±2.7 | 0.04 |
| Pneumonia (no. of patients) | 25 | 9 | 16 | 0.027 |

Upper digestive intolerance and pneumonia in early and delayed enteral nutrition

| | Patients without pneumonia | Patients with pneumonia | p-value |
|---|---|---|---|
| No. (male / female) | 27 (23/3) | 25 (21/4) | |
| Age | 36.9±17.7 | 48.2±15.7 | 0.02 |
| Mechanical ventilation (days) | 9.3±9.5 | 19.5±13.4 | 0.003 |
| Days in ICU | 12.8±11.3 | 24.0±15.7 | 0.005 |

**CONCLUSION.** Early gastric feeding in multiple injured, if properly administered, decreases incidence of upper intestinal intolerance and nosocomial pneumonia in ventilated patients.

**REFERENCES.** 1. Moore AF, Feliciano DV, Andrassy RJ et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. Ann Surg 1992; 216: 172-83. 2. Mentec H, Dupont H, Bocchetti M et al. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications . Crit Care Med 2001; 29; 1955-61.

## 507

### VENTILATOR-ASSOCIATED PNEUMONIA: EFFECTS OF HEAT MOISTURE EXCHANGERS AND HEATED WATER HUMIDIFICATORS

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**INTRODUCTION.** It has been suggested that the use of heat and moisture exchangers(HME)could be associated with a lower risk of ventilator associated pneumonia (VAP) than heat water humidifiers(HH).

**METHODS.** Study Design: Randomised multicenter trial conducted on 2 parallel groups in 5 ICUs. Patients expected to require mechanical ventilation (MV) for >24 hours were eligible. Patients already on MV for >24 hours, patients with hemoptysis, severe ARDS (ie, compliance <20 ml/cm H20), or severe hypothermia (<32°C) were not included. Patients were randomly assigned to receive airways humidification via either a HH or a HME, and were screened daily for VAP. A clinical suspicion of VAP was based on the presence of recent and persistent infiltrate(s) on chest X-ray and two of the following criteria: fever (>38.3°C) or hypothermia (<36.5°C), leukocytosis (>10.10$^9$/l) or leukopenia (<4.10$^9$/l), and purulent tracheal secretions. The diagnosis of VAP was confirmed when quantitative culture of a protected distal sample or of bronchoalveolar lavage respectively grew >10$^3$ CFU/ml or >10$^4$ CFU/ml of at least one microorganism.

**RESULTS.** 341 patients were enrolled, including 169 in the HH group and 172 in the HME group. There was no difference between the two groups in age, gender, LOD score at initiation of MV; patients assigned to HH had a slightly higher SAPS II score (48.8) than those assigned to HME (44.6; p=0.04). There was no difference in VAP rate or incidence between the two groups: HH vs. HME VAP rate [51(30%) vs. 43 (25%); p=0.33] and incidence [31,6/1000 vs. 27,4/1000 ventilator-days; p=0,53]. The mean duration of mechanical ventilation was not different between the two groups [14,3 vs 12,3 for HH vs HME, p=0,11]. Endotracheal tube occlusion occurred respectively in 5 and 1 patients in the HH and HME group (p=0.12). ICU mortality was identical (31.6%) in the two groups.

**CONCLUSION.** In this relatively large trial in a mixed medical-surgical population requiring mechanical ventilation for more than 24 hours, the use of HME or HH was associated with a similar risk of VAP.

# Oral Presentations
# Acute lung injury (I) – 508-512

## 508

### RELATIONSHIP BETWEEN ALI AND ARDS: THE ALIVE RESULTS.

Brun-Buisson C.[1], Minelli C.[2], Brazzi L.[3], Pimentel J.[4], Levandowski K.[5], Bion J.[6], Romand J.[7], Villar J.[8], Damas P.[9], Bertolini G.[10], Lemaire F.[1] [1]MICU, Hosp. Henri Mondor, Créteil, France, [2]MICU, Inst. Mario Negri, Bergamo, [3]MICU, Univ Hosp Maggiore, Milan, Italy, [4]MICU, Univ Hosp, Coimbra, Portugal, [5]MICU, Univ Hosp Charité, Berlin, Germany, [6]MICU, Univ Hosp., Birmingham, England, [7]MICU, CHUV, Geneve, Switzerland, [8]MICU, Univ Hosp. Canarias, Tenerife, Spain, [9]MICU, CHU, Liège, Belgium, [10]Epid, Inst. Mario Negri, Bergamo, Italy

**INTRODUCTION.** Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are considered as two stages of the same syndrome, with ALI identifying the early stage. The fraction of patients evolving from one stage to the other is not known, and whether there is a true continuum between the two stages remains debated.

**METHODS.** We conducted a 2-month survey in 78 ICUs from 10 European countries to analyse epidemiological features and outcome of patients with ALI and ARDS. All patients admitted for >4 hours were included. ALI and ARDS were defined following the European-North American consensus conference. For patients presenting ALI/ARDS, detailed information were recorded on causes, time of occurrence, and follow-up data (until ICU discharge). ICU and hospital outcome were recorded for all patients.

**RESULTS.** Of all 6,529 pts admitted, 3,230 (49.5%) stayed in the ICU for >24h. ICU mortality was 15% overall. There were 463 (7.1%) patients with ALI or ARDS. Both ALI and ARDS were mostly caused by direct lung injury, alone or in combination (82% and 78%). The median (mean; SD) ICU LOS was 8 (16.5; 19.1) in ALI pts., and 12 (16.4; 15.2) d in ARDS pts., and 2 (5.4; 10.0) overall. More than half (54%) pts. presenting with ALI evolved to ARDS, whereas ALI precedes ARDS for 18.5% of pts., including in <10% within the first 24h ICU stay (Table). The mortality of patients with ALI not evolving to ARDS was much lower than that of patients with ARDS; those pts. evolving from ALI to ARDS had an intermediate mortality.

| | ALI on admission (n=79) | ALI during ICU stay (n=57) |
|---|---|---|
| Evolved to ARDS (mortality %) | 38 (42%) | 36 (41%) |
| Remained ALI (mortality, %) | 41 (20%) | 21 (29%) |
| | ARDS on ICU admission (n=233) | ARDS during ICU stay (n=166) |
| ARDS from ALI on day 1 (mortality, %) | 23 (30%) | 8 (37%) |
| ARDS initially (mortality, %) | 210 (52%) | 158 (49%) |

**CONCLUSION.** Although most ALI/ARDS pts present with ARDS, about one-third of pts. presenting initially with ALI evolve to ARDS, within a short delay. Although associated to a similar length of ICU stay, ALI and ARDS have a distinctly different outcome. Pts with ALI who evolve to ARDS after a few days seem to have an intermediate outcome between ALI pts. who did not progress and pts. who initially present with ARDS.

Grant. Hoescht Marion Roussell

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### RISK FACTORS FOR ARDS IN ICU PATIENTS: THE ALIVE RESULTS

Brun-Buisson C.[1], Minelli C.[2], Brazzi L.[3], Pimentel J.[4], Levandowski K.[5], Bion J.[6], Romand J.[7], Villar J.[8], Damas A.[9], Lemaire F.[10], Bertolini G.[2] [1]MICU, Hosp. Henri Mondor, Créteil, France, [2]Epidemiology, Inst. Mario Negri, Bergamo, [3]ICU, Univ Hosp Maggiore, Milan, Italy, [4]ICU, Univ Hosp, Coimbra, Portugal, [5]ICU, Univ Hosp Charité, Berlin, Germany, [6]ICU, Univ Hosp, Birmingham, England, [7]ICU, CHUV, Geneve, Switzerland, [8]ICU, Univ Hosp Canarias, Tenerife, Spain, [9]ICU, CHU, Liege, Belgium, [10]MICU, Hosp. Henri Mondor, Créteil,

**INTRODUCTION.** Critically ill patients may be at high risk of ARDS during the ICU stay, as a consequence of acute disease or complications duriing the ICU stay. To examine the relationships between ALI and ARDS and other risk factors for the occurrence of ARDS, we analysed the ALIVE study database.

**METHODS.** The ALIVE database includes patients admitted during a 2-month period in 78 ICUs from 10 European countries, to analyse epidemiological features and outcome of patients with ALI and ARDS. ALI and ARDS were defined following the European-North American consensus conference. For patients presenting with ALI/ARDS, detailed information were recorded on causes, time of occurrence, and follow-up data (until ICU discharge). In this analysis, only patients staying for >24h and not having ARDS on admission (n=3271) were included. Variables associated with occurrence of ARDS were entered in a multiple regression model to identify independent risk factors.

**RESULTS.** Of the 401 patients with ARDS in the ALIVE study, 233 occurred on admission and 166 later during the ICU stay. Factors associated with the occurrence of ARDS were the presence of ALI or respiratory dysfunction on admission, of shock, of pneumonia, liver disease, trauma, and transfer from a medical/surgical ward. In the multivariate analysis, independent risk factors for ARDS (odds ratio, OR; 95CI) were : ALI on admission (OR= 13.7; 8.1-23.0), Shock on admission (2.8; 1.9-4.2), pneumonia (2.6; 1.7-3.9), liver disease (1.2; 1.1-4.1), trauma (2.1; 1.3-3.2), a medical or surgical ward transfer (1.7; 1.2-2.5), and respiratory dysfunction on admission (1.6; 1.0-2.7). The calibration of the model was excellent (Hosmer-lemeshow P=0.94).

**CONCLUSION.** In this large series of ARDS, ALI was a strong predictor of ARDS, in addition to liver disease, pulmonary dysfunction or pneumonia, and shock on admission. Our study allows to identify patients to whom optimisation of therapeutic approaches may be targeted early in the course of the syndrome.

Grant. Hoechst-Marion-Roussel

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**MULTIPLE LINEAR REGRESSION ANALYSIS (MLR) AND OCCLUSION TECHNIQUES IN ACUTE RESPIRATORY FAILURE**

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**INTRODUCTION.** Measurement of respiratory system mechanics is important in patients with acute respiratory failure (ARF). The current gold standard is the multiple occlusion technique, however this is time consuming and infrequently repeated. MLR using volume-dependent elastance offers an easily repeated and perhaps continuous measure. We compared both techniques in patients with ARF.

**METHODS.** 11 sedated and paralysed patients in ARF had airflow and pressure measured using a heated pneumotachograph and differential pressure transducer respectively. Flow and pressure were amplified, filtered and sampled at rate of 100Hz. Analysis was performed using Anadat software (RTH-infodat, Montreal, Canada). The multiple occlusion technique entailed constructing inspiratory and expiratory curves from 14-30 inspiratory and expiratory occlusions analysed. Lung and chest wall mechanics were partitioned using the oesophageal balloon technique. MLR was applied using the volume-dependent single compartment model (VDSCM) of the equation of motion: $P_{ao}=(E_1+E_2V)\ V+RV'+P_o$; where $E_1$ and $E_2$ are the linear and non-linear coefficients of the elastic pressure volume curve respectively. Occlusion and MLR derived airway ($P_1$), oesophageal ($P_2$) and transpulmonary ($P_3$) pressures were compared at their same corresponding volumes. Data are mean±Standard Deviation.

**RESULTS.** MLR derived airway pressure ($P_{1mlr}$) was highly correlated with occlusion airway pressure ($P_{1occl}$) in both inspiration and expiration. Inspiration$P_{1occl}$=-0.17+0.06pt+1.02$P_{1mlr}$, $R^2$=98.3%, p<0.001. Expiration $P_{1occl}$=0.7-0.11pt+1.02$P_{1mlr}$, $R^2$=98.6%, p<0.001. Bland Altman analysis comparing the average difference between the two methods also showed that $P_{1mlr}$ closely reflected $P_{1occl}$, inspiration bias was 0.4±0.7 $cmH_2o$ and expiration bias was 0.3±0.6$cmH_2o$. $P_3$ was more variable due to variation in $P_1$ despite an oesophageal balloon occlusion test ratio of 0.92±.033 and a low level of intrinsic PEEP 0.6±0.7$cmH_2o$, calculated using $P_{eocel}$-$P_o$, where $P_{eoccl}$ is the minimum end expiratory PEEP and $P_o$ is MLR derived intrinsic PEEP. Bland Altman analysis of $P_3$ obtained via MLR analysis and occlusion techniques showed a greater standard deviation. However the bias was also low, inspiration bias was 0.3±1.9$cmH_2o$, expiration bias was 0.5±2.7$cmH_2o$. Individual patient analysis suggested more error with the occlusion technique.

**CONCLUSION.** MLR is an acceptable substitute for pressure-volume analysis. Transpulmonary pressure data for both techniques are highly influenced by variability in oesophageal pressure.

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**IS MASSIVE TRANSFUSION LINKED TO THE DEVELOPMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME?**

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**INTRODUCTION.** Massive transfusion has been considered an etiologic factor of acute respiratory distress syndrome (ARDS). However, this relationship might be due to other factors, such as shock, occurring in situations where massive transfusion is needed. We hypothesized that development of ARDS in massively transfused patients is not linked to the number of red blood cells (RBC) units received.

**METHODS.** We reviewed clinical and laboratory data of patients hospitalised from September 2000 to June 2001 who received 6 or more RBC units. Following information was sought: demographic data, number of RBC units received on admission and on the subsequent 4 days, presence of shock, occurrence and risk factors for the development of ARDS and survival. Non-parametric tests were used for continuous variables while chi-square was used for nominal ones. Data are expressed as median (25-75% percentiles). P <0.05 was needed for statistical significance.

**RESULTS.** Of 103 massively transfused patients, 10 developed ARDS (9.7%) (table). ARDS developed in each patient during the first 3 days of admission.Among potential risk factors of ARDS other than shock, trauma was significantly more frequent in massively transfused patients (p=0.008). Death was related to the presence of shock (p<0.0001) more than the number of transfused RBC units (p=0.08).

| | No ARDS (93) | ARDS (10) | p value |
|---|---|---|---|
| Age (years) | 64 (46-76) | 60 (35-68) | 0.225 |
| Sex (male) | 55 | 9 | 0.085 |
| RBC units transfused | 9 (7-14) | 11 (8-23) | 0.184 |
| Circulatory shock (%) | 38.7 | 80 | 0.011 |
| Survival (%) | 76 | 50 | 0.089 |

**CONCLUSION.** The presence of shock, and not the number of transfused RBC units, is the most important factor in the development of ARDS in massively transfused patients. A prospective study to confirm this finding would be needed.

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**QUALITY OF LIFE IN ARDS SURVIVORS**

Masclans J. R.[1], Laborda C.[2], Dela Rosa D.[3], Muñoz X.[3], Pallisa E.[4], Morell F.[3], De Latorre F.[2] [1]Intensive Care Unit, Hospital General Universitari Vall d'Hebron, Barcelona, Spain, [2]Intensive Care Unit, [3]Pneumology, [4]Radiology, Hospital General Universitari Vall d'Hebron, Barcelona

**INTRODUCTION.** Despite a great deal of information about the ARDS hypoxemic period, very little is known about the quality of life in ARDS survivors. The purpose of this study was to analyse prospectively all the ARDS survivors from our ICU, who accepted and/or been able to participate into the study, in the beginning first and six months after ARDS. We measured a Nottingham Health Profile , from the Spanish version (1).

**METHODS.** We studied in 1998-2000, 35 subjects (48±14 yrs; 51% F; n=21 at first month and n=18 the 6 months after ARDS). The questionnaire values 6 dimensions: energy, pain, emotional reaction, sleep, social privacy and physical mobility. We compared differences between 1st and 6th month with the Wilcoxon test, accepting p as significant values <0.05.

**RESULTS.** In the table 1 we present the values of each dimension and the global health quality, obtained at both period after ARDS and the differences between both values, as well as the reference values from the Barcelona's general population. These results coincided with a severe restriction in the respiratory functional test at the 1st month that improved until a ligh-moderade restriction after 6 months (2).

| | 1st month | 6th months | p (1st-6th m) | Reference |
|---|---|---|---|---|
| Energy | 44.5∂34.4 | 25.9∂11.6 | 0.28 | 14.1∂28 |
| Pain | 32.1∂15 | 16.6∂12.2 | 0.01 | 15.6∂25.9 |
| Emotion.React. | 30.7∂11.2 | 27.1∂11.6 | 0.31 | 20.8∂22.8 |
| Sleep | 46.7∂16.6 | 34.4∂13.2 | 0.04 | 23.2∂29.2 |
| Social Privacity | 30.5∂12.9 | 21.1∂9.1 | 0.22 | 7.2∂15 |
| Mobility | 54.7∂20.2 | 29.8∂21 | 0.01 | 14.9∂20.3 |
| GLOBAL | 39.9∂18.9 | 25.6∂14.5 | <0.005 | 15.5∂17.5 |

**CONCLUSION.** In summary, ARDS survivors presents at short term a poor life quality, that improve with time, but they remain for 6th months with severe alterations, basically with values relationed with the social isolation and the energy. These parameters also should been considered when we compared different therapeutic strategies, apart from the classical clinical results at short term.

**REFERENCES.** (1) Alonso J, Antó JM, Moreno C. Am J Public Health 1990; 80 (6): 704-708. (2) Masclans JR, et al. ARDS prospective survivors study follow-up. Intensive Care Med 2000; 26: S298. (Best poster award, ESICM-Rome 2000)

# Oral Presentations Poisoning/intoxication – 513-517

## 513

**SIX-YEAR REVIEW OF SELF-POISONING ADMISSIONS TO SCOTTISH INTENSIVE CARE UNITS**

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**INTRODUCTION.** Scotland has a population of around 5.1 million. Around 4% of all acute medical admissions are related to drug overdoses, with a mortality rate less than 0.5%1. Although the number of admissions for poisoning between 1997 and 2000 has declined, by approximately 10% (21,121–18,970), poisoning by narcotics and pschodysleptics has more than doubled. Paracetamol remains an important drug of misuse, accounting for 35% of all poisoning admissions in 2000. It is estimated that 55,800 individuals are misusing opiates or benzodiazepines, representing 2% of the Scottish population aged between 15 and 54 years of age2. On this background we investigated the characteristics of overdose admissions to Scottish intensive care units (ICUs).

**METHODS.** Audit data are collected prospectively for consecutive admissions to Scottish ICUs using Ward Watcher software (Critical Care Audit Ltd, Yorkshire). We identified all ICU admissions between 1995 & 2000 on a central database, admitted with a drug overdose or poisoning.

**RESULTS.** Three percent (1,374) of all ICU admissions were due to drug overdoses. The admission rate increased substantially between 1998 & 2000, with a 20% rise in 2000 compared to 1999. The rate of admissions between January & May was lower when compared with the rest of the year. The majority (70%) were admitted directly from the emergency department, however, in the last 3 years the inter-ICU transfer rate has more than doubled to over 40 transfers in 2000. The female to male ratio was 1:1. The 20 to 40 year age group accounted for 53% of admissions; 6% were older than 60 years. An ICU stay of 7 days or more was necessary in 7% of patients, however, 53% stayed in ICU less than 24 hours. Within 48 hours, 78% of all overdoses had been discharged from ICU. Intubation and ventilation was required by 85% of patients. Renal replacement therapy was performed in 34 patients (2.5%). Over the 6 years reviewed the average hospital mortality rate was 7%. Patients older than 50 years have a significantly higher mortality, of more than 12.5%, compared to less than 6% in patients younger than 30 years.

**CONCLUSION.** Although over the last 4 years the total number of drug poisoning cases in Scotland admitted to hospitals has declined it seems that more patients require intensive care treatment. This may indicate a higher incidence of more severe drug poisoning, although the overall mortality has not significantly changed over the years.

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# 514

## (GAMMA)-HYDROXYBUTYRATE OVERDOSES REQUIRING MECHANICAL VENTILATION

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**INTRODUCTION.** (Gamma)-Hydroxybutyrate also known as, sodium oxybate, GBH, and liquid ecstasy is an interesting recreational drug that is popular in the UK Dance Culture. First reported as a drug of misuse in North America in 1990, it has been available in Britain since 1994. GHB is misused for it's neurological properties, hallucinogenic, euphoric, dis-inhibition, and increased sensuality. Onset of its action is 15-30 minutes, lasting 3-6 hours, without a "hang over". However GHB can have severe respiratory, cardiac and neurological side effects with some patients rapidly progressing to respiratory arrest. 72 Deaths have been documented in the USA from 1995-2001. Recommended management of acute GHB intoxication includes prevention of aspiration, atropine for persistent symptomatic bradycardia, consideration of neostigmine as a reversal agent, and treatment for co-ingested substances.
**METHODS.** The Aim of this study is to Asses the prevalence of respiratory failure requiring artificial ventilation following (Gamma)-Hydroxybutyrate misuse in city center Manchester. Ethics committee approved this study. We accessed the ICU admission Database from three city center hospitals in Manchester from 1996-2002. All patients admitted following an episode of self-poisoning were reviewed with regards to Drug(s) of misuse. We also included patients ventilated in the Emergency Department of one hospital (Manchester Royal Infirmary) following a GHB overdose. As no routine Toxicological screen can identify the presence of GHB, confirmed cases were identified by history. Non-parametric data were analyzed using Mann-Whitney test.
**RESULTS.** 252 patients from 3 hospitals were reviewed following an episode of self-poisoning. 13 admissions were related to GHB, 12 admitted to taking GHB with 1 strongly suspicious history. All of the patients were admitted over the weekend and all required mechanical ventilation. None of the GHB patients died, the length of ICU Management was short usually <24hrs. The GHB cohort were significantly younger median age 22yrs versus 33yrs ($p<0.01$)

| | Pt(n) | Age(yrs) | Admission Date | Gender |
|---|---|---|---|---|
| All Self Poisoners | 252 | Median 33 Range 16-80 | April 00 (April 96-Mar 02) | M 130 F122 |
| GHB | 13 (5%) | Median22 Range18-40 | June 01(July 97-Mar 02) | M 10 F 3 |

Patient characteristics are as follows; time is expressed as median (range)

**CONCLUSION.** GHB is an increasing health care issue in the UK, stretching already overworked healthcare facilities. (Three patients attended one emergency department simultaneously all requiring immediate Ventilation). GHB indulgence represents a potentially life threatening event to a younger population than the usual age group for self-poisoners. Increasing popularity of GHB as a "Party Drug" has resulted in an increased incidence of adverse events. Thankful with appropriate management Death is a very rare event.

# 515

## LIQUID EXTASIS INTOXICATION: ABOUT 66 CASES IN BARCELONA

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**INTRODUCTION.** Liquid extasis or gamma-hidroxi buthiric acid is becoming a very common drug of abuse. Few articles describe this intoxication characteristics,so we decided to evaluate the clinical presentation on pre-hospitalary field.

**METHODS.** A retrospective study from January to June 2001. We studied the age, sex, weekday, hour and place of attendance, associated intoxications, symptoms, blood pressure, heart and breath rate, oxygen blood saturation, Glasgow coma scale (GCS), blood glucose measurement, pupils, and need of breath support.

**RESULTS.** During the studied period we attended 1640 intoxications, 66 of them caused by liquid extasis (4'02%). The average age was 22.25+3.7 with a male/female ratio of 2. 63 cases (94.9%) were during the week-end, all of them between 21:00 and 12:00. 39 cases (59.1%) were attended on public road, 22 (33.3%) in public places and 5 (7.6%) at home. The most frequent associated toxics were: alcohol in 34 cases (53.12%), amphetamine products in 6 (9'1%), and 2 or more different toxics in 14 (21.21%). Clinical evaluation showed low conscious level in 57 cases (86.36%), vomiting in 9 cases (13.63%) and seizures in 2 cases (3.03%). No important blood pressure alterations were observed. Sinus tachycardia was observed in 9 cases (13.6%), sinus bradychardia in 13 cases (16.7%). No other arrhytmias were seen. Blood oxygen saturation was below 95% in 8 cases (12.1%). The GCS was lower than 9 in 29 cases (43.9%), between 9-13 in 17 cases (25.8%). In 27 cases (40.9%), pupils were mydriatic. Oxygen by Ventimaskâ was needed in 13 cases (19.7%).

**CONCLUSION.** 1. Liquid extasis intoxication is frequent in our society. 2. The average patient is a young man with a low conscious level in a public road or place, during the weekend and at night time. 3. This intoxication is usually associated to others, specially alcohol. 4. Coma and mydriasis are very frequent. 5. Even if the average lifetime of the toxic is short, one should think about the possibility of orotracheal intubation as the association of vomiting and low consciousness enhance the risk of broncoaspiration.

# 516

## ECG FINDINGS, ARRHYTHMIAS AND OUTCOME IN ICU PATIENTS WITH PRESUMED ANTIDEPRESSANT INTOXICATION

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**INTRODUCTION.** A QRS interval <0.1s within six hours after admission has a high negative predictive value for adverse events after tricyclic antidepressant intoxication. It is not known however, whether this is also the case of patients with presumed intoxication who ingested several classes of drugs. In addition, there is an ongoing controversy of how long such patients should be monitored.
**METHODS.** Prospective observational study. Over a period of two years, all patients transferred to our 20-bed medical ICU with a presumed diagnosis of antidepressant intoxication were enrolled into the study. Drugs were identified by patient history, urinalysis and measurement of serum levels. ECG recordings were taken continuously. QRS prolongation was defined as >0.1s and QTc prolongation as >0.44s. All patients were prospectively followed for adverse effects in terms of mortality, arrhythmias, and duration of ICU stay. Patients were discharged after at least 12 hours of uneventful ECG monitoring.
**RESULTS.** 103 patients were enrolled. Mean APACHE II score was 9.5 (SD ± 6.0). Mixed intoxication was present in 66 (64%). Tricyclic antidepressants were identified in 88 (85%), and serotonin-reuptake inhibitors in 25 (24%) of the patients. Three patients (3%) died. Arrhythmias affected 15 (15%) patients with normal (<0.1s) and prolonged (>0.1s) QRS interval (Table). 3 patients had more than one adverse cardiac event. Significantly less cardiac events were recorded from our patients with normal QRS intervals ($p=0.03$), however arrhythmias did not exclusively occur in the presence of a prolonged QRS length. All adverse events occurred within 6 hours. Median duration of ICU stay was 1 day (range 12 hours to 6 days). No major adverse events were reported after discharge, despite the presence of a still prolonged QRS interval in 16 (16%) and QTc intervals in 62 (60%) of the patients at discharge.

| | conduction delay | torsade de pointes | ventricular fibrillation | ventricular tachycardia | supraventr tachycardia | ICUlar | all |
|---|---|---|---|---|---|---|---|
| number of adverse events | 6 | 4 | 3 | 4 | 2 | | 19 |
| QRS <0.1 | 3 | 3 | 1 | 4 | 2 | | 13 |
| QRS >0.1 | 3 | 1 | 2 | 0 | 0 | | 6 |
| QTc <0.44 | 2 | 1 | 0 | 0 | 1 | | 4 |
| QTc >0.44 | 4 | 3 | 3 | 4 | 1 | | 15 |

Adverse cardiac events in 15 of 103 patients with presumed antidepressant intoxication

**CONCLUSION.** Normal ECG recordings and QRS intervals reduce the probability of, however do not exclude, the occurrence of serious arrhythmias in ICU patients with a presumed diagnosis of antidepressant overdose. However, after 12 hours of uneventful ECG monitoring patients may be safely discharged even in the presence of a still prolonged QRS and/or QTc length.

Grant. Astra Zeneca

# 517

## AVAILABILITY OF POISONING ANTIDOTES IN THE FRENCH MILITARY HOSPITALS

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**INTRODUCTION.** Previous surveys showed a lack of availability of antidotes in various countries [1, 2]. In France, there was no study in hospitals on this subject. The aim of this survey was to evaluate qualitative and quantitative availability of antidotes in the French military hospitals.
**METHODS.** In May 2001, a questionnaire was mailed to the pharmacy directors of the 9 military hospitals. The 21 studied antidotes were selected according to the classification of the Internationnal Programme on Chemical Safety [3]. Amounts of available stocks, as well as associated costs, were noted on the day of reception of the questionnaire. Were considered insufficient, either complete lack of the antidote, or having less than the amount needed to initiate treatment of a single 70-kg patient.
**RESULTS.** The response rate was 100 %. All the questionnaires were complete. The proportion of hospitals with a sufficient stock of antidotes varied from 100% – for atropine, calcium gluconate, diazepam, flumazenil, isoprenaline, N-acetylcysteine or pralidoxime – to 0% for digoxine immune Fab. The number of antidotes stored in unsuited quantity varied from 3 (in 3 hospitals) to 11 (in 1 hospital) out of the 21 studied products. On average, 5 antidotes were not available or insufficiently stored. Glucagon was present in all hospitals but, in 56% of the cases, the available quantities would not permit to deal with b-blocking intoxication. 4 methyl-pyrazole was not found in 3 hospitals, and available in insufficient quantity to treat an intoxication with ethylene glycol in 7 hospitals. Regarding digoxine immune Fab, 22% of pharmacies hold it in a very insufficient quantity and 78% did not have it at all. The storage cost of the antidotes in our selection varied from 4150 to 17820 euros, with an average of 7480 euros for the 9 hospitals

**CONCLUSION.** The qualitative and quantitative availability of lifesaving antidotes was found to be inappropriate for a proper running of urgencies or reanimation operations in the questioned hospitals. This insufficiency was probably due to the ignorance of the antidotes and to their important cost. It is necessary to make the medical profession sensitive to the importance of an immediate and permanent availability of this type of therapeutics.

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# Oral Presentations
# Fungi are not fun guys! – 518-522

## 518

**BACTERIAL AND FUNGAL POSITIVE CULTURES IN ORGAN DONORS: CLINICAL IMPACT ON LIVER TRANSPLANTATION**

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**INTRODUCTION.** Organ transplantation from bacteremic donors is controversial. A low incidence (5%) of bacteremic donors is reported (1,2); no transmission of the isolated bacteria from the donor to the recipient is documented. We have recently extended criteria for donor selection to include patients with bacteremia. We aimed: 1) to assess the incidence of positive cultures (CP) on samples obtained from liver donors before harvesting, at harvesting and on preservation fluid (PF); 2) to determine factors related to CP in the donor, 3) to analyse the bacterial/fungal transmission from donor to recipient. 4) to verify the influence of donor culture positivity on graft and patient survival.
**METHODS.** In 481 liver donors (January 1998- October 2001), cultures results at pre-harvesting (blood, tracheal aspirate, urine), at harvesting (peritoneal swab, bile, blood) and on PF were correlated with donor age and length of stay (LOS) in intensive care unit (ICU). When a donor was CP, the recipient was screened for infection and for the microrganism. The follow-up lasted 1 month when bacteria were involved and up to 6 months when the isolates were fungi. When CP was notified, the recipient anti-microbial prophylaxis was altered to better cover the donor organism. One-year survival and retransplantation rates were determined for patients receiving livers from CP and non CP donors.
**RESULTS.** Cultures were positive in 232 of 481 (48%) donors. Age was not different between CP and non CP donors, ICU LOS was significantly longer (mean ± SD: 4.9 days±4 vs3.7±3). A pre-harvesting positive culture was present in 71 of 481(15%) donors (tracheal aspirate:54; blood:20;urine:14). C.albicans, Enterococci, E.Coli were most frequently isolated. One or more cultures at harvesting and on PF were positive in 200 of 481 (41%) donors (PF:120; blood:86; bile:27; peritoneal swab:16). Staphylococci and Fungi were most frequently isolated. Donors positive on before-harvesting cultures had a higher risk to be positive also on at-after harvesting cultures (Odd-Ratio 1.87). Only in 9 cases of CP donors (4%) there was transmission of the pathogen from the infected donor to the graft recipient. Blood and PF were most frequently responsible for transmission. No differences in one-year survival and retransplantation rates were found between patients receiving livers from CP and non CP donors.
**CONCLUSION.** Even if rare, donor to host infection transmission is proven. This could be due to the high number of culture-positive donors reported. Careful microbiological surveillance and treatment can reduce the clinical negative impact on recipent outcome. Because of the species of donor isolates, a review of the anti-microbial treatment of candidates to organ donation is recommended.
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## 519

**ASPERGILLUS SPP ISOLATION IN NON-NEUTROPENIC CRITICALLY ILL PATIENTS: EPIDEMIOLOGY, THERAPY AND OUTCOME**

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**INTRODUCTION.** To analyse the epidemiological and clinical features of Aspergillus spp isolation in tracheal aspirate of non-neutropenic critically ill patients as well as the therapeutic approach.

**METHODS.** A multicenter prospective study was conducted during a 9-months period in 73 intensive care units (ICUs), and included 1765 patients with ICU stay >7 days. Weekly, the following screening have been made: tracheal aspirate (BAS), urine, oropharynx and gastric swabs were performed and cultured. Additional tests were carried out depending on patients' symptoms. At the admission to the ICU and at the initiation of antifungal therapy, severity of illness was evaluated by APACHE II score. Retrospectively, isolation of Aspergillus spp as colonisation if the patient did not fulfil criteria of pneumonia, and as infections if the patient gather criteria of pulmonary infection and the clinician in charge considered the isolation as clinically valuable. Risk factors, antifungal use and duration of therapy were noted. Results of necropsy in available cases are also reported. Results are expressed as mean (standard desviation).

**RESULTS.** Aspergillus spp was isolated in 36 patients: 14 were classified as colonisation (COL), 20 as infections (INF) and 2 as undetermined. Mean age: 58.7 (16.6) years. APACHE II score 21.6 (6.9). Length of ICU stay prior to isolation: 32.1 (21.4) days. Underlying diseases: COPD 16, corticosteroids therapy 10, renal dysfunction 10. In COL group, 4 patients died in the ICU. Three patients were treated with Amphotericin B Liposomal. In INF group, all patients received antifungal therapy although in seven cases another pathogen was also isolated in respiratory sample. APACHE II score at the initiation of therapy was 28.61 (range 11-45). Amphotericin B deoxycolate was administered in 8 cases, Amphotericin B Liposomal in 8 patients, Amphotericin B lipid complex in 3 cases and itraconazole in 1 patient. Mean duration of treatment was 12 days. ICU mortality was 65% (13 patients). Necropsy was performed in six of these patients and invasive aspergillosis was confirmed in all cases.

**CONCLUSION.** Aspergillus spp isolation in respiratory samples of non-neutropenic critically ill patients, especially COPD and corticosteroids therapy, with infectious clinical symptoms might be considered and early treatment should be initiated. Mortality remains very high what may be justified by the underlying severity of illness.

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**CANDIDA SEPTICAEMIA AND MORTALITY ON SEVERE BURN PATIENTS: WHEN TO START ANTIFUNGAL THERAPY**

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**INTRODUCTION.** Burn patients are at a great risk of fungal infection due to loss of the skin barrier. Several recent reports have suggested that Candida sepsis is major complication of severe burn injury (1).

**METHODS.** During a three year period (1999-2001), consecutive adult burn patients admitted to polyvalent intensive care unit (ICU) were studied. The general data recorded for each patient included: age, sex, SAPS II and SOFA on admission, percentage of total body surface area burned (% TBSA), length of ICU stay (LOS), ICU and hospital mortality. Blood, wound, urine samples and distal bronchial samplings were collected on admission and at least twice a week after that. Candida septicaemia (CS) was diagnosed on the basis of clinical signs of sepsis and by the presence of positive blood culture for Candida species. Data was analysed using Student's t-test ($p<0.05$).

**RESULTS.** Twenty-nine adult burn patients were admitted to the ICU (18 male, 11 female). Their mean age was 53.8±19.9; they had a mean of percentage of TBSA burned of 50±23; the SAPS II and SOFA on admission were respectively 30.5±15.5 and 3.9±3.8. Six of the burn patients developed CS (20.6%). The first positive blood culture for Candida species occurred 35.1±20.8 days on admission. Before the beginning of the CS, these patients had a greater number of positive wound samples for Candida species than the patients without CS (4/6 vs 1/23); also we noted an important difference in positive urine samples (4/6 vs 2/23). On the contrary, in the burn patients without CS quite a lot of distal bronchial samplings was positive (5/23). Even, the patients with CS had a longer LOS than the others (62.3±30 vs 12±9.8, $p<0.05$); their ICU and hospital mortality were greater than patients without CS (66.6% vs 39.1% and 66.6% vs 52.1%, respectively).

**CONCLUSION.** According to international literature (2), we conclude that sepsis due to Candida infection increases the mortality on severely burn patients. It emerged from the study that is preferable to start antifungal therapy when at least one positive wound sample for Candida species appears, because there is an elevated incidence of hematogenous infection; moreover, it's important to consider positive urine samples for yeasts. On the contrary, in presence of positive bronchial sampling, the antifungal therapy is questionable.

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## 521

**YEAST COLONISATION AND INFECTION IN PATIENTS WITH MODS: A ONE YEAR PROSPECTIVE OBSERVATIONAL STUDY**

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**INTRODUCTION.** Infection and infection control are main issues in intensive care medicine. Former studies have shown that the prevalence of yeast infection may reach 17% [1]. However, it may vary from one ICU to another due to case mix and antibiotic use. It is known that progressive colonisation can lead to infection. The present study was conducted to determine yeast colonisation and to explore to which extend this colonisation results in infection.

**METHODS.** A prospective observational study was carried out over 12 months in an 11 bed mixed medical – surgical ICU. All patients admitted were included but we restricted our analysis to the microbiology data derived from patients with multi organ dysfunction syndrome (MODS). Cultures were taken from throat, rectum, and trachea twice weekly. Urine cultures were taken on admission and when indicated. The presence of yeast Infection was defined as described by Pelz [2]. All other yeasts were categorised as colonisation. Comparison of groups was performed with the Chi-square test.

**RESULTS.** 529 patients were included. 5050 cultures were taken from 265 mechanically ventilated patients. The mean APACHE II was 19.4. 177 patients were colonised with yeasts (68%). Yeasts were found in 928 cultures (521 albicans, 373 species, 24 tropicalis, 6 krusei, 5 other). The location of these yeasts were rectum 288, throat 274, tracheal 252, abdomen 35, urine 33, wounds/other 34, blood 2, lines 2, bile 1. The cumulative incidence of yeast infection in colonised patients was 10% (18/177): 16 peritonitis, 1 bile infection and 1 line infection. Of these infections 14 were c. albicans, 1 c. species and 3 mixed types of candida. Infected patients had significantly more colonised sites compared to non-infected patients ($p<0.001$). Infected patients had a Relative Risk of mortality of 1.3 (95% CI 0.76-2.2) compared to non-infected patients. The ratio of the length of ICU stay of infected to non-infected patients was 2.56 (95% CI 1.85-3.44).

**CONCLUSION.** Two thirds of patients with MODS are colonised with yeasts, however, yeast infection was relatively uncommon compared to former published studies. Majority of infections were candida albicans. Infected patients had significantly more colonised sites, significantly longer ICU stay and a trend towards higher mortality.

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## 522

**RISK FACTORS FOR CANDIDURIA IN ICU PATIENTS**

Alvarez-Lerma F.[1], Nolla J.[2], Benazzouz M.[2], Josic Z.[2] [1]Intensive Care Medicine, Hospital del Mar, Barcelona, Spain, [2]Intensive Care Medicine, Hospital del Mar, Barcelona

**INTRODUCTION.** Objective: To define the characteristics of critically ill patients with candiduria and to determine risk factors facilitating candiduria.

**METHODS.** Prospective, cohort, observational, and multicenter study. Urine cultures were performed once a week to all patients admitted to the ICU. Samples were processed at the different clinical microbiology laboratories of the participating hospital using specific culture medium (Sabouraud) and the BACTEC technique and the A20C (Biomerieux) system for the identification of species. Candiduria was defined as < 104 CFU of Candida spp. in the urine. Demographic features, clinical data (underlying and associated disorders), risk factors, and previous treatments were recorded for each patient. Independent risk factors associated with candiduria were assessed by logistic regression analysis of statistically significant variables in the univariate analysis.

**RESULTS.** RESULTS. A total of 1765 patients admitted > 7 days to the 70 participating ICUs between May 1998 to January 1999 were included in the study. One ore more Candida spp. in the urine were recovered in 389 (22%) patients. Independent risk factors associated with candiduria were previous use of antibiotics (OR 2.48, 95% CI 1.03 to 6.01, P=0.043); female gender (OR 2.35, 95% CI 1.86 to 2.99, P<0.001); age >65 years (OR 1.47, 95% CI 1.15 to 1.86, P=0.001); diabetes mellitus (OR 1.86, 95% CI 1.37 to 2.54, P=0.001); previous stay in hospital (OR 1.01, 95% CI 1.003 to 1.02, P=0.007); mechanical ventilation (OR 2.73, 95% CI 1.5 to 5.0, P=0.01); and total parenteral nutrition (OR 1.82, 95% CI 1.43 to 2.32, P<0.001).

**CONCLUSION.** Conclusions: A clinical profile of the critically ill patient with candiduria has been described. Most risk factors for candiduria cannot be modified.

**REFERENCES.** EPCAN Group

## 524

**BOMBESIN & BRONCHIAL IGA IN ICU PATIENTS UNDER ENTERAL & SHORT TERM TOTAL PARENTERAL NUTRITION**

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**INTRODUCTION.** The purpose of the study was to examine the influence of enteral (EN) and short term total parenteral nutrition (STTPN) on the serum Bombesin (BN) and on the bronchial IgA in critically ill patients.

**METHODS.** Sixteen ICU patients who received STTPN and seventeen patients, who received EN were included in the study. Both groups were matched for age and severity of illness. Serum BN and bronchial IgA levels were measured on the 1st and 5th ICU hospitalization day. The differences between the first and the second measurement for the BN and the IgA were expressed as % of the first measurement (% BN & % IgA). The correlation between % BN and % IgA was investigated with the aid of simple linear regression for each group. Comparisons between the two groups for the % BN and the % IgA were done with the aid of t-test (p=0.05).

**RESULTS.** Values of BN (ngl/ml), IgA levels, % BN and % IgA as mean values ± standard deviations in the 2 groups of patients are presented in the following table:
There is a significant correlation between % BB and % IgA in the STTPN (r=0.78, p<0.001) as well as in the EN groups (r=0.67, p=0.002). The % BN and % IgA did not differ significantly between groups (p>0.05).

| | STTPN group | | | EN group | | |
|---|---|---|---|---|---|---|
| | 1st measurement | 2nd measurement | d | 1st measurement | 2nd measurement | d |
| BN | 9.7±9.14 | 11.4±10.10 | -134.8±254.92 | 8.5±9.03 | 13.0±11.07 | -236.7±350.37 |
| bronchial IgA | 8.0±3.07 | 4.6±2.69 | 27.5±58.77 | 7.6±2.07 | 7.7±2.31 | -14.3±61.56 |

**CONCLUSION.** The present study confirm that BN is a crucial factor for upper respiratory tract immunity. Our results show a strong correlation between the serum levels of BN and the bronchial IgA levels in both the STTPN and EN groups. It is clinically important that STTPN, which is very often used during ICU hospitalization does not induce a significantly different influence on serum BN and bronchial IgA.

**REFERENCES.** Janu PG et al Effect of bombesin on impairment of upper respiratory tract immunity induced by total parenteral nutrition. Arch Surg. 1997;132: 89-93.

# Oral Presentations Nutrition (I) – 523-527

## 523

**PULMONARY HISTOPATHOLOGIC EFFECTS OF LIPID CONTENT OF ENTERAL SOLUTIONS AFTER ASPIRATION IN RATS**

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**INTRODUCTION.** High lipid content of aspirated enteral formulas has been shown to cause lipoid pneumonia in children(1). The aim of this study was to compare the pulmonary histopathologic effects of different enteral solutions with various lipid contents after aspiration.

**METHODS.** The study protocol was approved by the institutional animal care ethic committee. Fifty, Wistar Albino rats weighing 180-300 g were randomly divided into 5 groups(n=10). Anesthesia was induced with ketamin 100 mg/kg intraperitoneally. After endotracheal intubation,in group I 0.9% saline, group II Impact, group III Jevity, group IV Biosorb energy plus, group V Pulmocare with lipid contents 0,28,39,58 and 93 g/dl respectively were injected into the lungs in a volume of 3 ml/kg. 7 days later, after intraperitoneal ketamin administration, bilateral toracal incisions were performed and rats were sacrificed by intracardiac 10% formalin injection. The lungs were removed as a whole, fixed in 10% formol and were assessed histopathologically by a blind pathologist. The lung specimens were examined for the existence of peribronchial inflammatory infiltration, alveolar septal infiltration, alveolar edema, alveolar exudate, alveolar histiocytes, interstitial fibrosis, granuloma formation, necrosis and the severity were cathegorized with a four point scale. One way ANOVA and Student-Newman-Keuls tests were used for statistical analysis(p<0.05).

**RESULTS.** Peribronchial inflammatory infiltration was present in all groups but was significantly more severe in Impact group than control, Biosorb and Pulmocare groups(p<0.05). Alveolar edema was significantly higher in only Impact group compared with control(p<0.05). Alveolar septal infiltration was significantly higher in Biosorb group compared with control. Alveolar histiocytes were significantly higher in Impact, Jevity(p<0.05) and Biosorb, Pulmocare groups(p<0.05) compared to control.

**CONCLUSION.** The pulmonary histopathologic effects of Impact aspiration were severe peribronchial inflammatory infiltration and higher alveolar histiocytes, alveolar edema compared with control group although Impact has the lowest lipid content. We suggested that the antioxidant beta-karoten in Pulmocare with the highest lipid content may have protective effects against inflammation and fibrosis but further studies are needed.

**REFERENCES.** 1)Wolfson BJ, Allen JL, Panitch HB, Karmazin N. Lipid aspiration pneumonia due to gastroesophageal reflux. Pediatr Radiol 1989;19(8);545-47.

## 525

**DYSPHAGIA FOLLOWING INTENSIVE CARE: EFFECT OF TRACHEOSTOMY AND DURATION OF VENTILATION**

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**INTRODUCTION.** Long term complications of ICU tracheostomy have not been fully investigated (1). Previously our group has reported dysphagia in 10% of ICU survivors (2). This was associated with chest infections following discharge. The aim of this study is to identify airway related risk factors for dysphagia. We will also compare percutaneous and surgical tracheostomy.

**METHODS.** A prospective observational study based in the ICU follow up clinic of a teaching hospital. All patients are invited to attend clinic 3 months after ICU discharge. We reviewed consecutive patients attending clinic between June 1999 and Oct 2001.The method of tracheostomy and duration of ventilation with oro-tracheal or tracheostomy tube was noted. Patients were asked to report any changes in swallow. Non parametric data were analysed using Fisher's exact test.

**RESULTS.** 205 ICU survivors were seen. 37 were never intubated (median length of stay mLOS 2.06d), 81 had endotracheal intubation only (mLOS 3.5d) and 87 had tracheostomy (mLOS 21.4d). The method of tracheostomy was surgical in 32 and percutaneous serial dilatation in 55 patients. 19 (9%) reported problems swallowing since discharge. 16 of these were in the tracheostomy group (p=0.01). 8 had percutaneous and 8 had surgical tracheostomy. The length of stay in both tracheostomy groups was similar: median 17 days for surgical and 19 days for percutaneous.

| | Total | Not Intubated | Intubated orally only | Tracheostomy |
|---|---|---|---|---|
| Number of Patients | 205 | 37 | 81 | 87 |
| Problems swallowing | 19 | 0 | 3 | 16* |
| Length of stay median | 5 | 1 | 2 | 19 |
| Length of stay range | 1 to 88 | 1 to 9 | 1 to 29 | 1 to 88 |

Swallowing Problems following ICU

**CONCLUSION.** Swallowing problems following ICU stay are common. This will imapct upon delivery of nutrition and risk of nosocomial pneumonia. Dysphagia in ICU patients may be related to prolonged intubation and / or tracheostomy. The method of tracheostomy does not seem to influence the incidence of dysphagia.

**REFERENCES.** 1. Susanto I Comparing percutaneous tracheostomy with open surgical tracheostomy BMJ 2002;324:3-4 editorial 2. Conway DH, Dawson S, McJannett L Eddleston J. Chest infection following intensive care. Intensive Care Medicine Vol 27 Supplement 2 S191

## 526

**THE COMPARISON OF THREE DIFFERENT METHODS USED FOR THE ASSESSMENT OF NASODUODENAL TUBE POSITION**

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**INTRODUCTION.** The aim of this study was to compare the methods used for the assessment of nasoduodenal tube position in critically ill patients according to the success rate; time spent to successful placement and cost effectivity.

**METHODS.** The study population consisted of 56 critically ill patients aged 20-70 years, with ASA II-III status, with institutional ethic committee approval and patients' written consent. They were scheduled for a nasoduodenal tube placement and divided in 3 groups. The assessment of the locaton of the nasoduodenal tube was done by the auscultation of the loudest sound in the epigastrium in the first group(A), by the pH determination of the duodenal aspirate in the second group(pH)and via fluoroscopic view in the third group(F). The place of the tube was confirmed with an abdominal X ray. The failure criteria was the placement of the tube in the stomach in all groups, the necessity of having more than two abdominal X rays in (A) and (pH); and the duration of fluoroscopy more than 10 minutes in (F). The success rate and the total finance of all groups were determined and compared statistically with one-way ANOVA and Fisher's exact test.

**RESULTS.** There was no difference in demograpfic characteristics of patients between groups. The success rate was significantly higher in fluoroscopy group (A=60%, pH=55%, F=93.75) and there was no statistical differences between groups concerning the total cost. The time to successful placement of the tube was significantly shorter in fluoroscopy group.

**CONCLUSION.** For patients with high aspiration risk and requiring immediate nutritional support, the placement of the nasoduodenal tubes fluoroscopically should be preferred because it is more successful, quicker and cost effective than the other methods.

**REFERENCES.** Welch SK, Hanlon MD. Comparison of four bedside idicators used to predict duodenal tube placement with radiography. JPEN J Parenter Enteral Nutr 1994 Nov-Dec; 18(6):525-30

## 527

**EFFECT OF IMMUNONUTRITION ON INTESTINAL MUCOSAL APOPITOSIS AND ATROPHY IN HEAD INJURED RATS**

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**INTRODUCTION.** Intestinal mucosa displays metabolic, endocrine, and immunologic function and serves as a major local defense barrier, preventing intraluminal bacteria and endotoxins from migrating to extraintestinal tissues and entering systemic circulation(1). In animal models of shock and trauma were demostrated apopitotic cell death in gastrointestinal associated lymphocytes and intestinal epitelial cells(2). In this experimental study, we assessed the effect of immunonutrition for the prevention of mucosal atrophy and apopitosis in the intestine in experimentally induced head injured rats.

**METHODS.** Following moderate closed head injury,twenty-seven rats were randomized into four groups. Deprived from access to food and water for 24 hours the 1st group (Group1, n=7) intook immunonutrition (Stresson; Nutricia), 2nd group(Group2, n=7) intook standard enteral nutrition (Biosorb;Nutricia), and 3rd group(Group3, n=7) intook TPN, and 4th group (Group 4,n=7) intook parenteral salin (Malnutrion) respectively for seven days. The rats were sacrified and removel of the segments of the jejenum and ileum for microscobic examination.Villus height, count of villi intestine, and apopitotic index were measured.Data were analysed by Kruskal-Wallis and Mann Whitney-U tests, $p<0.05$ and $p<0.008$ were considered significant respectively.

**RESULTS.** In Group 1 and Group 2 villus height and villus count were significantly higher, and apopitotic index counts were significantly lower than Group 3 and Group 4($p<0.05$). In Group 1 villus counts were significantly higher, and apopitotic index counts were significantly lower than Group 2($p<0.05$).The difference in intestinal villus count and villous height of the group 3 and 4 were not statistically significant($p>0.05$), but apopitotic index counts in group3 were significantly lower than the group of 4($p<0.05$).

| | Villus Height (mm) | Villus Count | Apopitotic Index |
|---|---|---|---|
| Group 1(Immunonutrition) | 0.39±0.17* | 69±14.35* | 2±0.82* |
| Group 2(Standart enteral nutrition) | 0.27±0.08* | 39.43±12.31* | 4.86±1.95* |
| Group 3 ( TPN) | 0.19±0.13 | 23.57±10.75 | 8.71±1.38* |
| Group 4 (PE Saline) | 0.14±0.15 | 13.50±1.65 | 11.29±8.06 |

**CONCLUSION.** The experimentally model allowed to show that the enteral immunonutrition prevents atrophy of the intestinal mucosa and apopitotic cell death in brain injured rats when compared with standart enteral nutrition and TPN protocols.

**REFERENCES.** 1)Deitch EA.Arch Surg 1990,125:403-434. 2)Xu YX.,Ayala A.,Monfils B. Et al: J Surg Res 1997;70:55-60.

# Oral Presentations
# Pathomechanisms of sepsis: Experimental approaches – 528-532

## 528

**ANGIOPOIETIN1 INHIBITS ENDOTHELIAL PERMEABILITY AND NEUTROPHIL ADHERENCE INDUCED BY $H_2O_2$ OR THROMBIN**

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**INTRODUCTION.** Angiopoietin-1 (Ang1) is a growth factor that selectively binds to the vascular endothelium and inhibits vascular permeability *in vivo*. We investigated whether Ang1 can counteract the effects of various inflammatory mediators on endothelial barrier function and whether it prevents neutrophil (PMN) adherence to endothelial cells (EC), *in vitro*. Since several inflammatory agents promote reactive oxygen species (ROS) release from EC, we also determined whether Ang1 affects ROS-mediated increases in PMN adherence.

**METHODS.** The cells used were immortalized human umbilical vein endothelial cells (EA.hy 926 cells). For permeability experiments, tight monolayers on porous filters were exposed to Ang-1 or solvent, before adding inflammatory stimuli. Horseradish peroxidase (HRP) was added to the apical side, and its passage into the basolateral compartment was then quantified by colorimetry. For neutrophil adherence experiments, human neutrophils (PMN) were isolated from whole blood. Confluent EC were incubated with Ang-1 or solvent, before adding inflammatory stimuli and PMN. Adherent PMN were quantified by measuring the activity of myeloperoxidase by colorimetry.

**RESULTS.** Monolayers pretreated with Ang1 displayed a reduced increase in permeability when challenged by either by PAF (62.5±5.7 % of the permeability seen in the absence of Ang1, mean±SEM of 13 samples from 4 exp, $p<0.001$), bradykinin (64.2 ± 7.9 %, 6 samples from 2 exp, $p<0.01$), histamine (67±4.1 %, 11 samples from 3 exp, $p<0.001$), as well as thrombin (62.7±6.6 %, 8 samples from 2 exp, $p<0.01$). Whereas Ang1 did not affect the number of PMN adhering to EC in response to histamine, PAF, or TNFa, PMN adherence was lower in Ang1-treated cells in response to thrombin (74.4±2.1 %, 26 samples from 7 exp, $p<0.001$), or $H_2O_2$(61.4 ± 2.6 %, 26 samples from 7 exp, $p<0.001$), suggesting that Ang1 has the potential to prevent oxidative stress-induced damage.

**CONCLUSION.** We conclude that Ang1 selectively inhibits PMN adherence in response to specific mediators, whereas it can counteract the increase in transendothelial permeability induced by a range of edemagenic agents.

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**EFFECTS OF EPIDURAL ANAESTHESIA ON SPLANCHNIC OXYGENATION DURING ENDOTOXAEMIA**

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**INTRODUCTION.** Previous studies revealed, that systemic endotoxaemia is accompanied by early disturbance of splanchnic perfusion and mucosal hypoxia. The aim of this study was to assess, whether a reduction of regional sympathetic activity induced by thoracic epidural anaesthesia has a protective effect on mucosal oxygenation.

**METHODS.** Following approval by the local animal ethics committee 22 anaesthetised, ventilated and acutely instrumented pigs (catheterisation of epidural space with catheter tip at T 8/9, pulmonary artery, portal vein, hepatic vein and femoral artery catheter, ultrasound flowprobes around superior mesenteric artery, hepatic artery and portal vein, intestinal tonometer and $pO_2$-electrode onto liver, intestinal serosa and mucosa) were randomly assigned to 2 groups (group 1: intraportal endotoxine application; group 2: epidural anaesthesia before intraportal endotoxine application). Following baseline measurements 0.75 ml /segment bupivacaine 0.5% were injected into the epidural catheter, aiming for a block T5 to T12 in group 2; both groups received 0.5 mg/kg/h endotoxine into the portal vein. Measurements were repeated hourly up to 6 hours.

**RESULTS.** Animals of group 1 confirmed results of previous studies with biphasic decrease of splanchnic blood flow and mucosal oxygenation. All animals survived the whole time of the experiment despite increases of systolic pulmonary artery pressure up to 80 mmHg. All animals of group 2 died during the increase of pulmonary artery pressure showing signs of right heart decompensation (increase of central venous pressure). Effects regarding splanchnic perfusion could not be determined.

**CONCLUSION.** Reduced regional sympathetic activity of the splanchnic region induced by epidural anaesthesia increased mortality during induced endotoxaemia. Besides blocking sympathetic supply to liver and gut the thoracic epidural anaesthesia blocks the adrenal glands. Possibly a missing supply with catecholamines from the adrenal glands might play a pivotal role during the increase of the pulmonary artery pressure leading to right heart decompensation. With regard to perioperative endotoxaemia great care should be taken when using supplementary epidural anaesthesia for major abdominal operations.

**REFERENCES.** Nöldge-Schomburg et al.: Intensive Care Med 1996; 22: 795-804.

## 530

**MONITORING OF LYMPHOCYTE NF-KB ACTIVATION BY FLOW CYTOMETRY**

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**INTRODUCTION.** The activity of the nuclear factor kB (NF-kB) has been demonstrated to be a predictive value for the survival of patients with sepsis. NF-kB activity is higher in non-survivers(1). Our aim was to evaluate the use of flow cytometry for monitoring NF-kB acitvation in a clinical setting.

**METHODS.** Inactive NF-kB is present in cells as a heterodimer consisting of a p50 and a p65 subunit stabilized by the inhibitory IkB. For analysis we chose an antibody directed against the nuclear location signal of p65 which is demasked by activation. After lysis and permeabilisation of human whole blood, active p65 is labelled by anti-p65. The number of positive cells is quantified using flowcytometry, and the mean activation level is obtained as mean fluorescence intensity in reference to unspecific antibody binding. The presence of active p65 in leukocyte subopulations is determined by forward/sideward scatter gating and or co-labelling with a subpopulation-specific surface marker.

**RESULTS.** Analysis of lymphocytes from healthy donors revealed a low basal activity of >95% of the cell population. Stimulation with lipopolysaccharide (LPS) resulted in an increased fluorescent signal, indicating further demasking of the nuclear location sequence of p65. NF-kB activation was confirmed by confocal laser microscopy. LPS stimulation resulted in an increased overall fluorescence signal and a translocation of the p65 subunit into the nucleus.

**CONCLUSION.** The method enables rapid and non-radioactive assessment of NF-kB activation in lymphocyte subsets.. The assay may be a useful tool for monitoring the immune system in septic patients.

**REFERENCES.** (1) BohrerH et al.: Role of NFkappaB in the mortality of sepsis. J. Clin. Invest. 1997, 100:972-985

Grant. BONFOR

## 531

**ROLE OF ALVEOLAR MACROPHAGES IN ENDOTOXIN-INDUCED LUNG INJURY**

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**INTRODUCTION.** Alveolar macrophages (AM) play an important role during the development of acute lung inflammation (1). To assess the role of AM in endotoxin-induced lung injury, selective AM depletion *in vivo* was performed and cellular and molecular characteristics were analyzed.

**METHODS.** 300g male Wistar rats were anesthetized and dichloromethylene diphosphonate-($Cl_2$MDP)-liposomes as phagolysozymes or control liposomes were applied intratracheally. After 72 hours, 150mg lipopolysaccharide (LPS) was instilled into lungs and inflammatory reaction was assessed 4 hours later. Pulmonary vascular system was flushed and lungs were lavaged four times with cold phosphate-buffered saline (PBS). Cells in bronchoalveolar lavage (BAL) were analyzed by Diff-Quick, neutrophil content by determination of myeloperoxidase (MPO). Whole lung mRNA for tumor necrosis factor-a (TNF-a) interleukin-1b (IL-1b), macrophage inflammatory protein-1b (MIP-1b), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) was assessed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) using a kit (Perkin-Elmer, Branchburg, NJ).

**RESULTS.** After intratracheal instillation of LPS for 4 hours a 320% increase of cells was observed in depleted LPS-animals compared to LPS-animals with AM. Thereby, Diff-Quick-staining showed an almost exclusive recruitment of neutrophils. The additional measurement of MPO-activity confirmed these results. Whole lung mRNA for TNF-a, IL-1b, MIP-1b and MCP-1 of depleted LPS-animals were decreased compared to non-depleted LPS-animals. Expression of the adhesion molecules ICAM-1 and VCAM-1 demonstrated no significant difference between non-depleted and AM-depleted LPS-animals.

**CONCLUSION.** These data suggest that AM are the main effector cells and fulfil a dominant role in early endotoxin-induced lung injury concerning neutrophil recruitment and inflammatory mediators.

**REFERENCES.** (1) Broug-Holub E. et al. Alveolar macrophages are required for protective pulmonary defenses in murine Klebsiella pneumonia: elimination of alveolar macrophages increases neutrophil recruitment but decreases bacterial clearance and survival. Infect Immun 1997; 65: 1139-46.

Grant. Gebert Ruef Stiftung, Switzerland, Swiss National Science Fondation

## 532

**MITOCHONDRIAL DYSFUNCTION IN A RODENT MODEL OF SEPSIS AND MULTI ORGAN DYSFUNCTION**

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**INTRODUCTION.** We have previously demonstrated in human septic shock that mitochondrial dysfunction may be an important mechanism in the pathogenesis of multiple organ dysfunction syndrome (MODS)1. We are attempting to simulate these findings in a long-term rodent model of faecal peritonitis and MODS.

**METHODS.** Adult male Wistar rats were anaesthetized, cannulated and allowed to recover. They were attached to a tether system allowing unimpeded movement around their cage, continuous haemodynamic monitoring and fluid resuscitation. Sepsis was induced the following day with an i.p. injection of a faecal suspension, followed by fluid resuscitation two hours' later. The rats were sacrificed at 24, 48 or 72 hours, at which timepoints clinical severity of illness was scored and blood sampled for liver function tests. Hepatic tissue was taken for analysis of mitochondrial respiratory chain activity (complex I and IV) and histology. Comparison was made against sham operated controls.

**RESULTS.** Clinical illness severity (mild, moderate, severe) matched the degree of biochemical and mitochondrial dysfunction, and histological damage. Complex I activity fell with increasing severity whereas Complex IV rose. The table is illustrative of these changes at 24 hours (mean and (standard error)), demonstrating significant decreases in complex I activity in the moderate and severely affected animals compared to shams ($p<0.05$ and $p<0.005$ respectively, ANOVA) .

| | Sham n=13 | Mild n=8 | Moderate n=8 | Severe n=9 |
|---|---|---|---|---|
| Complex I activity | 0.26 (0.01) | 0.24 (0.02) | 0.021 (0.01) | 0.19 (0.01) |
| Complex IV activity | 0.020 (0.001) | 0.020 (0.001) | 0.021 (0.002) | 0.023 (0.001) |

**CONCLUSION.** This rodent model replicates many features of human sepsis. The changes in liver mitochondrial activity mirror those we found in skeletal muscle in septic patients, suggesting that 'vital' organs are similarly affected. The association between organ and mitochondrial dysfunction enable us to use this model to verify the bioenergetic failure hypothesis and test putative therapies.

**REFERENCES.** 1.Brealey D et al. Intensive Care Med. 2001; 27: S137.

Grant. Wellcome Trust and Medical Research Council

# Oral Presentations Nephrology – 533-537

## 533

**RENAL DYSFUNCTION AND ABDOMINAL HYPERTENSION AFTER LIVER TRANSPLANT**

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**INTRODUCTION.** Intra-abdominal pressure (IAP) measurement in the critical ill regained of interest recently.Subjects undergoing Orthotopic Liver Transplantation (OLT) are at risk for abdominal hypertension (IAH) in the perioperative period, when their renal function can be frequently threatened.We assessed any possible association between IAH and renal dysfunction in the days immediately following OLT

**METHODS.** This study involved a population of consecutive OLT recipients.A preoperative renal impairment was considered exclusion criteria.IAP was measured every 8 hours for the first 3 post-operative days with the urinary bladder technique.Renal function was evaluated by the patients hourly urinary output,serum creatinine,measured on the second and fourth post-operative days and daily Filtration Gradient (FG).Generally accepted definition for acute renal failure (ARF) was used and it was considered to be potentially related to increased IAP if they occurred within 48 hours of each other.After completion of the study those with a persistent (at least 2 consecutive measurements) IAH (defined as IAP equal or greater than 25 mmHg) were grouped together (group H) as were those with normal or only sporadically elevated IAP (group N).Statistical analysis included the Pearson's and Yates's $c^2$ tests and the t test for unpaired data;a forward stepwise logistic regression analysis was used to evaluate the effect of predetermined risk factors on renal function. Significance was set at the 0.05 level.

**RESULTS.** Our population consisted of 108 recipients transplanted because of a terminal liver disease. Thirty-four subjects (31.5%) showed a persistently elevated IAP (group H) whereas it was within or only seldom above 25 mmHg in the remaining 74 (group N). ARF occurred in 17 recipients (15.7%): 11 from Group H and 6 from group N ($p<0.01$).Subjects with ARF had a greater mean IAP value then those without it ($p < 0.001$).Mean serum creatinine was higher in group H ($p<0.01$);mean hourly urinary output did not differ in the two groups ($p=0.2$) but patients with IAH received more frequently loop diuretics to maintain an adequate diuresis ($p<0.001$) despite larger amounts of IV fluids ($p<0.01$) and showed a reduced daily FG ($p<0.01$).The two groups did not differ relating to hemodynamic parameters or the need for inotropic drugs. Intraoperative blood transfusions greater then 15 units,respiratory failure and IAH were significantly and independently associated to renal impairment ($p<0.01$). ICU length of stay was similar in the two groups ($p=0.02$) but patients with IAH had a worst ICU outcome ( $p<0.05$)

**CONCLUSION.** IAH may be frequent after OLT and represents a serious and indipendent risk factor for renal failure during its early postoperative course. In our experience this threat was not prevented by intravenous fluids extra-loading and by stable and adequate hemodynamic parameters. Frequent IAP monitoring should be considered in OLT recipients

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### ASSOCIATED ORGAN FAILURE HAS A GREATER IMPACT THAN SEVERITY OF ACUTE RENAL FAILURE IN ICU PATIENTS

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**INTRODUCTION.** A proposal was made to distinguish between different degrees of acute renal failure in the intensive care unit (ICU). (1) Acute renal injury (ARI) was defined as serum creatinine > 120 and < 240 umol/L, urea > 8 and < 16 mmol/L, and / or urine output between 400 and 800 ml/24hrs; acute renal failure syndrome (ARFS) was defined as serum creatinine > 240 umol/L, urea > 16 mmol/L and urine output < 400 ml/24hrs; patients who needed renal replacement therapy in the presence of ARI or ARFS were classified as having severe acute renal failure syndrome (SARFS). This study aims to analyse whether outcome is different in patients with ARI, ARFS and SARFS, and whether degree of renal failure has a greater impact on outcome than associated maximum organ failure.
**METHODS.** We analysed the RIPUG database which contains the data of 26,689 patients admitted to 21 ICUs in the United Kingdom between June 1989 and September 1996.
**RESULTS.** Table 1 a) Outcome of patients with ARI, ARFS or SARFS and b) ICU mortality in patients with ARI, ARFS or SARFS alone compared to patients with ARI, ARFS or SARFS in combination with other failed organs
Relative risk of ICU mortality among patients with ARI + organ failure versus patients with ARI alone: 9.4 Relative risk of ICU mortality among patients with ARFS + organ failure versus patients with ARFS alone: 6.3 Relative risk of ICU mortality among patients with SARFS + organ failure versus patients with SARFS alone: 3.6

| | ARI (n=5130) | ARFS (n=3243) | SARFS (n=1025) | ARFS vs ARI | SARFS vs ARI |
|---|---|---|---|---|---|
| ICU mortality | 19.9 % | 41.9 % | 49.9 % | p<0.001 | p<0.001 |
| Hospital mortality | 30.5 % | 53.5 % | 59.2 % | p<0.001 | p<0.001 |

| | ARFS | ARI | p-value and RR | SARFS | ARI | p-value and RR |
|---|---|---|---|---|---|---|
| Number of patients | Only ARFS: 779 | Only ARI: 1831 | | Only SARFS: 95 | Only ARI: 1831 | |
| ICU mortality | 8.3% | 3.1 % | p<0.001; RR 2.7 | 14.7 % | 3.1 % | p<0.001; RR 4.7 |
| Number of patients | ARFS+OF: 2464 | ARI+OF: 3299 | | SARFS+OF: 930 | ARI+OF: 3299 | |
| ICU mortality | 52.5 % | 29.3 % | p<0.001; RR 1.8 | 53.4 % | 29.3 % | p<0.001; RR 1.8 |

OF = organ failure; RR = relative risk

**CONCLUSION.** In ICU patients with acute renal failure associated organ failure has a greater impact on mortality than the degree of renal failure.
**REFERENCES.** 1. Bellomo R et al. Acute renal failure: time for consensus. Intensive Care Med 2001;27:1685-1688

## 535

### PROPHYLAXIS OF CONTRAST-INDUCED NEPHROPATHY: ACETYLCYSTEINE, THEOPHYLLINE OR BOTH-A RANDOMIZED STUDY

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**INTRODUCTION.** The incidence of contrast-induced nephropathy (CIN; definition: increase in serum creatinine of >=0.5mg/dl within 48h) strongly depends on the presence of risk factors (RF). Many of these RFs such as impaired renal function, diabetes, amount of contrast-medium (CM) and nephrotoxic co-medications are frequently found in ICU-patients. Recent studies have shown a prophylactic effect of acetylcysteine (ACC; 600mg b.i.d.; start 24h before CM) and theophylline (single dose of 200mg IV 30 min. before CM).Aim of the study: comparison of the prophylactic effect of ACC, theophylline and the combination of both agents.
**METHODS.** Patients with at least one RF for CIN and >=100ml of CM were randomized to receive:Group A: theophylline 200mg IV 30 min. before CM. Group B: ACC 600 mg IV on the day of CM-application before CM and 12h after CM. Additionally 600mg ACC b.i.d. on the day before CM, if possible (no emergency examination on the day of randomization). Group C: combination of A and B. Patients who were already under treatment with theophylline or ACC, were exclusively randomized into the groups including the pre-existing prophylactic agent. Primary endpoint: incidence of CIN. Secondary endpoint: time course of creatinine and BUN. Chi-square-test, Wilcoxon-test.
**RESULTS.** Number of patients n=124; group A:B:C = 41:45:38. The 3 groups were comparable with regard to baseline creatinine (1.32∂0.58 vs. 1.24∂0.74 vs. 1.36∂0.81 mg/dl), BUN (25.2∂12.3 vs. 26.6∂20.7 vs. 37.7∂22.0 mg/dl) and the number of additional RFs (4.2 vs. 4.1 vs. 3.9). Only the amount of CM (179.9∂75.6 vs. 147.1∂28.6 vs. 155.4∂44.3 ml) was significantly higher in group A than in group B. Incidence of CIN: group A 1/41 (2.4%), group B 5/45 (11.1%, p=0.099 vs. group A), group C 3/38 (7.9%; p=0.26 vs. group A; p=0.62 vs. group B). 5 of the 8 patients with CIN despite a prophylaxis including ACC had received four doses of ACC, starting the day before CM. The other three patients had only received 2 doses of ACC on the day of CM-application. Mean creatinine levels significantly decreased 48h after CM in group A (p=0.0108) and in group C (P=0.043) compared to baseline. Mean BUN levels significantly decreased 12h after CM in group C (p=0.035) and 24h after CM in group A (p=0.007) and in group C (p=0.044). All other mean serum creatinine- and BUN-levels did not change after CM.
**CONCLUSION.** The overall incidence of CIN was low (7.3%). A comparison of the incidences within the 3 groups did not show a significant difference. However, the time course of serum creatinine and BUN was more favourable within the 2 groups receiving theophylline (group A and group C).
2.) Another advantage of theophylline might be, that it was effective as a single infusion 30 min. before CM, whereas ACC should be started 24h before CM. Therefore, theophylline prophylaxis should be used in all emergency contrast-enhanced procedures until further data about the efficiency of a single dose of ACC before CM are available.

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### CONTINUOUS ADMINISTRATION OF LOW-MOLECULAR HEPARIN IN HEMODIAFILTRATION. COMPARISON TO HEPARIN

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**INTRODUCTION.** heparin is the anticoagulant of choise in continuous renal replacement therapy. The purpose of our study was to measure the efficacy and safety of continuous fixed-dose administration of low-molecular heparin as compared to standard heparin therapy in patients treated with continuous veno-venous hemodiafiltration

**METHODS.** seventeen patients with acute renal failure subjected to continuous hemodiafiltration were randomized to receive either continuous infusion of nardoparin (8 patients)or heparin (9 patients). Hemodiafiltration was delivered by means of an automated machine (multimat lb). Filters were primed with 1 liter of normal saline containing 5000 units of each anticoagulant. Nadroparin treated patients reveived a commensemed bolus of 30 units/kg and a maintenance infusion of 10 units/kg/hr. Heparin-treated patients received a bolus 0f 5000 units and infusion of 10 units/kg/hr titrated to achieve an activated partial thromboplastin time of 55-65 secs. Time to failure of the hemofilters was compared using survival analysis. Hemoglobin and platelet counts were measured pre and after hemodiafiltration sessions and comparison between groups was made with student's t-test. Bleeding episodes and need for transfusion were compared using the chi-square test.

**RESULTS.** thirty three and 38 hemofilters were used in nadroparin and heparin groups respectively. Survival analysis showed no significant difference in the time to failure between the two groups (log rank test, p=0,26). Kaplan-weier mean time to failure was 30,6 hrs in dadroparin and 27,5 hrs in heparin group. Hemoglobin and platelet reduction was comparable in both groups (p=0.45). Episodes of significant hemorhage were more in heparin group (4 vs 1). The mean packed-cell transfusion volume was 280 ml for nadroparin and 305 ml for heparin (p=0.90)

**CONCLUSION.** continuous administration of fixed dose low-molecular heparin in continuous hemodiafiltration seems to be equally effective to heparin therapy and safe, without the necessity of performing blood coagulation tests.

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### THE EFFICACY OF LOOP DIURETICS IN ACUTE RENAL FAILURE ASSESSED BY META-ANALYTIC TECHNIQUES

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**INTRODUCTION.** A recent review(1) found no evidence of the efficacy of frusemide in acute renal failure(ARF); however the number of trials assessed was limited. Meta-analytic techniques were used to assess the evidence of the efficacy of loop diuretics in acute renal failure, based on an extended search.
**METHODS.** Studies using loop diuretics (frusemide, bumetanide and torasemide) in ARF were identified from the MEDLINE(1966-2002), EMBASE, CINAHL and Cochrane databases. Bibliographies of retrieved articles and review articles on acute renal failure were further searched for relevant articles. Studies were included if they were controlled trials or cohort studies, and, chronic renal failure had been excluded. The outcomes of interest were mortality, the time taken for normalisation of renal function, and the number of dialyses. Evidence of publication bias was examined for by using funnel plots, and "trim and fill" techniques. Treatment effects were assessed and expressed as a (i) Risk ratio(RR) for mortality, and, (ii) as weighted mean differences(WMD) for continuous measures. The treatment effects were estimated using the random effect models of DerSimonian and Laird.
**RESULTS.** Out of 14 studies only 8 were suitable for quantitative analysis. Of the 8 studies only one was randomised, double-blinded and controlled, two were randomised controlled trials, four were controlled trials and only one was a cohort study. Missing treatment effect outcomes were noted in most studies. Funnel plots and the tests of publication bias (a) Egger's test (p=0.016) and (b) Begg's test (p=0.015) showed evidence of bias, but the "trim and fill" methodology demonstrated no change in treatment effect estimates, which are tabulated below:

| | Trials: n= | RR/WMD | 95% CI | p value | Heterogenity p value |
|---|---|---|---|---|---|
| Mortality | 6 | 1.05 | 0.83 to 1.32 | 0.65 | 0.36 |
| Time to normal creatinine(days) | 5 | -1.3 (days) | -3.43 to 0.83 | 0.23 | 0.101 |
| Time to output more than 1500 ml(days) | 3 | -7.07 | -10.9 to -3.17 | 0.001 | 0.001 |
| Number of dialyses | 3 | -2.73 | -5.6 to 0.15 | 0.06 | 0.001 |

Pooled treatment effect estimates.

**CONCLUSION.** Loop diuretics produced no change in the mortality in ARF. However their administration in ARF appears to decrease the period of oliguria and uraemia, and reduce the number of dialyses, although the estimates were affected by heterogeneity. Further studies to clarify these issues would appear to be mandated.

**REFERENCES.** 1) Kellum J A, Leblanc M.: Kidney disorders-Interventions in acute renal failure. Clinical Evidence. Vol 6, April 2001.

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