1. Circulation and Hemodynamics

Pericardial pressure correlates with dynamical indices in mechanically ventilated patients

B Lansdorp1,2, J Lemson2, C Hofhuijzen2, H van Swieten1, JG van der Hoeven2, P Pickkers2
1 University of Twente, MIRA - Institute for biomedical technology and Technical Medicine, Enschede, The Netherlands
2 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands

Background: Fluid administration is a daily intervention on the intensive care unit. However fluid administration increases cardiac output only when the heart is on the steep part of the Frank Starling curve. Although dynamic indices are accurate predictors of volume responsiveness (VR), they are only applicable in patients during controlled mechanical ventilation with volumes > 8ml/kg. The goal of this study is to provide insight in the way the ventilatory pressures are being distributed within thorax and to analyze their correlation with arterial pressure variations.

Methods: Following informed consent, we included patients scheduled for coronary artery bypass grafting. During surgery, small non-compliant balloon-catheters were positioned in the pleural and pericardial cavity for continuous pressure measurements. Pressure monitoring included intra-arterial pressure (IAP), airway pressure (Paw), pericardial pressure (Ppc) and pleural pressure (Ppl). Recording was performed during controlled ventilation (PRVC) at tidal volumes (Tv) of 4, 6, 8 and 10 mL/kg for four minutes each. From the IAP-signal and ECG the following dynamic indices were calculated: pulse pressure variation (PPV), systolic pressure variation (sPV) and pre-ejection period variation (∆PEP). Stroke volume variation (sVV) was calculated from pulse contour analysis. Intrathoracic pressures (Ppl and Ppc) were correlated with the dynamic indices.

Results: Six patients were included, figure 1 shows a representative trace of measured data. As a result of increasing Tv from 4 to 10 mL/kg mean ∆Paw (peak pressure - PEEP) varied from 11.7±0.6 to 19.0±3.6, ∆Ppl from 3.6±1.1 to 9.0±1.3 and ∆Ppc from 1.2±0.4 to 3.7±1.1 cmH₂O. An increasing percentage of the change in airway pressure due to mechanical ventilation is transferred to the pleural pressure and pericardial pressure with increasing tidal volumes (30±9% to 47±5% for Ppl and 10±3% to 19±7% for Ppc with tidal volumes varying from 4 to 10 ml/kg). Dynamic indices (PPV, SPV, SVV and ∆PEP) changed as a result of the increase in tidal volume, see figure 2. Correlations were significant (p<0.001) for both Ppl and Ppc with SPV (r=0.99 and r=0.98) and ∆PEP (r=0.99 and r=0.98), see figure 2.

Conclusions: With larger tidal volumes the percentage transferred airway pressure to the pericardial space increases. One fifth of the airway pressure is transferred to the pericard during ventilation with tidal volumes of 10 ml/kg. The change in pericardial pressure during controlled ventilation correlates best with the dynamical indices, in particular SPV and ∆PEP.
2. Circulation and Hemodynamics

Positive cultures from cardiopulmonary bypass: prevalence and relevance regarding postoperative infection

LAC Hamers1, CFM Linssen2, MD Lancé1, JG Maessen2, P Weerwind3, B Winkens4, DCJJ Bergmans1, WNKA van Mook1

1 Department of Intensive Care Medicine, Maastricht University Medical Centre+ and Maastricht University, Maastricht, The Netherlands
2 Department of Medical Microbiology, Maastricht University Medical Centre+ and Maastricht University, Maastricht, The Netherlands
3 Department of Cardiothoracic Surgery, Maastricht University Medical Centre+ and Maastricht University, Maastricht, The Netherlands
4 Department of Methodology and Statistics, Maastricht University Medical Centre+ and Maastricht University, Maastricht, The Netherlands

Objectives: Postoperative infections due to cardiopulmonary bypass (CPB) are associated with high morbidity and mortality [1]. The value of positive cultures taken from CPB priming fluid and CPB blood samples however is unclear. This study investigates the epidemiology of positive cultures from CPB and their relation to the occurrence of postoperative infection.

Methods: The study was conducted at the Maastricht University Medical Centre+, a 715-bed teaching hospital with 900-1000 surgeries requiring CPB annually. From January 1st 1998 until March 31st 2010, all patients with positive CPB cultures drawn either from priming fluid or blood were retrospectively studied. Moreover, 330 patients with a positive CPB culture were compared to 333 randomly assigned patients who underwent cardiothoracic surgery using CPB and had negative CPB cultures. Patients with active endocarditis were excluded. Demographic data and peri-operative parameters were documented. Outcome measures were: a relevant infection (acute infectious valve endocarditis, wound infection, intravascular catheter related infection and blood stream infection), occurrence of fever of unknown origin and 30-day mortality.

Results: 21840 cultures were analyzed, half being priming fluid and half CPB blood cultures. 111 out of 10920 (1.0%) priming fluid cultures and 598 out of 10920 (5.6%) blood cultures tested positive. Gram-positive cocci predominated both priming fluid and blood cultures (see Table 1). Relevant postoperative infections within 30 days after surgery were seen in 47/663 (7.1%) of patients overall, 27/330 in the CPB-culture-positive group (8.2%) and 20/333 in the CPB-culture-negative group (6.0%), p=0.275. 3847/663 (7.1%) of patients overall, 27/330 in the CPB-culture-positive group (8.2%) and 20/333 in the CPB-culture-negative group (6.0%), p=0.275. 3847/663 (7.1%) of patients overall, 27/330 in the CPB-culture-positive group (8.2%) and 20/333 in the CPB-culture-negative group (6.0%), p=0.275. 38

Conclusions: Positive cultures from both CPB priming fluid and CPB blood samples were not a rarity and mainly involved skin bacteria, arguing that contamination may have played a role. The risk of postoperative infection within 30 days after surgery was not increased in CPB-culture-positive patients. Therefore, no evidence was found to support routine culturing of CPB samples in patients undergoing cardiothoracic surgery.

References

Table 1, isolation rate of micro-organisms from CPB

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>CPB sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Priming fluid</td>
</tr>
<tr>
<td>Gram-negative rods (%)</td>
<td>10 (0.9)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Non-fermenters</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Gram-negative rods not otherwise specified</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Gram-positive cocci (%)</td>
<td>91 (8.1)</td>
</tr>
<tr>
<td>Streptococci / Enterococci</td>
<td>9 (8.1)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>78 (70.3)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Gram-positive cocci not otherwise specified</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Gram-positive rods (%)</td>
<td>8 (7.3)</td>
</tr>
<tr>
<td>Bacillus species</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Corynebacterium species</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Propionibacterium species</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Gram-positive rods not otherwise specified</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anaerobic bacteria (%)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Bacteroides fragiles group</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clostridium ramoses</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pasteurella species</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Multibacterial culture (%)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Total number of cultures (%)</td>
<td>111 (100)</td>
</tr>
</tbody>
</table>

Table 2, the effect of positive CPB cultures on the occurrence of relevant infections, fever of unknown origin and 30-day mortality

<table>
<thead>
<tr>
<th>Relevant infections (%)</th>
<th>Total (n = 663)</th>
<th>CPB-culture positive (n = 333)</th>
<th>CPB-culture negative (n = 333)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant infections (%)</td>
<td>47 (7.1)</td>
<td>27 (8.2)</td>
<td>20 (6.0)</td>
<td>0.275</td>
<td>1.395</td>
<td>0.77 - 2.54</td>
<td>0.277</td>
<td>1.368</td>
</tr>
<tr>
<td>Acute infective endocarditis (%)</td>
<td>1 (0.2)</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td>0.486</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection (%)</td>
<td>35 (5.3)</td>
<td>19 (5.8)</td>
<td>16 (4.8)</td>
<td>0.583</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravascular catheter related infection (%)</td>
<td>2 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood stream infection (%)</td>
<td>18 (2.7)</td>
<td>11 (3.3)</td>
<td>7 (2.1)</td>
<td>0.329</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin (%)</td>
<td>38 (5.7)</td>
<td>15 (4.5)</td>
<td>23 (6.9)</td>
<td>0.191</td>
<td>0.642</td>
<td>0.33 - 1.25</td>
<td>0.194</td>
<td>0.5632</td>
</tr>
<tr>
<td>Mortality (30 days) (%)</td>
<td>29 (4.4)</td>
<td>16 (4.8)</td>
<td>13 (3.9)</td>
<td>0.562</td>
<td>1.254</td>
<td>0.59 - 2.65</td>
<td>0.563</td>
<td>1.2803</td>
</tr>
</tbody>
</table>

1 Row 1 and row 3 show the number of patients affected by 1 or more relevant infection(s) or wound infection(s) respectively. Subsequently all separate infections within these patients are summarized. 2 Adjusted for diabetes, emergency surgery and insertion of prosthetics; 3 Adjusted for re-operation and age. CPB = cardiopulmonary bypass; CI = confidence interval; OR = odds ratio.
3. Circulation and Hemodynamics

Noninvasive measurement of pulse and systolic pressure variation using a finger cuff correspond with intra arterial measurements in mechanically ventilated patients

B Lansdorp1,2, D Ouweneel1, J Lemson2, JG van der Hoeven2, P Pickkers2

1 University of Twente, MIRA - Institute for biomedical technology and Technical Medicine, Enschede, The Netherlands
2 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands

Background: Pulse Pressure Variation (PPV) and Systolic Pressure Variation (SPV) are reliable predictors of fluid responsiveness in controlled mechanically ventilated patients [1]. PPV and SPV are calculated using an intra-arterial catheter. It is unknown whether an arterial pressure signal obtained with the Nexfin™ system [2] using only a finger cuff can be used to calculate PPV and SPV. Therefore, the aim of this study was to validate PPV and SPV measured with a finger cuff.

Methods: After their arrival on the ICU, sedated and mechanically ventilated patients after Coronary Artery Bypass Graft surgery (CABG) were included. Intra arterial pressure (IAP) was measured using an arterial catheter inserted in the radial artery, and non-invasively, using the finger cuff of the Nexfin™ monitor (BMEYE, The Netherlands). We took the mean value of PPV and SSV in a 1-minute time interval before and after the administration of a fluid challenge. Agreement of the PPV and SPV measured by the finger cuff and from the IAP signal were assessed using the method described by Bland and Altman.

Results: Nineteen patients were included and twenty-eight volume challenges were analyzed, resulting in 56 simultaneous measurements. PPV and SPV measured by the finger cuff correlated with PPV and SPV from IAP ($r^2=0.92$, $P<.0001$ and $r^2=0.93$, $P<.0001$, respectively), see figure 1. The mean bias was -0.95 and -0.22% for PPV and SSV respectively, and limits of agreement were -4.3% and 2.4% for PPV and -2.2% and 1.7% for SSV (see figure 2). There was no correlation between the bias and the mean value of the two measurement methods. The correlation between changes in PPV and SPV measured by the two different methods was $r^2=0.82$ ($p<.0001$) for PPV and $r^2=0.83$ ($p<.0001$) for SPV.

Conclusions: In ventilated ICU patients, PPV and SPV can be reliably calculated using the Nexfin™ monitor.

References

4. Circulation and Hemodynamics

Microalbuminuria in critically ill patients

N Godijn1, S Smits2, PHJ van der Voort1

1 Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
2 Department of Clinical Chemistry, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Purpose: To establish the behaviour of microalbuminuria over time and its relation to APACHE II score, SOFA score, infection parameters and outcome.

Methods: In a prospective cohort study, we measured microalbumin creatinine ratio (MACR) for all consecutively admitted patients at the ICU.

We recorded the following baseline variables: gender, age, admission diagnosis, type of admission (medical, surgical), length of stay, days of follow up. Patients were followed for ten days when possible.

Results: We included 150 patients, median age 68.6. The patients had a mean APACHE II score of 20.5 and a mean SOFA score of 5.0. In all patients the MACR increases in the first five days. Median MACR on day 1 = 29.2mg/mmol; Median MACR on day 5= 45.5 mg/mmol. For all subgroups except for the diabetes patients the MACR decreased after day five. MACR is significantly correlated to APACHE II, SOFA score and serum creatinine. Only in surgical patients a relation was found between MACR and CRP.

Conclusions: MACR increases the first five days in all patients on the ICU. A relation between MACR and physiologic scores of severity of disease was established, except for diabetes and medical patients. Serum creatinine is found to have a relation with MACR and is a confounder in the relation between MACR and the SOFA score.
5. Circulation and hemodynamics

The value of detecting changes in cardiac output by bedside monitoring parameters in an experimental newborn animal model

A Nusmeier¹, WP de Boode², JG van der Hoeven¹, J Lemson¹
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Neonatology, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: In clinical practice the effect of fluid loading is frequently monitored at the bedside by commonly available parameters like arterial blood pressure (ABP), central venous pressure (CVP) and heart rate (HR), although studies have already demonstrated their poor value of estimating the circulatory condition [1]. More advanced continuous parameters have been suggested for the use of predicting changes in cardiac output, like central venous saturation (ScvO₂) and near infrared saturation (NIRS). Also capnographic monitoring (end-tidal CO₂) may have clinical application in the assessment of circulatory changes. The goal of this study was to evaluate the value of several bedside parameters to reflect changes in cardiac output during fluid bolus administration in newborn lambs.

Method: We prospectively studied 8 mechanically ventilated lambs under general anaesthesia. The animals were bled into a hypovolaemic shock and subsequently volume resuscitated. During the experiment the ventilatory settings were kept unchanged. Cardiac output was monitored by an ultrasound perivascular flow probe (Transonic Systems, USA) around the main pulmonary artery (CO_PA). The fluid resuscitation consisted of 2 to 3 consecutive fluid (whole blood or hydroxyethyl starch) administrations of 10 ml/kg each bolus. All parameters were continuous registered. We compared the changes of the monitored parameters from baseline to 5 minutes after each fluid loading with the change in cardiac output (ΔCO_PA).

Results: A total of 22 fluid administrations in 8 lambs were analyzed. The mean±SD heart rate was 140±30 bpm, mean ABP 53±11 mmHg and CO_PA was 1.3±0.3 l/min. The increase of the CO_PA was 11.1 % (range -4% – 32%) and in 10 fluid administrations cardiac output increased >10%.

The correlation coefficients between the change of CO_PA and separate parameters are shown in table 1. None of the parameters demonstrated a significant correlation besides the ScvO₂. However this correlation was weak (r = 0.48).

Conclusions: This study underlines the necessity to measure cardiac output instead of using the studied bedside parameters, which failed to reflect changes of cardiac output as a result of fluid loading.

References

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtCO₂</td>
<td>-0.253 – 0.565</td>
</tr>
<tr>
<td>HR</td>
<td>-0.665</td>
</tr>
<tr>
<td>ABPmean</td>
<td>-0.032 – 0.7</td>
</tr>
<tr>
<td>CVP</td>
<td>-0.66 – 0.213</td>
</tr>
<tr>
<td>ScvO₂</td>
<td>-0.074 – 0.75</td>
</tr>
<tr>
<td>Brain NIRS</td>
<td>-0.164 – 0.625</td>
</tr>
<tr>
<td>Muscle NIRS</td>
<td>-0.386 – 0.475</td>
</tr>
</tbody>
</table>

Results: In 15 months 1026 patients underwent open heart surgery of which 33 developed acute kidney failure or acute-on-chronic kidney failure. The average length of mechanical ventilation in post-operative patients treated with CVVH was 9.6 vs 0.90 days (p<0.05) in patients without renal failure. The duration of hospital stay was 13.6 vs 1.6 days (P<0.05). In cardiothoracic patients with post operative renal failure a trend was shown towards reduction in duration of mechanical ventilation if CVVH was early initiated (p<0.054) (figure 1).

Conclusion: In our research group a clear relation was shown between post-operative renal failure and duration of mechanical ventilation...
and hospital stay. Early initiation (<24 hrs post operative) of CVVH in cardiothoracic surgery patients with renal failure seems to be related to a reduction in duration of mechanical ventilation. Implications must be examined in a larger prospective study, which is currently being developed.

7. Nephrology

The best prediction for the need of dialysis following cardiac surgery is obtained with the Mehta model

HD Kiers1, MCJ Schoenmakers1,2, HA van Swieten2, JG van der Hoeven1, S Heemskerk1,2, P Pickkers1
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Cardiothoracic Surgery, Radboud University Nijmegen Medical Centre, The Netherlands
3 Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Postoperative acute kidney injury requiring dialysis (AKI-D) occurs in 1 to 5% of patients after cardiac surgery with cardiopulmonary bypass (CPB) and is associated with a high mortality (30-60%) and prolonged increased Intensive Care Unit (ICU) length of stay (LOS). There are four models [1-4] using different covariates that aim to predict the risk of postoperative AKI-D in cardiac surgery patients. It is unclear which model performs best.

Objective: To investigate which model performs best in predicting AKI and AKI-D in our cardiac surgery population.

Methods: All adult patients undergoing cardiac surgery with CPB between October 2006 till January 2008 in our hospital were included in this study. Data on preoperative risk factors and postoperative changes in serum creatinine concentration of all patients was collected with the use of hospital databases and medical records. AKI was defined according to the RIFLE (Risk, Injury, Failure, Loss and End-stage Kidney Disease) classification. AKI-D was defined as the need for hemodialysis during the first 6 days following cardiac surgery. We assessed the discrimination of each model using the area under the curve of the receiver operating characteristics (AUC-ROC) curve for prediction of AKI and AKI-D.

Results: A total of 688 patients were included in this study, of which 636 medical records were available for review. The procedures performed were coronary artery bypass grafting (CABG) (n=436, 69%), single valve surgery (n=80, 12%) or CABG and valve or other surgery (n=120, 19%). The median change in serum creatinine was +6% (IQR -26% to +18%) during the first 6 days after surgery. AKI developed in 19 (3.0%) patients classified as Risk and in 19 (3.0%) patients classified as Injury. AKI-D developed in 12 (1.9%) patients. Table 1 shows the AUC-ROC curve for each model for the prediction of AKI and AKI-D.

Conclusion: The model of Mehta is the best predictor of AKI and AKI-D in our population.

Table 1. Area under receiver operating characteristics curve for four models for the prediction of AKI-D and AKI.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>AKI-D</th>
<th>p-value</th>
<th>AKI</th>
<th>AUC-ROC (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chertow 1997</td>
<td>636</td>
<td>0.76 (0.62-0.90)</td>
<td>0.002</td>
<td>0.67 (0.59-0.75)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Thakar 2004</td>
<td>636</td>
<td>0.89 (0.78-1.00)</td>
<td>&lt;0.0001</td>
<td>0.77 (0.69-0.84)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Mehta 2006</td>
<td>578</td>
<td>0.94 (0.89-0.98)</td>
<td>&lt;0.0001</td>
<td>0.79 (0.72-0.87)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Wijeysundera 2007</td>
<td>636</td>
<td>0.89 (0.83-0.96)</td>
<td>&lt;0.0001</td>
<td>0.74 (0.66-0.81)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

8. Nephrology

Prevalence of Vitamin D deficiency and correlation with outcome in intensive care patients in winter and summer

JJ Weenink1, HTKH Yap2, PHJ van der Voort3, EH Slaats2, HM Oudemans-van Straaten2
1 Department of Intensive Care, Spaarneziekenhuis, Hoofddorp, The Netherlands
2 Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
3 Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Vitamin D deficiency seems increasingly prevalent. Pleiotropic effects of vitamin D like immunomodulation and effects on muscle strength may be of special importance to critically ill patients [1]. However, vitamin D deficiency has only been studied in small and selected groups of ICU patients [2]. Aim of this study was to prospectively determine the prevalence of vitamin D deficiency in winter and summer and related vitamin D status to outcome in cohorts of critically ill patients.

Methods: In a prospective observational cohort study performed in a 20-bed mixed ICU we measured 25-hydroxyvitamin D on admission in all consecutive patients admitted in March/April 2009 and in an equally sized cohort in August/September 2009. Patients received enteral feeding. Additional vitamin D was not supplied. Vitamin D status was defined as: Adequate: >75, insufficient: 50-75, deficient: 25-50, severely deficient: < 25 nmol/L (to convert values to ng/ml, divide by 2.50). We compared observed and predicted mortality (APACHE IV) between the cohorts.

Results: Vitamin D was measured in 111 patients admitted in winter and 112 patients admitted in summer (Table). Mean vitamin D was significantly lower in winter than in summer. In winter, 85% was deficient, 49% severely deficient. In summer, 50% was deficient, 9% severely deficient. Predicted mortality was higher in winter and higher in vitamin D deficient patients. Observed mortality was lower than predicted in all groups, but not different between groups. Including both vitamin D and season in a Multiple Regression Analysis, winter (p=0.004) and not vitamin D (p=0.94) was related to predicted mortality.

References
Conclusions: Vitamin D was significantly lower in patients admitted in winter compared to summer. Half of the winter patients were severely deficient. Hospital mortality was not significantly different between cohorts. Predicted mortality was higher in the winter cohort and in patients with vitamin D deficiency. In a multiple regression analysis, winter and not vitamin D level was related to predicted mortality. However, vitamin D deficiency might increase the susceptibility to disease. Further studies are needed.

References
1. P Lee, ICM 2009:35;2028
2. P Lee, NEJM 2009:360;1912

Table: CI= confidence interval, * T-test, † Chi2 test

<table>
<thead>
<tr>
<th></th>
<th>all</th>
<th>winter</th>
<th>summer</th>
<th>p</th>
<th>Vit D≤25</th>
<th>&gt;25</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr</td>
<td>223</td>
<td>111</td>
<td>112</td>
<td></td>
<td>66</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>66</td>
<td>67</td>
<td>65</td>
<td>NS</td>
<td>67</td>
<td>66</td>
<td>NS</td>
</tr>
<tr>
<td>Vit D 95% CI</td>
<td>40.2</td>
<td>29.4</td>
<td>50.8</td>
<td>&lt;0.001*</td>
<td>26-33</td>
<td>47-55</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>13%</td>
<td>16%</td>
<td>11%</td>
<td>0.25†</td>
<td>9-18%</td>
<td>5-17%</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>9-18%</td>
<td>9-23%</td>
<td>11%</td>
<td></td>
<td>18%, 9-28%</td>
<td>11%, 6-17%</td>
<td>0.20†</td>
</tr>
<tr>
<td>APIVPM 95% CI</td>
<td>0.25</td>
<td>0.31</td>
<td>0.18</td>
<td>0.001*</td>
<td>0.25-0.37</td>
<td>0.13-0.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.21-0.29</td>
<td>0.25-0.37</td>
<td>0.13-0.24</td>
<td></td>
<td>0.33</td>
<td>0.21</td>
<td>0.17-0.26</td>
</tr>
</tbody>
</table>

9. Neurology

Rivastigmine in seriously ill patients with delirium: increased mortality?

Y Verhoeven, R Jansse, MS van der Steen
Department of Intensive Care, Gelderse Vallei Hospital Ede, The Netherlands

Introduction: Delirium is frequently (under)diagnosed in patients admitted to an intensive care unit (ICU). The disorder is characterized by rapid onset, altered consciousness, reduced attention and global cognitive impairment. Also, delirium is associated with longer duration of ICU-admission, higher mortality and morbidity, impaired cognitive performance may occur as a long-term consequence. Since disturbances in cholinergic neurotransmission have been postulated to be involved in the pathophysiology of delirium, treatment studies with cholinesterase inhibitors have been initiated. Although some cases have been reported suggesting potential effectivity of cholinesterase inhibitors in delirious patients, controlled studies did reveal equivocal effects [1,2]. Recently, in The Netherlands a multicentre clinical trial with rivastigmine in ICU-patients was started for which, however, further inclusion had to be stopped prematurely because of higher mortality.

Hypothesis: To investigate the (correct) indications, mortality, frequency of prescription and possible side effects of rivastigmine in ICU/MCU-patients with delirious states.

Methods: Retrospective observational study; January 2009 till June 2010.

Results: In 12 ICU/MCU-patients of the 1622 admitted patients (0.86%); mean age: 75 years; mean duration of admission: 21 days; Table 1) rivastigmine was administered upon recommendation of a geriatrician because of persistent delirium. Three patients used rivastigmine already before. Of the admitted patients the mean of the apache 4 score was 84.3 (±26.0) with a predicted mortality of 0.2-0.6. Five patients (nrs. 1,2,6,7 and 11; Table 1) died. In 2 patients (17%), side effects occurred i.e., bradycardia up to 40 beats per minute with hypotension (nr.10) and eye muscle spasm (nr. 11), respectively. These adverse reactions, however, disappeared after discontinuation of rivastigmine. In only 5 out of 12, patients occurrence of delirium was mentioned in the discharge letter.

Conclusion: In our limited series of ICU/MCU-patients with a delirium in 0.86% rivastigmine was prescribed, all were suffering from life threatening medical conditions. The mortality of 25% is in line with the predicted mortality of 20-60%. Because of the small group of patients no association can be made between the relationship of death in 5 out of 12 patients and treatment with rivastigmine. In 17% serious side effects occurred, it disappeared after discontinuation of rivastigmine.

References
**Table 1: Main characteristics of the patients**

<table>
<thead>
<tr>
<th>Nr/ gender</th>
<th>Reason of admission</th>
<th>Days ICU</th>
<th>Parkinson/dementia history</th>
<th>Used RVST* before</th>
<th>RVST*/days</th>
<th>CAM ICU</th>
<th>Died/ cause of death</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 78/m</td>
<td>Abdominal sepsis, bowel perforation</td>
<td>55</td>
<td>-</td>
<td>+/-#</td>
<td>not used</td>
<td>e-coli septicemia and pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. 82/v</td>
<td>Perforated diverticulitis</td>
<td>1</td>
<td>+/+</td>
<td>+/4</td>
<td>not used</td>
<td>No surgery for acute abdomen after consultation family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. 80/m</td>
<td>Respiratory insufficiency</td>
<td>4</td>
<td>+/-</td>
<td>+/+#</td>
<td>not used</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. 70/m</td>
<td>Aspiration pneumonia</td>
<td>7</td>
<td>+/-</td>
<td>+/-#</td>
<td>not used</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. 59/m</td>
<td>Sepsis post-operative</td>
<td>13</td>
<td>+/-</td>
<td>+/-#</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. 77/m</td>
<td>Aspiration pneumonia</td>
<td>13</td>
<td>+/-</td>
<td>+/-#</td>
<td>+</td>
<td>within 24 hours; respiratory failure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. 73/m</td>
<td>Post-operative abdominal aneurysm</td>
<td>33</td>
<td>+/-</td>
<td>+/-#</td>
<td>-</td>
<td>circulatory shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. 93/m</td>
<td>Hypotension</td>
<td>1</td>
<td>+/-</td>
<td>+/-#</td>
<td>not used</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. 57/v</td>
<td>Perforation duodenum</td>
<td>46</td>
<td>+/-</td>
<td>+/-#</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. 11/65/m</td>
<td>Ischemic bowel</td>
<td>11</td>
<td>+/-</td>
<td>+/-#</td>
<td>+</td>
<td>bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.87/m</td>
<td>Abdominal sepsis</td>
<td>41</td>
<td>+/-</td>
<td>+/-#</td>
<td>+/4</td>
<td>Died after discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.79/m</td>
<td>Pneumosepsis</td>
<td>13</td>
<td>+/-</td>
<td>+/-#</td>
<td>+</td>
<td>eye muscle spasm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*RVST = rivastigmine
> # = discharged with rivastagmine; unknown how long given

10. **Neurology**

**Development and validation of an 8-step flowchart based on the CAM-ICU: a quick and highly adaptable tool to determine the presence of delirium in the Intensive Care**

IJ Zaal, LM Peelen, D van Dijk, AJC Slooter

Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

**Objective:** Delirium is a frequent and serious disorder in the Intensive Care Unit (ICU). Several tools have been developed for standardized delirium testing of which the Confusion Assessment Method for the ICU (CAM-ICU) is the best validated and most widely used. Main limitations of the CAM-ICU are however that it is a very brief assessment of a highly fluctuating disorder, and that the test may lack sensitivity when administered in daily practice. For research purposes, we extended the CAM-ICU to classify patients as either awake without delirium, delirious or comatose.

**Design:** Ongoing prospective validation study.

**Setting and Participants:** In 55 patients (35 men, 63.6%; mean age 60.0 SD 17.9; mean Acute Physiology and Chronic Health Evaluation II score 18.7 SD 6.1), admitted to a 12-bed mixed medical and surgical ICU, 379 assessments were made during the whole ICU stay.

**Measurements and main results:** All patients were assessed daily and independently by two means: (1) a junior doctor or neurologist (gold standard) and (2) an 8 item flowchart, based on the CAM-ICU and the report of the bedside nurse as well as the administration of haloperidol. With both assessment methods, patients were classified as either awake without delirium, delirious for one or more moments in the past 24 hours, or comatose during the whole past 24 hours. The form showed a sensitivity of 85.0%, a specificity of 88.2%, a positive predictive value of 81.3% and a negative predictive value of 91.2%.

**Conclusion:** While the CAM-ICU is a tool to assess delirium during a brief observation period, this extension can be used to classify the presence of delirium in the previous 24 hours. The tool appeared to be easy to use and highly adaptable with good test characteristics.
11. Neurology

Predictors of poor neurologic outcome in patients after cardiac arrest treated with hypothermia

LLA Bisschops1, N van Alfen2, S Bons1, JG van der Hoeven1, CWE Hoedemaekers1
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Neurology and Clinical Neurophysiology, Radboud University Nijmegen Medical Centre, The Netherlands

Purpose: Outcome studies in patients with anoxic-ischemic encephalopathy focus on the early and reliable prediction of an outcome no better than a vegetative state or severe disability. Currently used predictors of outcome in patients with anoxic-ischemic encephalopathy are based on studies performed before the use of mild therapeutic hypothermia. There is increasing evidence in the literature that these parameters may not be applicable to patients treated with mild hypothermia. We determined the effect of mild therapeutic hypothermia on the validity of the currently used clinical practice parameters as described by the Quality Standards Subcommittee of the American Academy of Neurology (AAN). In addition, we studied the natural course of the clinical neurological parameters of patients with post-anoxic encephalopathy during and after treatment with hypothermia.

Conclusions: Our analysis shows that no single clinical or electrophysiological parameter has sufficient accuracy to determine prognosis and decision making in patients after cardiac arrest, treated with hypothermia. We demonstrated that the current clinical AAN guidelines cannot be safely applied to these patients. Early prognostication in patients with post-anoxic encephalopathy will probably require a multimodal approach, combining a number of clinical and electrophysiological tests. Prospective trials are needed to establish the optimal timing and combination of these parameters. Until the results from these trials are available, the AAN guidelines should not be used in their current form and survivors of cardiac arrest treated with hypothermia should be monitored for more than 3 days to determine neurological outcome.

12. Neurology

Rivastigmine does not decrease duration of delirium and may increase mortality in Intensive Care patients: a multicentre, double-blind, randomized, placebo-controlled add-on trial

MMJ van Eijk, KCB Roes, MLH Honing, MA Kuiper, A Karakus, M van der Jagt, PE Spronk, WA van Gool, RC van der Mast, J Kesecioglu, AJC Slooter
Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

Introduction: Delirium is frequently encountered in critically ill patients and is associated with adverse outcome. Impaired cholinergic neurotransmission seems to play an important role in the development of delirium. We aimed to study whether the cholinesterase inhibitor rivastigmine added to standard treatment shortens the duration of delirium in critically ill patients.

Methods: In this multicentre, double-blind trial, consecutive Intensive Care Unit (ICU) patients with delirium were randomized to increasing dosage of rivastigmine or placebo, as add-on medication to standard pharmacotherapy. The primary outcome was the duration of hospital delirium. A secondary outcome was 90 days mortality. We intended to include 440 patients. The Data Safety Monitoring Board (DSMB) performed unblinded interim analyses every three months.

Results: After inclusion of 104 patients with delirium, the DSMB recommended halting the trial because 12 of the 54 patients who received rivastigmine had died as compared to 4 of the 50 patients who received placebo (p=0.07, corrected for multiple interim analyses). At baseline, both groups were comparable, although in the rivastigmine group slightly more subjects were admitted in an emergency situation (67% versus 64%). The duration of hospital delirium in the rivastigmine group (median 5 days, range: 1 to 64 days) tended to be longer than in the placebo arm (median 3 days, range: 1 to 28 days), although not statistically significant (Mann-Whitney test, p=0.06). Furthermore, the severity of delirium, as measures by the Delirium Severity Index, was higher in the rivastigmine group as compared to the placebo group (p<0.005).

Conclusion: Our trial indicated that in ICU patients, rivastigmine did not decrease duration of delirium. As an increased mortality associated with the use of rivastigmine could not be ruled out, we do not recommend administering rivastigmine to delirious ICU patients.

Figure. Kaplan-Meier survival curve

Subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>Rivastigmine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>64</td>
<td>50</td>
</tr>
<tr>
<td>40-49</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>50-59</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>60-69</td>
<td>36</td>
<td>39</td>
</tr>
</tbody>
</table>
Limitations to the use of the Glasgow Coma Scale in intensive care patients with non-neurological primary disease: a search for alternatives

PV Dong1, OL Cremer1
1 Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

Introduction: Numerous scoring systems have been used to assess the severity of illness and predict outcome in critically ill patients in the Intensive Care Unit (ICU) [1]. The Glasgow Coma Scale (GCS) was originally developed to record changing states of altered consciousness after traumatic brain injury, but its use has since been extended to other patient categories, including both other acute neurological disorders and the general intensive care population. The GCS has also been incorporated as a component of the Apache, SAPS and SOFA scores. Over the years, some shortcomings of the GCS have been identified [2]. The GCS requires observation of a verbal score (which is often unavailable in the ICU), must be ‘interpreted’ in cases of concurrent sedation (which accounts for large interrater variability), and is insensitive to more subtle derangements of consciousness (such as delirium). Furthermore, its relationship with outcome may be non-linear. The aim of this study is to assess the predictive power of the GCS in patients with and without neurological primary disease in the ICU.

Materials & Methods: From January 2009 until September 2010, all adult patients admitted to the ICU of the University Medical Center Utrecht were studied. Patients following elective surgery, having a length of stay <96 hours, were excluded from analysis. Patient characteristics and various neurological assessment variables were extracted from our clinical information system, including the GCS-score (observed both by doctors and nurses), pupillary light reflex, symmetry and shape, as well as the use of mechanical ventilation and sedative drugs. Furthermore the Richmond Agitation Sedation Scale and the Confusion Assessment Method for the ICU were recorded twice daily. Subsequently, all variables were assessed for their ability to predict hospital mortality and length of stay, using multivariate regression analyses that included the variables of primary interest, as well as any relevant covariates.

Results: In total 1141 patients were included (62% males, mean age 58 ±17 years, 40% surgical vs. 60% non-surgical admissions). Overall, we observed a 26% hospital mortality rate (compared to 30% predicted by the Apache IV model). Median LOS in the ICU and hospital were 5 (IQR 2-10) and 8 (3-16) days, respectively. There was a strong univariate relation between the total GCS and mortality, although the motor component of the score behaved non-linearly. A stronger association was present for GCS scores observed by doctors than by nurses, especially for the motor- and verbal components. Pupillary asymmetry was only a weak predictor of mortality. Acute comorbidities and events, such as cerebrovascular accidents, intracranial mass lesions, and cardiopulmonary resuscitation, had a detrimental impact on outcome. Subsequently, we constructed various multivariate models to predict hospital mortality and length of stay.

Conclusion: The GCS is a widely used and generally accepted tool to assess neurological status in critically ill patients. However, difficult interpretation and inconsistent predictive power in various subgroups of patients form limitations to its use. The Full Outline of UnResponsiveness (FOUR) score may be a useful alternative in these cases, the practical applicability of which is presently under investigation by us.

References

Cerebral blood flow during prolonged mild hyperthermia and passive rewarming in cardiac arrest patients

LLA Bisschops, CWE Hoedemaekers, JG van der Hoeven
Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Mild therapeutic hypothermia improves outcome in patients after out-of-hospital cardiac arrest. Despite the cardiodepressive effects of hypothermia, therapeutic hypothermia reduces cerebral blood flow (CBF) without concurrent increase of cerebral oxygen extraction rate in the first 24 hours after cardiac arrest, indicating a lower cerebral metabolic activity with a preserved metabolic coupling [1].

Objective: The aim of this study was to assess the cerebral blood flow and jugular bulb oxygenation (SjbO2) in cardiac arrest patients treated with prolonged hypothermia.

Methods: Patients were included after restoration of spontaneous circulation after asystole, pulseless electrical activity based circulatory arrest or ventricular fibrillation based prolonged resuscitation. In this prospective observational study 10 comatose patients after cardiac arrest were treated with prolonged hypothermia for 72 hours. After 72 hours patients were passively rewarmed. Mean flow velocity in the middle cerebral artery (MFVmca), reflecting CBF, was low (31.0±15.4 cm/s) on admission, and gradually increased to 57.8±14.2 cm/s during mild hypothermia in the first 72 hours (p<0.001) (figure 2). After passive rewarming MFVmca further increased to 70.7±20.5 (p<0.01) cm/s after 94 hours and remained relatively stable after 96 and 108 hours (66.9±18.4 cm/s and 64.6±17.1 cm/s respectively (p=0.86)). SjbO2 at the start of the study was 57.9±9.9% and gradually increased to 82.0±7.3% after 72 hours and 78.7±10.6% after 114 hours (p<0.82)(figure 3).

Conclusions:
1) Cerebral blood flow was lower during hypothermia compared to physiological values and showed a gradual increase during prolonged mild hypothermia.
2) SjbO2 increased significantly in the first 36 hours of prolonged mild hypothermia. After 36 hours relatively stable SjbO2 values were shown.
3) Prolonged mild hypothermia results in lower cerebral blood flow with preserved metabolic coupling.

References
1. LLA Bisschops, Crit Care Med. 2010 Jul;38(7):1542-7
15. Neurology

Relationship between environmental factors and the incidence and course of delirium in the intensive care

IJ Zaal, CF Spruyt, LM Peelen, J Kesecioglu, AJC Slooter
Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

Objective: Delirium is a common and serious disorder in the intensive care unit (ICU). It has often been stated that the ICU environment may play a role in the development of delirium, but this has never been investigated. The aim of this study was to determine the relationship between environmental factors and the incidence and course of delirium in the ICU.

Design: A prospective observational before/after study.

Setting: A mixed ICU in a University Hospital in the Netherlands.

Intervention and Participants: In March 2010 the hospital opened a new ICU with all single – noise reduced – rooms including diurnal light variation and reorientation points. In the old ward like setting, patients beds were separated from each other with curtains only and there was no diurnal light. We included 55 patients in the old setting and 75 patients in the new setting.

Measurements and main results: All patients admitted to the ICU were daily assessed on delirium using the CAM-ICU by 2 junior doctors or a neurologist-intensivist (mean k = 0.94), during the whole ICU stay. Exclusion occurred when patients remained unresponsive (RASS < -3) during admission or when they were unable to understand Dutch/English. Preliminary analyses indicate that demographic characteristics were similar for both groups. However co-morbidity was more severe, APACHE II scores were higher, and emergency and surgical admissions were more frequent in the new setting. In the old setting, 449 evaluations were made, in the new setting 468. Delirium occurred in 28 (50.9%) patients in the old setting versus 34 (45.3%) patients in the new setting (p=0.53). Mean delirium duration was 4.3 (SD 4.7) versus 3.2 (SD 4.1) days (p=0.04) in respectively the old and the new setting. No difference could be observed in the prescription of haloperidol. In the new setting, there were significantly more days of intravenous sedative medications during IC admission with a mean (SD) of 3.2 (5.4) days in the new environment and 2.6 (4.9) days in the old setting (p=0.03).

Conclusion: This is the first study that prospective investigated the incidence and course of delirium in relation to ICU environment. The duration of delirium was found to be shorter in ICU patients who were treated in separate rooms despite a similar incidence of delirium. These preliminary results are not corrected for by example severity of illness or existing of co-morbidities. On the congress we can present the complete data.
16. Pediatrics

Children as donors: A national pediatric intensive care study to assess procurement of organs and tissues

M Siebelink, M Albers, P Roodbol, H van de Wiel
University Medical Centre Groningen, The Netherlands

Objectives: Shortage of size-matched organs and of tissues is the key factor limiting transplantation in children. Empirical data on the procurement process in children is sparse. This study aimed to gain insight into the recognition of potential pediatric donors in the Netherlands and the procurement process.

Methods: A national retrospective cohort study in the Dutch pediatric intensive care units. The records of 683 deceased children were analyzed by two independent donation experts and procurement process data were compared with the national protocol.

Results: from 2003 thru 2006, 74 (11%) of the deceased children were found to have been suitable for organ donation and 132 (19%) for tissue donation. Sixty-two (84%) potential organ donors had been correctly identified; parental consent had been obtained and donation effectuated in 26/62 children (42%). Sixty-three potential tissue donors (47%) had been correctly identified; parental consent had been obtained and donation effectuated in 17/63 children (27%).

Conclusion: Recognition of pediatric organ donors by medical professionals is good; recognition of tissue donors may be improved. Efforts to address the shortage of organs and tissues for transplantation in children should focus on the gap between recognition of donors and parental consent. We suggest such studies should not only assess the process itself, i.e. the competencies of the professional staff (micro-level) but also the influence of legislation, societal views on donation by children, and the potential relevance of children’s views on donation (macro-level).

17. Pediatrics

The reliability of End-Tidal CO₂ Capnography for estimating arterial carbon dioxide tension in mechanical ventilated children

GJ Truin, J Verhaeg, JG van der Hoeven, J Lemson
Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Capnography is a non-invasive tool for measuring carbon dioxide concentration in expired gas. In healthy individuals there is a strong correlation between end-tidal carbon dioxide tension (EtCO₂) and the arterial carbon dioxide tension (PaCO₂). Therefore capnography is widely used in clinical practice to provide a quick, continuous and non-invasive estimation of arterial carbon dioxide tension. However an optimal relationship between EtCO₂ and PaCO₂ only exists when there is a normal perfusion-ventilation ratio and a stable hemodynamic situation. The aim of the present study was to assess the correlation between EtCO₂ and PaCO₂ in a general population of mechanically ventilated critical ill patients admitted to the pediatric intensive care unit.

Methods: A single-centre prospective observational study on consecutive mechanically ventilated patients admitted to the pediatric intensive care unit. All patients were ventilated with a SERVOi ventilator (Siemens, Stockholm, Sweden) with correction for compressible volume. EtCO₂ was measured by continuous side stream capnography (Philips MP 70 monitoring system). Blood gas samples were drawn from an arterial line. Paired EtCO₂ and PaCO₂ levels were recorded. Per patient a maximum of 10 paired samples was collected. Demographic data together with ventilator settings and physiological patient data were recorded simultaneously.

Results: We recorded a total of 365 paired samples in 50 children of which 6 children eventually died. Table 1 depicts the demographic data. An average of 7 paired data samples per patient were recorded (range 1-10). Median PaCO₂ was 5.4 kPa, (range 3.3 – 8.2), median PEEP level 5 cmH₂O (range 3 – 14), median heart rate 135 bpm (range 58 – 205) and median mean arterial pressure 64.0 mmHg (range 39-103). The correlation between EtCO₂ and PaCO₂ was poor with r = 0.44 (95%CI 0.36 – 0.52; p < 0.0001) (figure 1). The mean bias was 0.9 kPa with limits of agreement (1.96 x SD of bias) of 1.9 kPa.

Conclusion: In this general PICU population EtCO₂ does not reliably reflect PaCO₂. Absolute values of EtCO₂ should therefore be used with caution as a marker for alveolar ventilation.
Medium Care patient characteristics, referral patterns and outcome

P Heutink, H Fijn, P Krijtenburg, MS van der Steen, ARH van Zanten, DHT Tjan
Department of Intensive Care, Gelderse Vallei Hospital Ede, The Netherlands

Introduction: Interest in medium care (MC) facilities has grown due to increasing demand for ICU beds and financial constraints in health care. A MC step-down facility may increase efficiency of ICU resources. A step-up function may improve care for the severely ill or high work-load patients in general wards.

Objective: To describe patient characteristics in a newly opened medium care facility and to compare characteristics of step-up and step-down patients, acute and planned admissions, length of stay (LOS), readmission rate and mortality in order to provide data for development of admission and discharge guidelines for MC facilities.

Methods: Retrospective analysis of 743 MC admissions (2008-2009) to a 5-bedded MC unit, as part of a closed-format ICU organisation in a 625-bedded teaching hospital. Admission were categorised as follows:

Planned: Admissions from the ICU, planned post-PACU or planned postoperative admissions. Acute: admissions from all general wards, ER, not-planned PACU, CCU and acute from ICU. Step-down patients were planned and came from the ICU, step-up were admitted from all other wards.

Results: Demographics are shown in table 1. Table 2 shows the referring ward of patients. LOS in the MC is 2.98 days [0-22 days]. MC mortality is 2.6%. MC readmission rate (< 48 hours after discharge) was 1.5%. Of the step-down admissions 38.9% were acute, while planned admissions were mostly step-down 99.2%. LOS is significantly shorter in step-up vs. step-down patients (P=0.0038). In 40 patients readmission to the ICU was indicated (10.7%). Discharge to general wards is more frequently encountered in step-down patients (86.6%), whilst discharge to ICU is more common in the step-up group (15.4%). The mortality in the step-up group is significantly higher (4.1%).

Conclusions: In our Medium Care most patients were planned and had an average LOS of 3 days. Readmission rates were extremely low as well as mortality. However, patient characteristics of planned and acute admissions and step-up and step-down patients varied markedly with respect to LOS, outcome and discharge locations. Transfer to the ICU is low (10%). This information may help to plan resources and design guidelines for admission and discharge criteria on a larger scale.

Table 1. Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=743)</th>
<th>Step up (n=370)</th>
<th>Step down (n=373)</th>
<th>P value Step up vs. step down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>55.7%</td>
<td>50%</td>
<td>59.4%</td>
<td>0.064</td>
</tr>
<tr>
<td>Mean age (SD; median; range)</td>
<td>66 (16.5; 68; 17-101)</td>
<td>66.8 (18.8; 67; 17-101)</td>
<td>72.7 (13.7; 68; 19-95)</td>
<td>0.077</td>
</tr>
<tr>
<td>Length of stay medium care (SD; median; range)</td>
<td>3.0 (2.0; 2; 0-22)</td>
<td>2.7 days (2.0; 2; 0-13)</td>
<td>3.3 days (3.3; 2; 0-22)</td>
<td>0.0038</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute admissions</td>
<td>147 (19.8%)</td>
<td>144 (38.9%)</td>
<td>3 (0.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Planned admissions</td>
<td>596 (80.2%)</td>
<td>226 (61.1%)</td>
<td>370 (99.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>19 (2.6%)</td>
<td>15 (4.1%)</td>
<td>4 (1.1%)</td>
<td>0.100</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortuary</td>
<td>588 (79.0%)</td>
<td>265 (71.6%)</td>
<td>4 (1.1%)</td>
<td>0.010</td>
</tr>
<tr>
<td>General ward</td>
<td>57 (7.7%)</td>
<td>57 (15.4%)</td>
<td>3 (0.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU</td>
<td>59 (8.0%)</td>
<td>323 (86.6%)</td>
<td>4 (0.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Home</td>
<td>15 (2.0%)</td>
<td>10 (2.9%)</td>
<td>3 (0.8%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Other hospital</td>
<td>12 (1.6%)</td>
<td>9 (2.4%)</td>
<td>3 (0.8%)</td>
<td>0.082</td>
</tr>
<tr>
<td>Other</td>
<td>3 (0.4%)</td>
<td>9 (2.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Referring wards

<table>
<thead>
<tr>
<th>General ward</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>369</td>
</tr>
<tr>
<td>General Surgery</td>
<td>109</td>
</tr>
<tr>
<td>Emergency Room</td>
<td>89</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>57</td>
</tr>
<tr>
<td>PACU</td>
<td>59</td>
</tr>
<tr>
<td>Neurology</td>
<td>15</td>
</tr>
<tr>
<td>Gynaecology/obstetrics</td>
<td>10</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>6</td>
</tr>
<tr>
<td>MC other hospital</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>5</td>
</tr>
<tr>
<td>ICU other hospital</td>
<td>4</td>
</tr>
<tr>
<td>Urology</td>
<td>3</td>
</tr>
<tr>
<td>Oncology</td>
<td>3</td>
</tr>
<tr>
<td>CCU</td>
<td>3</td>
</tr>
<tr>
<td>Cardiology</td>
<td>2</td>
</tr>
<tr>
<td>Home</td>
<td>2</td>
</tr>
<tr>
<td>Day care</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>743 patients</strong></td>
</tr>
</tbody>
</table>
19. Quality and Organisation

Quality and quantity of sleep in multiple versus single patient room Intensive Care Units

MMJ van Eijk, R van den Bossche, MJ Nouwen, FSS Leijten, A de Weerd, MME Schneider, J Kesecioglu, AJC Slooter
Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

Introduction: Sleep fragmentation and deprivation is common in Intensive Care Unit (ICU) patients and may increase the risk of delirium. It is generally assumed that the ICU environment, including over-exposure to sound and light in the night-time, is an important cause for disturbed sleep. In the University Medical Centre, Utrecht, the Netherlands, a new ICU was built with quiet, single-patient rooms with much daylight (see figure 1). This created an unique opportunity to study the effects of nursing environment on sleep quality and quantity in ICU patients.

Methods: We included 20 post-cardiothoracic surgery (either CABG or valve replacement) patients: ten subjects were admitted to the old, ward-like ICU, and ten patients to the new, single-room ICU. We exclude patients with an underlying sleep disorder. A 15-lead polysomnography recorded sleep patterns from 07:00 p.m. to 07:00 a.m. Subjects were asked to fill out a questionnaire concerning the subjective quality of sleep 24 hours before and 48 hours after registration.

Results: Both groups did not differ with respect to age, duration of surgery and administration of psychoactive medication. Polysomnography recordings showed that the total sleep time in both situations was equal and that both groups had frequent awakenings (on average 72 times versus 74 times per patient), one patient showed an astonishing 109 awakenings during the night. However, in the new, single-room ICU, subjects showed less superficial sleep (stage N1) and more deeper superficial sleep (stage N2), as compared to the old ICU (see figure 2 for an example). In the new ICU on average 8.0% of sleep time was in stage N1 as compared to 12.9% in the old ICU (p<0.05, ANOVA). 87.2% of the sleep time was in N2 stage in the new ICU as compared to 80.3% in the old situation (p<0.05, ANOVA). Patients in the old ICU experienced more deep sleep (stage N3) than patients in the new ICU (5.2% versus 2.5%, p<0.05, ANOVA). No significant differences between the subject's sleep experiences were found.

Conclusion: This study is the first study that shows quality of sleep in ICU patients can be influenced by nursing environment.

Figure 1. ‘Old’ and ‘New’ Intensive Care Unit

Figure 2. Polysomnography in the ‘Old’ and ‘New’ Intensive Care Unit

20. Quality and Organisation

Novel unobtrusive monitoring system for general wards: a prospective observational study

DHT Tjan1, B Feddes1, L Gourmelon2, G Douw1, T Sol1, ARH van Zanten1
1 Department of Intensive Care, Gelderse Vallei Hospital Ede, The Netherlands
2 Biomedical Sensor Systems, Philips Research, Eindhoven, The Netherlands

Introduction: Failure to timely recognize the deteriorating patient in general wards may lead to delay in treatment and negatively influence outcome. A reliable, comfortable and non-invasive vital signs monitor might improve quality of care allowing early recognition of alarming vital signs. Philips Research developed a monitor which measures respiratory rate (RR) and heart rate (HR) non-invasively using bed integrated technology. The system was previously tested for accuracy in a laboratory setting.

Objective: The aim of the study was to evaluate this new technology for measuring basic vital signs in a general ward population, and to address the relative contribution of the two vital signs - RR and HR - used in our local Early Warning Score (EWS).

Methods: We prospectively studied 116 adult patients admitted to a general surgical ward of a large tertiary hospital. Ten prototype monitoring systems were used to measure heart rate and respiration rate continuously when patients were lying in bed. From the patient records the nurse recorded...
recorded contribution of SpO₂, blood pressure and temperature to the EWS were extracted as well.

Only data was included for which both continuous measurements and all spot check data was available, in total 427 patient days, with ~10,300 hours of continuous data. The average daily contribution to the EWS of the HR, RR (from the measurements) and Blood Pressure, SpO₂, temperature (from the spot checks) were derived from this. Nursing staff were questioned regarding the usability of the device.

**Results:** The monitors functioned well. Nurses stated that it was easy to operate with no recorded complications. Figure 1 shows the relative contributions of the different abnormal vital signs to the total alarm score. The average number of EWS points scored on respiration is by far the highest. About 75% of the EWS points are covered by the two vital signs that the bed integrated technology can monitor (RR and HR).

Respiration was extremely infrequently self-recorded by the nursing staff.

**Discussion:** Abnormal RR and HR signals provide alarms signal and contributed to the EWS in the majority of the cases. Nurse recorded data often lack RR, while RR most strongly contributed to the EWS. The device can help identify those patients that are at risk of deteriorating. Because it is non-invasive and easy to operate patient compliance was high. Furthermore patients and relatives found it reassuring that extra monitoring was in place.

**Conclusion:** This study demonstrates that a novel unobtrusive bed integrated monitoring system can measure RR and HR adequately when the patients are in bed on a general ward. RR and HR are essential parameters for the EWS. This is an important new strategy for patient safety on the general wards potentially leading to earlier recognition and treatment in imminent life-threatening situations.

---

### Table 1. ANCOVA results of SF-36, CIS-8 and the CFQ measurements 18 months after ICU discharge

<table>
<thead>
<tr>
<th></th>
<th>Non-delirious Patients (N=744)</th>
<th>Delirious Patients (N=171)</th>
<th>P-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>67 ±28</td>
<td>52 ±30</td>
<td>0.18</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>54 ±43</td>
<td>41 ±40</td>
<td>0.20</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>76 ±26</td>
<td>73 ±26</td>
<td>0.26</td>
</tr>
<tr>
<td>General Health</td>
<td>57 ±23</td>
<td>52 ±23</td>
<td>0.90</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>77 ±25</td>
<td>70 ±25</td>
<td>0.65</td>
</tr>
<tr>
<td>Vitality</td>
<td>61 ±21</td>
<td>56 ±20</td>
<td>0.94</td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>73 ±39</td>
<td>65 ±42</td>
<td>0.64</td>
</tr>
<tr>
<td>Mental Health</td>
<td>76 ±18</td>
<td>71 ±19</td>
<td>0.26</td>
</tr>
<tr>
<td>CIS-fatigue total</td>
<td>28 ±14</td>
<td>32 ±13</td>
<td>0.13</td>
</tr>
<tr>
<td>CFQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent-mindedness</td>
<td>7.0 ±4.5</td>
<td>7.7 ±4.5</td>
<td>0.02*</td>
</tr>
<tr>
<td>Absent-mindedness in social situations</td>
<td>4.7 ±2.9</td>
<td>5.0 ±3.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Names and words</td>
<td>5.1 ±2.6</td>
<td>5.2 ±2.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Orientation</td>
<td>2.1 ±2.1</td>
<td>2.3 ±2.2</td>
<td>0.55</td>
</tr>
<tr>
<td>CFQ-total</td>
<td>27 ±15</td>
<td>30 ±15</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

† adjusted for age, gender, urgent admission, APACHE-II score, sepsis and LOS-ICU using log transformed data (not shown)

* <0.05
22. Quality and Organisation

Does implementing a Rapid Response System decrease the number of in-hospital cardiac arrests?

RKL So1,2, V van Bruggen1, HH Ponssen1, P Barendrecht1, A Geense1, E van Dijk1, M Achilleos1, M Meijer1, A Deykers1, G Verwoerd1, E Oskam2, MCLJ Taks2

1 Department of Intensive Care, Albert Schweitzer Hospital, Dordrecht, The Netherlands
2 Department of Quality, Safety and Innovation, Albert Schweitzer Hospital, Dordrecht, The Netherlands

Introduction: Resulting from the Dutch VMS Safety Program 'Prevent injury, work safely' we recently started to implement a Rapid Response System (RRS) in our hospital. The RRS consists of: a “warning signs” pocket card, a Rapid Response Team (RRT) and an evaluation system. The purpose of the RRS is to recognize and treat the patients with clinical warning signs early on the ward to reduce preventable hospital-wide “avoidable injury”. We present the first “outcome” data of the implementation of the RRS.

Methods: From may 1st 2008 – may 1st 2009 we implemented on two both clinical locations of our hospital a rapid response system, which has three basic limbs: an afferent limb (RRS activation card), a physician-led medical emergency team (MET) and an evaluation/feedback limb.

A special multidisciplinary change team (ICU nurses, general ward nurses, A&E physician, intensivist and a quality & safety officer) coordinated this process.

We collected data regarding all MET-calls from may 1st 2008 – july 1st 2010 and we focussed on the number of in-hospital cardiac arrests (CA).

Results:

<table>
<thead>
<tr>
<th>Number MET calls per 1000 discharged patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dordrecht</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Zwijndrecht</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number in-hospital CA per 1000 discharged patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dordrecht</td>
</tr>
<tr>
<td>1,4</td>
</tr>
<tr>
<td>Zwijndrecht</td>
</tr>
</tbody>
</table>

Conclusions: Implementation of a rapid response system can decrease the number of in-hospital cardiac arrests dramatically and thus avoid (serious) adverse events and possible deaths. Possible success factors include:
- timely activation of the rapid response system
- degree of implementation of the rapid response system
- timely agree restrictive measurements on the general ward

23. Quality and Organisation

Effects of the opening of a Medium Care facility on sepsis related survival

P Heutink, DHT Tjan, P Krijtenburg, HBM Fijn, MS van der Steen, ARH van Zanten

Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands

Introduction: Intensive care facilities have reduced mortality and morbidity in critically ill sepsis patients. Information on the impact of medium care facilities on sepsis outcome is scarce. Performance may be monitored using diagnose related case-mix corrected standardised mortality data. In the Netherlands for this the National Intensive Care Evaluation (NICE) provides data on sepsis related mortality based on several scoring systems.

In contrast to widely felt positive effects of MC facilities on sepsis outcome Peelen and coworkers published data suggesting that a MC as an ICU step-down facility was associated with a significantly higher in-hospital mortality [1]. An ongoing debate on the validity and relevance of these multicenter data combining also non-intensivist driven MC facilities urged us to prospectively address this in a single-center before and after design setting.

Objective: To evaluate the effect on sepsis related mortality before and after the opening a new MC facility.

Methods: We retrospectively analyzed 559 ICU admission data (2007) before the opening of a 5-bedded MC, embedded but separately located in a closed format ICU organisation (12 ICU beds) and supervised by intensivists, in November 2008 and compared these data with 545 ICU and 442 MC admissions after the wash-in period of the new MC (2009). Severity of illness data were prospectively acquired and uploaded to the national NICE database. The APACHE IV-system was used for sepsis related mortality through variable life adjusted display (VLAD)-analysis. No staffing or protocol changes were implemented during this period. Surviving Sepsis Campaign protocols were implemented in 2006.

Results: Patient characteristics are shown in Table 1. Sepsis related mortality VLAD-analysis is depicted in figure 1. A marked survival improvement is seen in the beginning of 2009, after the wash in period of the newly started MC in our hospital.

Conclusions: The opening of a medium care, in contrast to earlier publications, improves sepsis-related mortality in our hospital, meaning a medium care facility contributes to the survival in critically ill sepsis patients.

Table 1: patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ICU patients 2007</th>
<th>ICU patients 2009</th>
<th>MC patients 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>559</td>
<td>545</td>
<td>442</td>
</tr>
<tr>
<td>Mean age (y) (SD; median; range)</td>
<td>331 (59.3 %) 66 (16; 69; 17-100)</td>
<td>325 (59.6%) 65 (16; 68; 17-100)</td>
<td>257 (58.1%) 65 (17; 68; 17-101)</td>
</tr>
<tr>
<td>Length of stay (days) (SD; median; range)</td>
<td>7.4 (11.3; 3; 1-98)</td>
<td>6.2 (8.0; 3; 1-71)</td>
<td>3.0 (2.6; 2; 0-21)</td>
</tr>
<tr>
<td>Acute admissions Mortality</td>
<td>449 (80.3%) 94 (16.8%)</td>
<td>436 (80.0%) 88 (16.6%)</td>
<td>136 (30.8%) 13 (2.9%)</td>
</tr>
</tbody>
</table>

Figure 1. VLAD curve ICU according to the apache IV criteria.

An increasing survival is seen in the beginning of 2009, after the wash in period of the newly started MC.

References

24. Quality and Organisation

Which Intensive Care quality indicators are publicly available and how do they relate to the quality of care in Dutch Intensive Care Units?

NN Barneveld Binkhuysen, PHJ van der Voort
Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Background: In healthcare, quality of care becomes rather more important. To measure quality of care, quality indicators are used, which give an impression of the quality of care.

Objective: The aim of this study is to show how the quality of care in Dutch Intensive Care Units has developed throughout the years, comparing the hospitals to each other and individually.

Methods: In this four month retrospective observational study only external quality indicators concerning Intensive Care Medicine are included. The data are publicly available on the website www.ziekenhuistransparant.nl. All data available over the years 2003 up until 2008 will be collected, for 2003 is the first year quality indicators were scored and 2008 is the last year we will be able to include.

Results: Several indicators were selected to show the development of the Dutch Intensive Care Units in time. These indicators were chosen by the virtue of their clinical relevance, the fact that they were scored over more than one year and the information they provided on the quality of care. The results of this study show a positive increase within most quality indicators. The FTE of intensivists, number of days of mechanical ventilation, external audits and use of complication registration systems are rapidly developing. However, in 26,3% of all 613 hospitals included between 2003 and 2008, either one or more indicators were invalid. Different types of mistakes often occurred.

Conclusion: The validity of the quality indicators now available for external audit is insufficient and can not lead to firm conclusions concerning the quality of care.

25. Quality and Organisation

Workload of a Critical Care Outreach Team in a large tertiary referral teaching hospital

P Krijtenburg, HBM Fijn, P Heutink, B Brons, M van de Beem, M Kiestra-Ubachs, ARH van Zanten, DHT Tjan
Department of Intensive Care, Gelderse Vallei Hospital Ede, The Netherlands

Introduction: An outreach team (OT) is designed to prevent deaths outside the intensive care unit (ICU) by providing a specialized critical care team that can be called at all times. The OT comprises critical care nurses and ICU physicians. Its function is to support ward nurses and doctors in the care of non-ICU patients through assessment, advice, immediate interventions, and education. In our hospital an OT has been instituted since 2008. The goals are to improve care, facilitate discharges from critical care units, educate ward staff in the management of deteriorating patients, facilitate transfer to critical care and reduce cardiopulmonary arrest on general wards and readmission rates to critical care.

Although there are inconclusive data to confirm a positive impact of outreach teams on reduction of morbidity and mortality there is growing interest in the resource utilization and costs that are incurred through OT’s.

Objective: The aim of the study was to determine the workload and resource utilization of our OT since 2008.

Methods: We retrospectively analysed all OT consultations since 2008. Number of patient visits were differentiated into pre-ICU and post-ICU consultations. Activities were recorded and average time per consultation was analysed.

Results: Data are shown in table 1. OT consultations and activities were registered in 2008, 2009 and extrapolated in 2010 (based on data from January-August). Both the number of pre-ICU and post-ICU visits has increased markedly. The increase in pre-ICU consultations is more profound. A decline in time spend for all consultations was noted over the years. No relevant change in EWS-patient ratio was observed. However, an important reduction in interventions and activities per patient were recorded.

Conclusions: A marked increase in the number of OT consultations in general ward patients is observed. Pre-ICU consultations have increased substantially and even more than post-ICU consultations. Time spend per patient has decreased, possibly indicating knowledge and experience in the OT staff. Furthermore, the reduction in number of interventions and activities may also suggest a learning curve on the general wards. In 2010 more than 900 hours are spend in Outreach activities incurring relevant costs to the hospital’s budget. Further cost-benefit research is warranted.

Table 1. Outreach team activities

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients (n)</th>
<th>Pre-ICU (n)</th>
<th>Post-ICU (n)</th>
<th>Pre-post Ratio</th>
<th>Mean Pre-ICU time (min)</th>
<th>Mean Post-ICU time (min)</th>
<th>Activities (n)</th>
<th>Activity-patient ratio</th>
<th>EWS observations (n)</th>
<th>EWS obs-patient ratio</th>
<th>Interventions (n)</th>
<th>Intervention-patient ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>431</td>
<td>220</td>
<td>211</td>
<td>1.04</td>
<td>41.1</td>
<td>10.6</td>
<td>2437</td>
<td>5.65</td>
<td>1645</td>
<td>3.82</td>
<td>764</td>
<td>1.77</td>
</tr>
<tr>
<td>2009</td>
<td>407</td>
<td>241</td>
<td>166</td>
<td>1.45</td>
<td>38.3</td>
<td>10.6</td>
<td>2205</td>
<td>5.42</td>
<td>1678</td>
<td>4.12</td>
<td>521</td>
<td>1.28</td>
</tr>
<tr>
<td>2010*</td>
<td>701</td>
<td>396</td>
<td>305</td>
<td>1.30</td>
<td>36.5</td>
<td>8.7</td>
<td>2013</td>
<td>2.87</td>
<td>2577</td>
<td>3.68</td>
<td>594</td>
<td>0.85</td>
</tr>
</tbody>
</table>
26. Quality and Organisation

The influence of age on mortality, length-of-stay and ICU readmission rate in critically ill patients: A single centre cohort study

JA IJzerman, IA Meynaar
Department of Intensive Care, Reinier de Graaf Hospital, Delft, The Netherlands

Introduction: Increasingly, elderly patients are admitted to the intensive care unit. Age itself is not a reason for ICU admission or refusal of ICU admission; elderly patients often have more co-morbid conditions and as such may have a worse outcome. We studied our ICU database to see if increasing age is associated with mortality and with a higher resource utilisation expressed by length of stay and readmission rate.

Methods: In this retrospective cohort study we included all consecutive patients admitted to the ten-bed mixed closed format intensive care unit of the Reinier de Graaf Hospital Delft between January 1st, 2004 and December 31st, 2009. In analogy with the APACHE II criteria, patients younger than 16 years, patients with a length-of-stay (LOS) in ICU less than 8 hours and patients that were readmitted to the ICU were excluded from the analysis. Mortality with respect to age was studied in all patients mentioned above, but the association between age and both LOS and ICU readmission rate was studied in the subset of patients that were discharged alive from the hospital.

Results: A total of 3776 patients were included in the study, of which 3240 were discharged alive from the hospital. Unadjusted ICU mortality and hospital mortality increased significantly with increasing age (Table 1). Older patients were significantly more likely to die on the ward after ICU discharge than younger patients (p<0.001, Table 1). In patients discharged alive from the hospital, the ICU readmission rate and the ratio between hospital LOS and ICU LOS increased significantly with age (Table 2). Even with adjustment for illness severity (APACHE II score) and admission type in multivariate analysis, age was a significant risk factor for mortality (p<0.001, OR 1.036, 95% CI 1.028-1.045, P<0.001) was an independent risk factor for hospital mortality, after correction for APACHE II score and admission type.

Conclusion: Even after correction for illness severity (APACHE II score), age is an independent predictor for hospital mortality and for increased length of stay in hospital after ICU discharge. Older patients are more often readmitted to ICU, but after correction for illness severity this difference was not statistically significant.

Table 1. Mean APACHE II score and unadjusted observed mortality.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N = 3776</th>
<th>Mean APACHE II score (SD)</th>
<th>ICU mortality (%)</th>
<th>Ward mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>602</td>
<td>9.9 (±7.3)</td>
<td>16 (2.7%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>50-59,9</td>
<td>563</td>
<td>12.1 (±7.5)</td>
<td>42 (7.4%)</td>
<td>16 (2.9%)</td>
</tr>
<tr>
<td>60-69,9</td>
<td>806</td>
<td>13.4 (±7.2)</td>
<td>59 (7.3%)</td>
<td>36 (4.5%)</td>
</tr>
<tr>
<td>69,9-79,9</td>
<td>1115</td>
<td>15.2 (±7.2)</td>
<td>100 (9.0%)</td>
<td>76 (6.8%)</td>
</tr>
<tr>
<td>80+</td>
<td>690</td>
<td>16.2 (±7.2)</td>
<td>94 (13.6%)</td>
<td>88 (12.8%)</td>
</tr>
</tbody>
</table>

In multivariate analysis and age (OR 1.036, 95% CI 1.028-1.045, P<0.001) was an independent risk factor for hospital mortality, after correction for APACHE II score and admission type.

Table 2. ICU readmission rate and the ratio between hospital and ICU LOS in hospital survivors.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N = 3240</th>
<th>ICU readmission rate (N (%))</th>
<th>Median (Hosp LOS)/ (ICU LOS) (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>577</td>
<td>20 (3.5%)</td>
<td>3.8 (1.6-7.9)</td>
</tr>
<tr>
<td>50-59,9</td>
<td>505</td>
<td>19 (2.8%)</td>
<td>5.6 (2.5-10.0)</td>
</tr>
<tr>
<td>60-69,9</td>
<td>711</td>
<td>45 (6.2%)</td>
<td>7.4 (3.5-12.6)</td>
</tr>
<tr>
<td>69,9-79,9</td>
<td>939</td>
<td>56 (6.2%)</td>
<td>8.1 (3.9-12.6)</td>
</tr>
<tr>
<td>80+</td>
<td>508</td>
<td>39 (7.7%)</td>
<td>9.6 (4.9-17.4)</td>
</tr>
</tbody>
</table>

In multivariate analysis, correcting for illness severity and admission type, age was not significantly related to ICU readmission (P=0.08), but on the contrary the ratio between hospital and ICU LOS did increase significantly with age (P<0.001).

27. Respiration and Ventilation

Non-invasive mechanical ventilation for diagnostic bronchoscopy using a new face mask

CJR de Bruin1, JG van der Hoeven1, HFM van der Heijden2, LMA Heunks1
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Bronchoscopy is an indispensable tool for invasive pulmonary evaluation with high diagnostic yield and low incidence of major complications. However, hypoxemia increases the risk of complications, in particular during or after bronchoalveolar lavage. Therefore, clinicians may be reluctant to perform diagnostic bronchoscopy in hypoxic patients, in spite of the high diagnostic yield, even in critically ill patients. Non-invasive positive pressure ventilation (NPPV) may prevent hypoxemia associated with bronchoalveolar lavage. The purpose of this study is to present a modified total face mask to aid bronchoscopy during non-invasive positive pressure ventilation.

Methods: A commercially available full face mask was modified to allow introduction of the bronchoscope without interfering with the ventilator circuit [Fig. 1]. Twelve non-ICU patients with indications for bronchoscopy with bronchoalveolar lavage, but refusal by an experienced pulmonologist to perform this procedure because of hypoxemia or severe respiratory distress, were included and prospectively analyzed. Patients were admitted to the ICU solely for the purpose of bronchoscopy. Twenty minutes before bronchoscopy, patients were connected to NPPV. Positive end expiratory pressure (PEEP) was set at 6 cmH2O, pressure support 10 cmH2O en FiO2 1.0. Arterial blood gases were withdrawn before starting NPPV, during

**Figure 1**

With bronchoalveolar lavage, but refusal by an experienced pulmonologist to perform this procedure because of hypoxemia or severe respiratory distress, were included and prospectively analyzed. Patients were admitted to the ICU solely for the purpose of bronchoscopy. Twenty minutes before bronchoscopy, patients were connected to NPPV. Positive end expiratory pressure (PEEP) was set at 6 cmH2O, pressure support 10 cmH2O en FiO2 1.0. Arterial blood gases were withdrawn before starting NPPV, during
NPPV before and after bronchoscopy, and after discontinuing NPPV. **Results:** Patients had severely impaired oxygen uptake as indicated by PaO$_2$ / FiO$_2$ ratio 192 +/- 23 mmHg before bronchoscopy. Oxygenation improved after initiation of non-invasive positive pressure ventilation. On average, patients were on NPPV for 6 hours (range 2 – 24 h). Ten out of twelve patients were transferred to the general ward within 24 hours after ICU bronchoscopy. In all patients the procedure could be completed without subsequent complications, although in one patient SpO$_2$ decreased until 86% during bronchoscopy. A microbiological diagnosis could be established in 8 of 12 patients with suspected for infection.

The mask that has been used has several advantages, such as the ability to deliver pressure support ventilation, which seems reasonable during bronchoscopy to reduce the work of breathing. In addition, the increased distance between the mask and face of the patient allows better positioning of the bronchoscope, and the bronchoscope is not directly inserted into the ventilator circuit. Finally, no specific equipment is required. **Conclusion:** In hypoxemic patients physicians may either decline bronchoscopy or choose to intubate the patient. Our newly developed face mask for NPPV is a valuable tool to aid diagnostic bronchoscopy in hypoxemic patients.

**28. Respiration and Ventilation**

**Correlation of transcutaneous oxygen saturation and arterial partial oxygen pressure at low oxygenation targets**

HH Scholten, E de Jonge

Department of Intensive Care, Leiden University Medical Centre, Leiden, The Netherlands

**Introduction:** International guidelines suggest to adjust ventilator settings aiming at an arterial partial oxygen pressure (PaO$_2$) higher than 7.8 kPa which is much lower than present oxygenation targets used in Dutch ICUs [1]. A retrospective study showed an increased mortality with high FiO2 and when high PaO2 were achieved [2]. It is unknown if monitoring the transcutaneously measured oxygen saturation is safe when applying low oxygenation targets. This study was set up to describe the correlation between transcutaneous oxygen saturation (SpO2) and arterial oxygen saturation (SaO2) in ICU patients and to determine the minimal peripheral transcutaneous oxygen saturation that should be targeted to keep the PaO2 higher than 7.8 kPa.

**Methods and results:** In a single mixed medical/surgical ICU, all (n=35754) arterial blood gas samples taken from 1922 patients between april 1st 2009 and april 1st 2010, with concurrent transcutaneous oxygen saturations were retrieved from the patient data management system. Mean age was 61 ± 15 years, APACHE IV score 62 ± 31 points, 31.6% were medical patients, 15.1% after urgent surgery and 53.3% after planned surgery. Figure 1 shows the correlation between SaO2 and SaO2, table 1 shows the correlation between SpO2 and PaO2.

**Conclusion:** A SpO2 between 91 and 95% appears to be appropriate to achieve the recommended PaO2 levels higher than 7.8 kPa. In our study, with lower transcutaneous saturation levels, more than 50% of PaO2 values were lower than recommended. When accepting a SpO2 below 91% serial blood gasses should be taken as relying on the SpO2 solely carries a high risk of deep hypoxemia.

**References**


**Table 1. Correlation between transcutaneously measured SpO2 and PaO2**

<table>
<thead>
<tr>
<th>SpO2 (%)</th>
<th>N=</th>
<th>PaO2 (PERCENTILES)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10th</td>
<td>25th</td>
</tr>
<tr>
<td>71-75</td>
<td>320</td>
<td>4.5</td>
</tr>
<tr>
<td>76-80</td>
<td>502</td>
<td>4.8</td>
</tr>
<tr>
<td>81-85</td>
<td>667</td>
<td>5.2</td>
</tr>
<tr>
<td>86-90</td>
<td>1252</td>
<td>5.9</td>
</tr>
<tr>
<td>91-95</td>
<td>5801</td>
<td>7.9</td>
</tr>
<tr>
<td>96-100</td>
<td>27212</td>
<td>10.0</td>
</tr>
</tbody>
</table>

**Figure 1. Correlation between SaO2 (median and IQR) and transcutaneously measured SpO2.**
29. Respiration and Ventilation

Alternative diagnosis in the ventilator-associated pneumonia suspected bronchoalveolar-lavage negative patient

RJ Schoemakers1, R Schnabel1, GJ Oudhuis1, CF Linssen1, WNKA van Mook1, A Verbon2, DCJJ Bergmans1
1 Department of Intensive Care, Maastricht University Medical Centre+, Maastricht, The Netherlands
2 Department of Medical Microbiology, Maastricht University Medical Centre+, Maastricht, The Netherlands
3 Department of Infectious Diseases, Erasmus Medical Centre, Rotterdam, The Netherlands

Introduction: Other infectious and non-infectious diseases have been proven responsible for mimicking the clinical picture of ventilator-associated pneumonia (VAP). Aim of this study was to determine potential alternative diagnosis in patients suspected of VAP with negative bronchoalveolar-lavage (BAL) results.

Methods: All adult intensive care patients with a clinical suspicion of VAP and negative BAL results were included. The clinical suspicion of VAP was based on the combination of clinical, radiological, and microbiological criteria. BAL was considered positive if cell differentiation revealed ≥2% cells with intracellular organisms and/or quantitative culture results of ≥104 cfu/ml. Retrospectively, the most likely alternative diagnosis of the fever, the pulmonary densities and both combined were determined by two independent authors, based on records and test results.

Results: 110 patients with suspected VAP and negative BAL results were included. Table 1 presents the alternative causes of fever and pulmonary densities. Regarding fever, bacteremia was considered in 9 (13.2%) cases. Causes included central venous line infection (n=2), infected ascitis (n=1), urinary tract infection (n=3), infected hematoma (n=1). In two cases its origin remained obscure. Resorption fever was considered in 8 (11.8%) patients originating from neurotrauma (n=3), multitrauma (n=2), lung bleeding (n=1), brainstem hemorrhage (n=1) and a postoperative bleeding after thoracic-abdominal aortic aneurysm repair (n=1). Ischemia was found to be the alternative cause of fever in 6 (8.8%) patients, 5 due to intestinal ischemia and 1 due to a large ischemic cerebrovascular, accident.

In 53.6% of patients an alternative diagnosis of fever and pulmonary densities combined was found. Non-bacterial infectious pneumonia was diagnosed in 12 patients. Herpes simplex virus 1 (HSV-1) was the causative pathogen in 7 cases, followed by Cytomegalovirus in 2, Pneumocystis jiroveci, Proteus mirabilis and Candida Albicans each 1 case. HSV-1 pneumonia was diagnosed by a HSV-1 load in BALF >10^6 ge/ml. In 8 patients non-infectious pneumonia was diagnosed. BOOP (n=3) and drug-induced pneumonia (n=3) were the leading causes, followed by eosinophilic pneumonia (n=1) and Wegener’s granulomatosis (n=1).

Conclusion: Our results show that there is a wide spectrum of alternative diagnosis in patients suspected of VAP without BAL results. Most frequently found alternative diagnoses are viral pneumonia and non-infectious pneumonitis. Early identification of the exact cause may be vital for initiation of adequate treatment and thereby patient outcome.

<table>
<thead>
<tr>
<th>Alternative diagnosis of fever</th>
<th>Alternative diagnosis of pulmonary densities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Patients n (%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (17.6)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Non-infectious pneumonia</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Resorption fever</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Othera</td>
<td>21 (30.9)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (100.0)</td>
</tr>
</tbody>
</table>

a Less frequent causes are endocarditis (n=2), pleural empyema (n=2), pereitonitis (n=2), abdominal abscess (n=2), catheter related infection (n=2), subarachnoid hemorrhage (n=2), complicated urinary tract infection (n=2), pancreatitis (n=1), pulmonary abscess (n=1), pulmonary embolism (n=1), pyelonefritis (n=1), cholangitis (n=1), multi organ failure e.c.i. (n=1) and graft versus host disease (n=1)

b Less frequent causes are intestinal lung disease (n=1), alveolar hemorrhage (n=1), empyema (n=2), malignancy (n=1), pulmonary abscess (n=1) and pulmonary embolism (n=1)

30. Sepsis and Inflammation

Human Septic Plasma Induces Muscle Wasting in vitro

WJMV Schellekens, HWH van Hees, M Linkels, GJ Scheffer, JG van der Hoeven, R Dekhuijzen, LMA Heunks
Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Respiratory muscle weakness commonly occurs in patients with sepsis and is associated with difficult weaning from mechanical ventilation and increased mortality. The underlying mechanisms of sepsis-induced muscle weakness are largely unknown. The present study investigates the role of blood borne factors in the development of ICU associated muscle weakness. In addition, we examined whether systemically induced muscle wasting changes in the course of ICU admission.

Methods: Plasma was derived from patients with septic shock at admission and 2, 5 and 7 days after ICU admission (n=9). Age matched hospital employees served as controls (n=11). Cultured muscle cells were incubated with plasma from 1) septic patients 2) controls or 3) culture medium. After 24h cells were harvested and content of the contractile protein myosin was determined by Western blotting. Expression of proteolysis-related genes MuRF1 and MAFbx was assessed with Quantitative-PCR. Activity of the “inflammatory” transcription factor NFkappaB was analyzed by means of electrophoretic mobility shift assay 1h after incubation with septic or control plasma. Levels of IL-6 and IL-8 were measured by ELISA assay.

Results: Myosin content in muscle exposed to plasma from septic patients was 25% lower than in muscle exposed to plasma from healthy subjects (p<0.05). MuRF1 and MAFbax mRNA levels were three to four fold increased in cells exposed to septic plasma compared to control (P<0.01). NFkappaB activity was higher in muscle cells treated with septic plasma than in cells treated with plasma from controls. Plasma levels of IL-6 and IL-8 were significantly higher in septic patients than in control (p<0.001). Subsequent time-series experiments showed that myosin loss and enhancement of MAFbax expression were most severe when muscle cells were exposed to sepsis plasma derived at day 0.

Conclusion: The results from this study demonstrate that plasma from patients with sepsis contains factors that induce muscle atrophy by activating key regulators of proteolysis. The atrophic response appears most prominent during the first 24 hours of ICU admission.
31. Sepsis and Inflammation

Biomarkers in delirious patients at the critical care unit

M van den Boogaard1, L Schoonhoven2, K Quinn3, M Kox1, C Hoedemaekers1, JG van der Hoeven1, P Pickkers1
1 Department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, The Netherlands
2 IQ healthcare, Radboud University Nijmegen Medical Centre, The Netherlands
3 Departments of Anesthesia and Critical Care St. Michael’s Hospital, Toronto, Ontario, Canada

Introduction: Delirium occurs frequently in critically ill patients, and especially in severely ill and infectious patients. Although several pathways for delirium have been described, the role of biomarkers in ICU patients is unknown. We examined differences in levels of several biomarkers and their correlations between delirious and non-delirious patients admitted to the intensive care unit (ICU) with and without clinical evidence of an infection.

Methods: Delirium in adult ICU patients was diagnosed using the confusion assessment method-ICU (CAM-ICU). Delirious and non-delirious patients were matched for age, APACHE-II score, the presence of absence infection or SIRS criteria, and length of ICU stay at the moment of blood withdrawal. Neurology and trauma patients were excluded. Within 24 hours after the development of delirium blood was drawn for determination of biomarkers. ANCOVA and multivariate logistic regression analyses were performed.

Results: 50 delirious ICU patients were matched with 50 non-delirious patients. Delirious patients with infection or SIRS had significantly higher levels of IL-6, IL-18, IL-1ra, MCP-1, and procalcitonine compared with the non-delirious patients with an infection (table 1). Non-inflamed delirious patients had significantly higher levels of IL-6, IL-8, IL-1ra, IL-10 and procalcitonine compared with non-inflamed, non-delirious patients. When corrected for infection or positive SIRS, levels of IL-8 (p=0.04), IL-10 (p=0.03), MCP-1 (p=0.004), cortisol (p=0.009) and procalcitonine (p=0.04) were significantly higher in the delirious group compared to the non-delirious patients. IL-8, MCP-1 and PCT were significantly correlated with delirium; p=0.03, p=0.006 and p=0.02, respectively.

Conclusion: In ICU patients, delirium is associated with significantly increased concentrations of several cytokines, even after adjusting for the presence of infection. We conclude that IL-8, MCP-1 and procalcitonine are associated with delirium in ICU patients, and could serve as possible biomarkers.

Table 1. Biomarkers in delirious and non-delirious ICU patients

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>delirium (n=26)</th>
<th>Infection or positive SIRS patients (n=46)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no delirium (n=20)</td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>73 [38–143]</td>
<td>41 [21–90]</td>
<td>0.09</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td>31 [24–44]</td>
<td>17 [9–26]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-18 (pg/mL)</td>
<td>136 [88–187]</td>
<td>84 [65–132]</td>
<td>0.03</td>
</tr>
<tr>
<td>MIF (pg/mL)</td>
<td>438 [294–796]</td>
<td>257 [157–576]</td>
<td>0.13</td>
</tr>
<tr>
<td>IL-1ra (pg/mL)</td>
<td>48 [27–74]</td>
<td>32 [18–47]</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>23 [13–47]</td>
<td>13 [9–35]</td>
<td>0.08</td>
</tr>
<tr>
<td>MCP-1 (pg/mL)</td>
<td>516 [295–822]</td>
<td>251 [199–339]</td>
<td>0.001</td>
</tr>
<tr>
<td>HNP (µg/mL)</td>
<td>0.06 [0.02–0.13]</td>
<td>0.07 [0.02–0.12]</td>
<td>0.60</td>
</tr>
<tr>
<td>Procalcitonine (ng/mL)</td>
<td>1.0 [0.23–2.0]</td>
<td>0.28 [0.12–0.64]</td>
<td>0.003</td>
</tr>
<tr>
<td>Cortisol (µmol/L)</td>
<td>0.59 [0.34–0.98]</td>
<td>0.48 [0.18–0.61]</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Tested with ANCOVA with log transformed data

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>delirium (n=24)</th>
<th>Non-inflamed patients (n=54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no delirium (n=30)</td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>50 [29–90]</td>
<td>34 [22–64]</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td>20 [12–32]</td>
<td>14 [9–22]</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-18 (pg/mL)</td>
<td>82 [66–141]</td>
<td>88 [72–120]</td>
<td>0.54</td>
</tr>
<tr>
<td>MIF (pg/mL)</td>
<td>334 [214–561]</td>
<td>249 [179–702]</td>
<td>0.08</td>
</tr>
<tr>
<td>IL-1ra (pg/mL)</td>
<td>24 [17–51]</td>
<td>16 [11–25]</td>
<td>0.02</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>28 [12–44]</td>
<td>22 [9–46]</td>
<td>0.03</td>
</tr>
<tr>
<td>MCP-1 (pg/mL)</td>
<td>288 [192–398]</td>
<td>233 [175–306]</td>
<td>0.15</td>
</tr>
<tr>
<td>HNP (µg/mL)</td>
<td>0.06 [0.04–0.10]</td>
<td>0.04 [0.03–0.10]</td>
<td>0.51</td>
</tr>
<tr>
<td>Procalcitonine (ng/mL)</td>
<td>0.22 [0.11–0.55]</td>
<td>0.12 [0.06–0.18]</td>
<td>0.01</td>
</tr>
<tr>
<td>Cortisol (µmol/L)</td>
<td>0.46 [0.23–0.72]</td>
<td>0.30 [0.06–0.66]</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Tested with ANCOVA with log transformed data
32. Sepsis and Inflammation

Adequacy of antimicrobial therapy of complicated intra-abdominal infections: Healthcare-associated versus community-acquired

VM Meijering, MB Ekkelenkamp, R Tepaske, DW de Lange
Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

Background: Intra-abdominal infections (IAIs) represent an important cause of morbidity and are frequently associated with a poor prognosis. Mortality has been reported between 20 and 45%, depending on the population that is studied. Adequate and timely antimicrobial therapy is essential, but often empirical therapy has to be initiated before culture results become available. Furthermore, controversy exist about which cultured micro-organisms (if not all) require treatment. We set out to investigate the influence of the microbial flora cultured from abdominal fluid-organisms and the appropriateness of empirical antimicrobial therapy on survival, in a cohort of 193 patients with IAI.

Methods: All patients with peritonitis, with a positive abdominal microbiological culture, over a six-year interval were retrospectively included. The cohort was divided into a group with health-care associated intra-abdominal infection (HA-IAI) and a group with community-acquired infection (CA-IAI). The cohort was divided into a group with health-care associated intra-abdominal infection (HA-IAI) and a group with community-acquired infection (CA-IAI). In addition, a distinction was made between the adequate vs. inadequate antimicrobial treatment of patients. Patient characteristics and outcomes of these groups were compared.

Results: One hundred ninety three patients were included, 140 with HA-IAI and 53 with CA-IAI. Patients with CA-IAI were more severely ill (APACHE II scores of 21.8 vs. 16.4), however patients with HA-IAI had longer lengths of stay (51 days vs. 14 days) and were admitted to the ICU more often (75% vs. 49%). No difference in mortality between patients with HA-IAI and CA-IAI was found (24.6% vs. 25.2%). 125/157 patients (80%) received empirical treatment which did not cover all cultured micro-organisms (so-called inadequate treatment). Inadequate treatment was associated with a higher mortality, in patients with CA-IAI, but not in patients with HA-IAI. The presence of enterococci and Candida species was not associated with higher mortality, even when these micro-organisms were not covered by the empirical antimicrobial therapy.

Conclusion: Overall mortality in patients with IAI in our cohort was 25.3%. No difference in mortality is found between HA-IAI and CA-IAI. The majority of patients with complicated IAI initially receive inadequate antimicrobial therapy, which is associated with a higher in-hospital mortality, especially in patients with CA-IAI. Prognosis of patients with CA-IAI compared to their HA-IAI counterparts is better, with a shorter length of stay, less admissions to the intensive care unit (ICU) and lower mortality rates, provided that they are adequately treated. However, mortality rates for patients with CA-IAI increase significantly if antimicrobial treatment is inadequate. However, our findings may not be applicable to all patients with IAI, partly due to a small number of patients with CA-IAI.

33. Sepsis and Inflammation

Enteral Lipid- and Protein-Enriched Nutrition limits Inflammation During Experimental Human Endotoxemia

M Kox1, T Lubbers1, JJ de Haan1, JW Greve1, JC Pompe1, BP Ramakers1, P Pickkers1, WA Buurman2
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre+, The Netherlands
3 Department of Surgery, Atrium Medical Centre, Heerlen, The Netherlands

Rationale: A dysregulated inflammatory response is an important cause of morbidity and mortality in critically ill patients. Apart from immunomodulating nutritional compounds such as omega-3 fatty acids, animal studies have demonstrated that enteral administration of lipid-enriched nutrition devoid of intrinsically anti-inflammatory constituents limits inflammation and organ damage. These anti-inflammatory effects are mediated via a cholecystokinin (CCK)-mediated vagovagal reflex, resulting in activation of the so-called cholinergic anti-inflammatory pathway.

Objective: The current proof-of-principle study investigates the immunomodulatory potential of enteral lipid- and protein-enriched nutrition during experimental human endotoxemia.

Methods: Following informed consent and screening of the participant, a nasojejunal tube was inserted the evening prior to the endotoxemia experiment. After an overnight fast, 18 healthy male subjects received an intravenous bolus of Escherichia coli lipopolysaccharide (LPS 2 ng/kg). Correct placement of the nasojejunal tube was verified by pH-measurement. Subjects in the intervention groups were fed lipid- and protein-enriched (n=6) or isocaloric (1 kcal/mL) control (n=6) enteral nutrition, starting 1 hour prior to LPS administration until 6 hours afterwards, while subjects in the fasted group (n=6) were deprived of food throughout the study. The rate of feeding for each subject was determined by calculating the basal metabolic rate using the Harris-Benedict equation. Serial blood samples for the determination of cytokines were drawn.

Results: Overall mortality in patients with IAI in our cohort was 25.3%. No difference in mortality is found between HA-IAI and CA-IAI. The majority of patients with complicated IAI initially receive inadequate antimicrobial therapy, which is associated with a higher in-hospital mortality, especially in patients with CA-IAI. Prognosis of patients with CA-IAI compared to their HA-IAI counterparts is better, with a shorter length of stay, less admissions to the intensive care unit (ICU) and lower mortality rates, provided that they are adequately treated. However, mortality rates for patients with CA-IAI increase significantly if antimicrobial treatment is inadequate. However, our findings may not be applicable to all patients with IAI, partly due to a small number of patients with CA-IAI.

Conclusion: Overall mortality in patients with IAI in our cohort was 25.3%. No difference in mortality is found between HA-IAI and CA-IAI. The majority of patients with complicated IAI initially receive inadequate antimicrobial therapy, which is associated with a higher in-hospital mortality, especially in patients with CA-IAI. Prognosis of patients with CA-IAI compared to their HA-IAI counterparts is better, with a shorter length of stay, less admissions to the intensive care unit (ICU) and lower mortality rates, provided that they are adequately treated. However, mortality rates for patients with CA-IAI increase significantly if antimicrobial treatment is inadequate. However, our findings may not be applicable to all patients with IAI, partly due to a small number of patients with CA-IAI.

Figure 1. Plasma cytokine levels during experimental human endotoxemia in subjects receiving either enriched, control or no nutrition. Data are presented as mean ± SEM of 6 subjects per group. Overall p-value represents two-way ANOVA of all three groups. Other p-values represent two-way ANOVA of two designated groups.
Oral treatment with dipyridamole modulates inflammation during human endotoxemia

BP Ramakers1, NP Riksen1, T Stal2, P van den Broek1, JG van der Hoeven1, P Smits1, P Pickkers2

1 Department of Pharmacology-Toxicology, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
3 Department of Internal Medicine Division of Vascular Medicine, Radboud University Nijmegen Medical Centre, The Netherlands

Background: Preclinical studies have shown that the endogenous nucleoside adenosine is able to modulate the immune response and to prevent tissue injury during systemic inflammation. Dipyridamole, an adenosine re-uptake inhibitor that increases the local adenosine concentration during unfavorable conditions, e.g. during inflammation, may as such attenuate the inflammatory response and subsequent organ injury. In the present study we aimed to determine whether oral treatment with dipyridamole is able to modulate the innate immune response and subsequent organ injury during experimental human endotoxemia.

Methods: In a double-blind placebo-controlled randomized trial, 20 healthy male subjects received 2 ng/kg E. Coli LPs intravenously with or without pretreatment (7 days) with the adenosine reuptake inhibitor dipyrdamole, 200 mg retard twice daily. Serial blood samples for the determination of cytokines and markers of endothelial function were drawn and forearm blood flow during intrabrachial norepinephrine administration was determined.

Results: Dipyridamole treatment significantly reduced uridine transporter activity with 89±2% (p<0.0001; n=10, paired students t-test). Although dipyridamole treatment did not influence peak concentrations of the pro-inflammatory cytokines TNF-α and IL-6, the decrease in these cytokines following the initial peak concentration was more pronounced in the dipyridamole-treated group. In addition, dipyridamole treatment significantly augmented the anti-inflammatory IL-10 response during endotoxemia (p=0.0001, two-way ANOVA (figure 1)). Moreover, IL-10 peak levels correlated with the degree of TNF-α decline (Pearson r=0.54, p=0.018), while this was not the case for IL-6 (r=0.32, p=0.18). The LPs-induced increase in ICAM and VCAM levels (markers of endothelial function) was also attenuated in dipyridamole treated subjects compared to the placebo group; 115±14% compared to 76±6% for ICAM and 59±4% compared to 43±2% for VCAM, p=0.07 and 0.018, respectively. Interestingly, again, IL-10 peak levels significantly correlated with the attenuated rise in soluble VCAM (Pearson r=-0.48, p=0.037). Finally, endotoxemia induced a significant decrease in norepinephrine sensitivity in the placebo group, while this was not the case in the subjects treated with dipyridamole (figure 2).

Conclusions: Dipyridamole treatment augments the anti-inflammatory response to a large extent and this effect is associated with a more pronounced clearance of pro-inflammatory cytokines, less endothelial dysfunction and prevention of the endotoxia-induced decrease in the vascular norepinephrine sensitivity.

Figure 1. Cytokine response after LPs administration (2ng/kg body weight) in placebo treated subjects (open symbols, dotted line) and dipyridamole treated subjects (solid symbols).

Figure 2. Dose-response curve of intrabrachial infusion of norepinephrine on FBF before (open symbols, dotted line) and 4 hours after (solid symbols) administration of 2 ng/kg E coli LPs. Data are presented as percentages of baseline FBF ratio of the intervention arm (mean ± SEM; n=10 per group).

Hypothermia does not increase the risk of infection: a case control study

M Kamps, LLA Bischops, JG van der Hoeven, CWE Hoedemaekers

Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Hypothermia may improve outcome in patients after traumatic brain injury, especially when hypothermia is maintained for more than 48 hours. In the acute phase, patients with severe brain injury are more vulnerable to infections. Prolonged hypothermic treatment may further enhance the risk of infection. Selective decontamination of the digestive tract (SDD) reduces the risk of respiratory tract infections. Aim of the study was to investigate the incidence of infections in patients treated with hypothermia and normothermia while receiving SDD.

Methods: In this retrospective case control study 35 patients treated with prolonged hypothermia (cases) were identified and 169 patients with severe brain injury were included (controls). Propensity score matching was performed to correct for differences in baseline characteristics and clinical parameters. Primary outcome was the incidence of infection. The secondary endpoints were the micro-organisms found in the surveillance cultures and infection. In addition, a number of clinical characteristics were assessed.

Results: The demographic and clinical data indicated that the cases and controls were well matched. The overall risk of infection during ICU stay was 20% in the hypothermia groups versus 34.4% in the normothermia group (p=0.388) (Table 1). Pneumonia was diagnosed in 11.4% of patients in both groups (p=1.000). The incidence of meningitis, wound infection,
bacteremia, and urinary tract infection was low and comparable between the groups. SDD surveillance cultures indicated a higher colonization with gram-negative bacteria in the rectal samples of the hypothermia patients (Table 2).

**Conclusion:** SDD is a safe method to decrease the risk of infectious complications in patients treated with mild hypothermia for more than 24 hours. Based on the surveillance cultures, it seems that oropharyngeal decontamination is the most effective part of the SDD regimen in the prevention of pneumonia. Selective oropharyngeal decontamination (SOD) may thus be as effective as SDD in this population. Further studies are needed to establish the exact role of SDD and SOD in the prevention of infectious complications during hypothermia.

### Table 1. Incidence of infections in both groups

<table>
<thead>
<tr>
<th></th>
<th>Normothermia (n=35)</th>
<th>Hypothermia (n=35)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an infection n(%)</td>
<td>12 (34.3%)</td>
<td>7 (20.0%)</td>
<td>0.267</td>
</tr>
<tr>
<td>Pneumonia n(%)</td>
<td>4 (11.4%)</td>
<td>4 (11.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Meningitis n(%)</td>
<td>3 (8.6%)</td>
<td>1 (2.9%)</td>
<td>0.625</td>
</tr>
<tr>
<td>Bacteremia n(%)</td>
<td>3 (8.6%)</td>
<td>2 (5.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Wound infection n(%)</td>
<td>3 (8.6%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>UTI n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Total prescribed antibiotics N(%)</td>
<td>20 (57.1%)</td>
<td>20 (57.1%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are presented as absolute numbers with percentage points. UTI: Urinary tract infection

### Table 2. Positive surveillance cultures

<table>
<thead>
<tr>
<th></th>
<th>Normothermia (n=35)</th>
<th>Hypothermia (n=35)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pts with gram negative bacteria in surveillance culture n(%)</td>
<td>9(25.7%)</td>
<td>18 (51.4%)</td>
<td>0.049</td>
</tr>
<tr>
<td>rectum n (%)</td>
<td>7 (20.0%)</td>
<td>17 (48.6%)</td>
<td>0.041</td>
</tr>
<tr>
<td>oropharynx/sputum n (%)</td>
<td>3 (8.6%)</td>
<td>5 (14.3%)</td>
<td>0.687</td>
</tr>
<tr>
<td>Number of pts with candida spp in surveillance culture n(%)</td>
<td>11(31.4%)</td>
<td>15 (42.9%)</td>
<td>0.523</td>
</tr>
<tr>
<td>rectum n (%)</td>
<td>0 (0%)</td>
<td>0(0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>oropharynx n (%)</td>
<td>66 (31.4%)</td>
<td>15(42.9%)</td>
<td>0.523</td>
</tr>
</tbody>
</table>

Data are shown in absolute numbers with percentages.

36. Sepsis and Inflammation

### Implementation of the Survival Sepsis Campaign in a large teaching hospital,
“Attention the human factor”

**HH Ponssen**

*Department of Intensive Care, Albert Schweitzer Hospital, Dordrecht, The Netherlands*

**Context:** The improvement work was done in the two ICU’s and emergency departments. Our target was to reduce hospital mortality in severe septic patients. The improvement group consisted of:
- a communication advisor
- a psychologist
- 3 nurses
- an emergency physician
- an intensivist

**Problem:** Concerning proper treatment of sepsis we were faced with several aspects:
- a high mortality rate (48%) in severe septic ICU-patients in our hospital
- septic patients were not a “hot” issue
- earlier improvement programs in our hospital did not always reach targeted goals (e.g. outreach teams, hand-washing, reduction of postoperative wound infections, reduction of pain, feeding the sick patients etc.)

**Assessment of problem and analysis of its causes:** From the Dutch National Intensive Care Evaluation Database (NICE) we knew that our mortality rate was high (48%) in severe septic ICU-patients. Earlier improvement projects did not reach their set goals.

A cultural problem in our organisation was felt which consisted of lack of eagerness to improve.

**Intervention:** We invested a lot of time in designing our “implementing strategy” instead of just starting the project, as we did before.

**Period** | n = septic patients | n = patients leaving the hospital alive | n = died in the ICU | % died | predicted mortality (median) | n = extra lives saved since introduction of the program
---|---------------------|-----------------------------|-------------------|--------|-----------------------------|------------------|
1/1/2010 - 1/08/2010 | 66                  | 50                          | 16                | 24%    | 39%                        | 10               |
2009                | 108                 | 67                          | 37                | 35%    | 40%                        | 6                |
2008                | 52                  | 27                          | 25                | 48%    | 49%                        | 0                |
2007                | 58                  | 34                          | 24                | 41%    | 42%                        | 0                |

**Study design:** The intervention was no subject for research

**Strategy for change:** The implementation process consisted of:
- posters throughout the hospital
- advertisement on the intranet of the hospital
- education sessions
- feedback in every sepsis-case that was not treated properly (every time a
37. Sepsis and Inflammation

Atazanavir-induced (unconjugated) hyperbilirubinemia does not modulate pro-inflammatory markers, but attenuates IL-10 after lipopolysaccharide challenge in humans

MJ Dorresteijn1,2, D Dekker3, J Zwaag1,2, A Scharstuhl2, P Smits2, JG van der Hoeven1, FA Wagener2, P Pickkers1,2

1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Pharmacology and Toxicology, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Oxidative stress is considered an important factor in the development of organ damage in septic patients. Therefore, the eradication of free radicals with anti-oxidants is a potential target for preventing this deleterious chain of events. Unconjugated bilirubin is a powerful endogenous anti-oxidant. In animal experiments, bilirubin infusion protected against inflammation-induced mortality suggesting that artificially increasing bilirubin concentration could be a potential therapeutic intervention in inflammatory states. Unfortunately, bilirubin for human infusion is not available. However, atazanavir, a drug registered for use in HIV patients, is known to induce hyperbilirubinemia by inhibition of the enzyme UGT1A1.

Objective: To determine the effects of atazanavir-induced (unconjugated) hyperbilirubinemia on induction of the innate immune system, endothelial activation and clinical parameters after lipopolysaccharide (LPS) challenge in healthy humans.

Methods: In a double-blind placebo-controlled pilot study, 20 healthy male volunteers received 2 ng/kg of E.coli LPS. Prior to the LPS infusion, subjects were treated with atazanavir 300 mg twice daily for four days (n=10) or placebo in identical capsules (n=10). Blood was sampled at several time points to determine bilirubin, cytokines, and adhesion molecule concentrations. Blood pressure, heart rate and body temperature were recorded. Data are presented as mean±SEM.

Results: After treatment with atazanavir, total bilirubin concentration increased to 49±5 compared to 7±1 mmol/l in subjects treated with placebo. After LPS infusion, bilirubin increased to 80±5mmol/l in subjects treated with atazanavir versus 15±2 in the placebo-group at 4 hours after LPS infusion (between groups ANOVA RM p<0.01).

In all subjects, LPS infusion induced the production of cytokines but no differences were observed between groups, except for the production of the anti-inflammatory cytokine Interleukin-10 which was significantly reduced by hyperbilirubinemia (Table 1). Concentrations of adhesion molecules were all increased during endotoxemia, and did not differ between groups (Table 1). The LPS-induced changes in heart rate, blood pressure and body temperature were also not influenced by atazanavir-induced hyperbilirubinemia.

Conclusion: The present study is the first investigate the effects of the potent endogenous anti-oxidant bilirubin during human inflammation. Hyperbilirubinemia did not alter the response of pro-inflammatory cytokines, but attenuated the rise of the anti-inflammatory cytokine IL-10. Markers of endothelial activation and clinical parameters were not influenced by hyperbilirubinemia. Further research is needed to clarify if the promising results from animal studies can be translated to beneficial effects in humans.

Table 1. Cytokine and adhesion molecule concentrations after LPS infusion

<table>
<thead>
<tr>
<th>Cytokine/Molecule</th>
<th>Placebo</th>
<th>Hyperbilirubinemia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Necrosis Factor-α (pg/ml)</td>
<td>655±117</td>
<td>585±71</td>
<td>0.6</td>
</tr>
<tr>
<td>Interleukin-6 (pg/ml)</td>
<td>941±96</td>
<td>1035±77</td>
<td>0.4</td>
</tr>
<tr>
<td>Interleukin-8 (pg/ml)</td>
<td>613±93</td>
<td>638±49</td>
<td>0.6</td>
</tr>
<tr>
<td>Monocyte Chemotactic Protein-1 (pg/ml)</td>
<td>6619±736</td>
<td>5998±725</td>
<td>0.4</td>
</tr>
<tr>
<td>Interleukin-10 (pg/ml)</td>
<td>424±98</td>
<td>249±40</td>
<td>0.03</td>
</tr>
<tr>
<td>Vascular Cell Adhesion Molecule-1 (ng/ml)</td>
<td>251±26</td>
<td>226±22</td>
<td>0.1</td>
</tr>
<tr>
<td>P-selectin (ng/ml)</td>
<td>46±3</td>
<td>42±3</td>
<td>0.9</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>191±26</td>
<td>182±17</td>
<td>0.8</td>
</tr>
</tbody>
</table>
38. Sepsis and Inflammation

**Inflammation-induced increase in whole blood viscosity during human endotoxemia**

J Zwaag1, MJ Dorresteijn1,2, G Pop1, JG van der Hoeven1, P Pickkers1
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Pharmacology-toxicology, Radboud University Nijmegen Medical Centre, The Netherlands
3 Department of Cardiology, Radboud University Nijmegen Medical Centre, The Netherlands

**Introduction:** Whole blood viscosity is determined by three major factors: hematocrit, aggregating proteins and the shear rate of blood. During sepsis the increase of acute phase proteins may result in a rise of blood viscosity. It is unknown to what extent the inflammatory response and change in viscosity correlate. Our aim was to measure blood viscosity during a standardized activation of the innate immune system evoked by experimental human endotoxemia and correlate its change with the increase of several cytokines.

**Methods:** After obtaining informed consent, nine healthy male volunteers participated in our study. Before and after prehydration with 1.5L NaCl 0.45%/glucose 2.5% within 45 minutes, and following i.v. administration of 2ng/kg E.coli lipopolysaccharide (LPS), cytokines (Luminex), hematocrit, fibrinogen and whole blood viscosity were measured in arterially sampled blood. Viscosity measurements (Contraves Ls 30) were performed at an identical shear rate (0.5 sec−1) and temperature (37º Celsius). Data are expressed as Mean±SEM. Since data were normally distributed, statistics were performed using Student’s t-test and Pearson correlation coefficients.

**Results:** At baseline blood viscosity of 24.9±2.8 mPa.s−1 was measured. Hematocrit was 0.40±0.01 L/L and fibrinogen was 2633±56 mg/L. After hemodilution, the mean blood viscosity dropped to 19.9±2.4 mPa.s−1 (p=0.07) and hematocrit dropped to 0.38±0.01. Δviscosity tended to be correlated to Δ hematocrit (p=0.053). Peak concentrations of TNF-α were reached 1.5 hours after LPS-infusion and peak concentrations of IL-6, IL-8 and IL-10 were reached 2 hours after LPS-infusion. Viscosity significantly increased to 27.6±3.6 mPa.s 1.5 hours after LPS infusion (p=0.02). The increase in TNF-α correlated with the increase in whole blood viscosity (r= 0.57, p=0.051, see figure); after LPS- administration, fibrinogen and hematocrit did not change significantly during experimental human endotoxemia.

**Conclusion:** The hemodilution-induced decrease in hematocrit is associated with a decrease in whole blood viscosity. Systemic inflammation evoked by experimental human endotoxemia results in high cytokine concentrations, of which the increase in TNF-α is correlated with the rise in whole blood viscosity.

39. Sepsis and Inflammation

**Alkaline Phosphatase Improves Sepsis-induced Acute Kidney Injury: A Double blind Prospective Randomized Placebo-Controlled Phase II Trial**

P Pickkers1, J Schouten2, PF Laterre3, JL Vincent4, B Beishuizen5, P Jorens6, H Spapen7, M Bulitta8, S Heemskerk1, JG van der Hoeven1
1 Department of Intensive Care, Radboud University Nijmegen Medical Centre, The Netherlands
2 Department of Critical Care, Canisius Wilhelmina Ziekenhuis, Nijmegen, The Netherlands
3 Department of Intensive Care, Cliniques Universitaires Saint Luc-UCL, Brussels, Belgium
4 Department of Intensive Care, ULB Hospital Erasme, Brussels, Belgium
5 Department of Critical Care, Free University Medical Centre, Amsterdam, The Netherlands
6 Department of Intensive Care, University Hospital, Antwerp, Belgium
7 Department of Intensive Care, Free University Hospital, Brussels, Belgium
8 CRM Biometrics GmbH, Rheinbach, Germany

**On behalf of the APREN Study Group**

**Rationale:** Alkaline phosphatase (AP) is an endogenous detoxifying enzyme that is depleted in the kidney during an ischemic or inflammatory insult. Administration of AP improves outcomes in animal models and decreases urinary excretion of markers of tubular damage in a previous sepsis trial.
Objectives: To evaluate whether AP treatment improves renal function in sepsis patients with acute kidney injury (AKI). AP treatment was well-tolerated by patients with sepsis and AKI. Significant overall benefit of AP treatment on renal endpoints was observed (P<0.05). Creatinine clearance recovered more rapidly in the AP group (P=0.02), while relative duration of RRT was shorter (12 vs. 34% of total time in study, p<0.05) and fewer patients tended to require RRT (19 vs. 36%, p=0.29), supported by significant changes in biomarkers such as renal KIM-1. Furthermore, AP treatment reduced mean ICU length of stay (10.9 vs 24.5 days, p=0.02).

Conclusions: Alkaline phosphatase treatment attenuates renal damage and improves renal function in sepsis patients with AKI.

Methods:

Methods: A randomized double blind placebo controlled trial was carried out in which thirty healthy male volunteers were randomized to receive the iron chelator deferasirox (30 mg/kg, orally, t=-2 hrs), iron sucrose (1,25 mg/kg, intravenously, t=-1 hr), or placebo in advance of the intravenous administration of 67.5U/kg followed by continuous infusion of 132.5U/kg for 48h and patients were followed up for 28 days.

Measurements and Main Results: Progress in renal parameters was the primary endpoint (combined end point: creatinine clearance, requirement and duration of RRT). Secondary endpoints were clinical improvement (duration of ventilator support and ICU length of stay) and changes in the urinary excretion of biomarkers of renal injury.

Methods: A randomized double blind placebo controlled trial was carried out in which thirty healthy male volunteers were randomized to receive the iron chelator deferasirox (30 mg/kg, orally, t=-2 hrs), iron sucrose (1,25 mg/kg, intravenously, t=-1 hr), or placebo in advance of the intravenous administration of 67.5U/kg followed by continuous infusion of 132.5U/kg for 48h and patients were followed up for 28 days.

Measurements and Main Results: Progress in renal parameters was the primary endpoint (combined end point: creatinine clearance, requirement and duration of RRT). Secondary endpoints were clinical improvement (duration of ventilator support and ICU length of stay) and changes in the urinary excretion of biomarkers of renal injury.

Methods: A randomized double blind placebo controlled trial was carried out in which thirty healthy male volunteers were randomized to receive the iron chelator deferasirox (30 mg/kg, orally, t=-2 hrs), iron sucrose (1,25 mg/kg, intravenously, t=-1 hr), or placebo in advance of the intravenous administration of 67.5U/kg followed by continuous infusion of 132.5U/kg for 48h and patients were followed up for 28 days.

Measurements and Main Results: Progress in renal parameters was the primary endpoint (combined end point: creatinine clearance, requirement and duration of RRT). Secondary endpoints were clinical improvement (duration of ventilator support and ICU length of stay) and changes in the urinary excretion of biomarkers of renal injury.

Methods:

Methods: A randomized double blind placebo controlled trial was carried out in which thirty healthy male volunteers were randomized to receive the iron chelator deferasirox (30 mg/kg, orally, t=-2 hrs), iron sucrose (1,25 mg/kg, intravenously, t=-1 hr), or placebo in advance of the intravenous administration of 67.5U/kg followed by continuous infusion of 132.5U/kg for 48h and patients were followed up for 28 days.

Measurements and Main Results: Progress in renal parameters was the primary endpoint (combined end point: creatinine clearance, requirement and duration of RRT). Secondary endpoints were clinical improvement (duration of ventilator support and ICU length of stay) and changes in the urinary excretion of biomarkers of renal injury.

Methods: A randomized double blind placebo controlled trial was carried out in which thirty healthy male volunteers were randomized to receive the iron chelator deferasirox (30 mg/kg, orally, t=-2 hrs), iron sucrose (1,25 mg/kg, intravenously, t=-1 hr), or placebo in advance of the intravenous administration of 67.5U/kg followed by continuous infusion of 132.5U/kg for 48h and patients were followed up for 28 days.

Measurements and Main Results: Progress in renal parameters was the primary endpoint (combined end point: creatinine clearance, requirement and duration of RRT). Secondary endpoints were clinical improvement (duration of ventilator support and ICU length of stay) and changes in the urinary excretion of biomarkers of renal injury.

Methods: A randomized double blind placebo controlled trial was carried out in which thirty healthy male volunteers were randomized to receive the iron chelator deferasirox (30 mg/kg, orally, t=-2 hrs), iron sucrose (1,25 mg/kg, intravenously, t=-1 hr), or placebo in advance of the intravenous administration of 67.5U/kg followed by continuous infusion of 132.5U/kg for 48h and patients were followed up for 28 days.

Measurements and Main Results: Progress in renal parameters was the primary endpoint (combined end point: creatinine clearance, requirement and duration of RRT). Secondary endpoints were clinical improvement (duration of ventilator support and ICU length of stay) and changes in the urinary excretion of biomarkers of renal injury.
Abstracts Dutch annual Intensive Care meeting 2011

42. Circulation

The pharmacokinetics of intravenous vs oral nimodipine in ICU-patients with subarachnoidal haemorrhage

EL Sanders1, AJ Wilhelm1, BM Kors4, ARJ Girbes2, EL Swart4
1 Department of Clinical Pharmacology and Pharmacy, VU Medical Centre, Amsterdam, The Netherlands
2 Department of Intensive Care, VU Medical Centre, Amsterdam, The Netherlands

After a subarachnoidal haemorrhage (SAH) patients often experience secondary ischemia. This is one of the reasons for a poor outcome. Assumed is that ischemia is related to the occurrence of vascular spasms. The calciumantagonist nimodipine has been registered for the treatment of vascular spasms probably due to its neuroprotective character. Nimodipine exists as an infusion fluid and as a coated tablet. It is unclear which way of administration is preferred. Most studies on the effect of nimodipine are based upon its neurological outcome, showing a better outcome with oral administration [1]. However less data are available on its pharmacokinetics.

Because most SAH patients in the ICU are hemodynamically unstable en nimodipine decreases MAP, norepinephrine is often given aside if needed to maintain a MAP of at least >90 mmHg.

Aim of the present study is to describe the pharmacokinetics of nimodipine after intravenous and oral administration within the same ICU-patients with a SAH with a special focus on the oral bioavailability. To investigate the influence of nimodipine administration on the hemodynamics the administration of norepinephrine is monitored.

This study, a prospective, non randomised, observational trial, has taken place at the adult ICU at the VU Medical Centre in Amsterdam. Patients with a SAH aged 18 to 70 years administered to the ICU were included. All patients had a low GCS. Exclusion criteria where pregnancy, expected death within 24 hours, severe liver malfunctions and the use of medication that has a clinically relevant interaction with nimodipine.

Patients followed the existing SAH-protocol in which they first received nimodipine intravenously. Treatment started at 0.4 mg/h nimodipine by continuous infusion and was increased every hour until a level of 2 mg/h was reached with an acceptable blood pressure. If possible they were switched to nimodipine orally after 24 h (60 mg every 4 hours), in most case crushed and give via a probe. MAP was monitored and norepinephrine was administered if needed. Total period of therapy was 21 days.

Results:

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (Average, Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 11.3</td>
</tr>
<tr>
<td>Sex: man:woman</td>
<td>4:6</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>20.6 ± 4.9</td>
</tr>
<tr>
<td>Dosage nimodipine iv. (mg/h)</td>
<td>1.07 (0.54 - 1.95)</td>
</tr>
<tr>
<td>Dosage norepinephrine during nimodipine iv. (mg/h)</td>
<td>1.20 (0.77 - 1.88)</td>
</tr>
<tr>
<td>Dosage norepinephrine during nimodipine orally (mg/h)</td>
<td>0.85 (0.34 - 1.38)</td>
</tr>
<tr>
<td>Average number of norepinephrine pump changes per 24h (during administration nimodipine iv)</td>
<td>7.3 (3.3 - 18.5)</td>
</tr>
<tr>
<td>Average number of norepinephrine pump changes per 24h (during administration nimodipine po)</td>
<td>6.9 (0.6 - 16.6)</td>
</tr>
<tr>
<td>Clearance (Clm) (average, sem)</td>
<td>41.3 ± 43.9 L/uur</td>
</tr>
<tr>
<td>Volume of distribution (V1)</td>
<td>0.3 ± 0.2 L/kg</td>
</tr>
<tr>
<td>Oral bioavailability (Fpo) (median, range)</td>
<td>0.03 (0.01 – 0.32)</td>
</tr>
</tbody>
</table>
No patient reached the maximal infusion rate. A large inter-individual variability in oral bioavailability of nimodipine was found (1-32%). Nevertheless there was no significant difference between the dosage of norepinephrine needed during oral versus intravenous nimodipine therapy. Also the number of pump changes norepinephrine per 24 hour was not significantly different.

The pharmacokinetics were best described by a two-compartment model. Only Soppi et al.[2] studied the pharmacokinetics of nimodipine in SAH-patients. These were not specifically ICU patients and in general had a better GCS. They only measured the AUC and Cmax, therefore a comparison of the pharmacokinetics can not be made. Nevertheless the serum concentrations after oral and intravenous administration were comparable to our results.

In conclusion our study shows a large inter-individual variability in the oral bioavailability of nimodipine in ICU-patients with a SAH. There was no significant difference in dosage of norepinephrine between the patients receiving nimodipine orally versus intravenously.

Based upon the results, we prefer to administer nimodipine intravenously at the start of treatment.

References

1. Disseminated gastrointestinal zygomycosis after chemotherapy in a patient with acute myeloid leukemia

AHJW Janssen¹, CFM Linsen², EAM Beckers¹, WNKA van Mook¹, DCJJ Bergmans¹
1 Department of Intensive Care, Maastricht University Medical Centre+, The Netherlands
2 Department of Medical Microbiology, Maastricht University Medical Centre+, The Netherlands
3 Department of Hematology, Maastricht University Medical Centre+, The Netherlands

Introduction: A highly immuno-compromised patient with acute myeloid leukemia (AML) was successfully treated for disseminated gastrointestinal zygomycosis by Rhizomucor pusillus.

Case report: Two months after the diagnosis of AML a 59-year-old male was admitted to the intensive care unit (ICU). He had no prior medical history and was an occupational vegetable-grower. Induction chemotherapy was complicated by probable pulmonary invasive aspergillosis treated with voriconazol, neutropenic enterocolitis and upper gastrointestinal bleeding (UGIB) treated with hemoclip placement and coiling. Recovery and subsequent discharge followed with voriconazol maintenance therapy. High grade fever and leucocytosis without apparent cause necessitated re-admission. Amoxicillin-clavulanic acid and ciprofloxacin were started. His fever gradually subsided and second induction-chemotherapy was started. After 5 days fever returned and antibiotics were switched to piperacillin-tazobactam. Dyspnea, diarrhea and diffuse abdominal cramps developed. A high resolution CT (HRCT) scan revealed progressive pulmonary right lower lobe consolidation and scattered smaller bilateral consolidations. Fecal culture and clostridium toxin tests were negative, blood culture yielded Enterococcus faecium. Vancomycin was added. Over the next 6 days deterioration necessitated empirically switching of piperacillin-tazobactam to imipenem, ICU admission and intubation. An abdominal CT-scan revealed a thickened small bowel wall. Physical examination showed signs of an acute abdomen and sepsis. Operation revealed necrosis of the small bowel, necessitating partial jejunectomy with end-to-end anastomosis. Post-operatively septic shock worsened, a relaparotomy was negative. Pathological examination revealed multifocal hemorrhagic small bowel necrosis and non-septate, broad hyphae with right angle branching. Amphotericin B lipid complex was started under suspicion of zygomycete infection, resulting in gradual clinical improvement. DNA was isolated from paraffinated material and fungal polymerase chain reaction typed the zygomycete as Rhizomucor pusillus. After 4 weeks of ICU admission he was discharged to the hematology ward.

Discussion: Disseminated gastrointestinal zygomycosis is rare with high mortality. The diagnosis commonly results from postmortem histopathological evidence of fungal tissue invasion. The patient was severely immuno-compromised and a vegetable grower (promoting colonization with conidia of multiple fungi). Moreover, voriconazol treatment of aspergillosis allows zygomycetes to grow and disseminate, which explains the progression of infiltrates on HRCT scan. The UGIB, abdominal complaints and deterioration despite antibiotic treatment were other diagnostic clues.

Conclusion: A disseminated zygomycosis, which probably originated from the lungs and spread to the gastrointestinal tract, was successfully treated by surgical intervention and antifungal treatment.

2. A combination of clove oil and alcohol: a humane way to euthanize your fish, but a bad combination for toothache

L van Gulik, B Dyrbye, R Vink, J Horn
Department of Intensive Care, Academic Medical Center, Amsterdam, The Netherlands

Introduction: Clove oil is widely used in aromatherapy and in over-the-counter preparations used for toothache. Antiseptic and analgesic properties are attributed to eugenol, the main constituent of clove oil. Only a few case reports of intoxication with diluted clove oil in humans have been described and those concerned children.

Case report: A 67 year old man with a history of hypertension and alcohol abuse was taken to the hospital after he had been found confused, nauseous and unable to speak. Half an hour before that, he had appeared normal without any complaints. In the emergency room a restless moving man was presented with a Glasgow Coma Scale of E1M3V1 and a temperature of 34˚C. He had a Babinski’s sign on the left side and an dubious Babinski’s sign on the right. His pupils were equal in size and responsive to light. There was no neck stiffness. Thiamine was administered and he was intubated in order to make a CT-scan of the head, that showed some old vascular lesions, but no signs of bleeding, hematoma or ischemia. Arterial blood analysis showed pH 7.24, pCO₂ 5.5 kPa, HCO₃⁻ 17.2 mmol/l, pO₂ 11.9 kPa, base excess -9.8 mmol/l, sodium 141 mmol/l, potassium 4.8 mmol/l, creatinine 96 μmol/l, C1 103 mmol/l, albumin 37 g/l, phosphate 0.8 mmol/l, lactic acid 5.7 mmol/l (0.5-2), alcohol 1.62 ‰ (<0.5) and osmolality 334 mOsm/kg (280-295). Cerebrospinal fluid (CSF) analysis drawn via lumbar puncture, to exclude a meningo-encephalitis, showed no abnormalities. Although the increased osmolgap (334 mOsm/kg measured versus 302 mOsm/kg calculated) corresponded with the level of ethanol, the combined metabolic and respiratory acidosis with an anion gap of 24.4 could not be fully explained by the increased lactic acid and pCO₂. The depth of coma prior to the sedation for the intubation was also exceptional, given the fact that the patient was used to large amounts of alcohol. The patient’s wife then clarified that the patient had administered pure clove oil in his mouth to soothe a toothache caused by a broken molar. Ten hours after admission the patient was fully awake and could be extubated. He showed no cognitive impairment and explained that he used pure clove oil in his work with perfumes. He also used it to anesthetize his fish to trim their fins, but “the trick is”, he told one of the residents, “contrary to what you’ll find on most sites on the internet, to mix the clove oil with alcohol, otherwise it won’t work! And sometimes you’ll have bad luck and they won’t wake up again…”

Conclusion: In case of a patient with unexplained coma and metabolic acidosis, ingestion of alternative medicinal agents such as clove oil should be considered. Heteroanamnesis and laboratory investigations showing an anion gap can be helpful in this diagnosis.

References

www.wisegeek.com: A humane way to euthanize your fish.
Surviving a life-threatening 2,4-DNP intoxication; “Almost dying to be thin”

A van Veenendaal, P Pickkers
Department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Several case reports describe patients that die following 2,4-dinitrophenol (DNP) intoxication. DNP was used extensively in the 1930s as a dieting aid [1] and has regained popularity as an alternative measure to weight loss and is readily available over the internet. DNP is a cellular poison [2-4]. It uncouples oxidative phosphorylation in the mitochondria resulting in a rapid consumption of energy without generation of ATP. Hyperthermia and many other (fatal) sequelae can ensue. We describe a case of life-threatening DNP intoxication in which immediate and aggressive supportive management led to complete recovery.

Case report: A 20-year-old woman admitted to our hospital complained of dyspnea, fatigue, malaise and thirst. She used DNP as a dieting aid for several months and had tripled the dose on the day of admission. Initial examination revealed an excessively sweating, tachypnoeic (RR 37) and tachycardic (138 beats min^-1) female (BMI 26 kg/m^2) with a GCS of 15. Oxygen saturation 100%. Initial temperature 37.5˚C, rising to 38.5˚C within 15 minutes. Arterial blood gas revealed pH 7.49, pCO_2_ 3.8 kPa, pO_2_ 11.8 kPa, HCO_3^- 20.9 mmol/l and a base excess of -1.1 mmol/l. Creatinine kinase level of 18,170 U/l was present. Toxicology screening showed therapeutic levels of diazepam and fluoxetine and the presence of cannabinoids. Patients clinical condition deteriorated. Temperature rose above 39˚C. The fatal outcome described in case reports [1,5,6] convinced us to employ an aggressive strategy. She was sedated and intubated because of progressive respiratory failure and the need for active cooling with a hypothermia blanket (target temperature 37˚C). Dantrolene (1mg/kg) was given intravenously and repeated several times in the first 24 hours without the occurrence of any side-effects. Maximal CK levels reached 30,150 U/l and decreased after 24 hours. Active cooling was terminated at day 4, when CK levels declined below 10,000 U/l. The patient was successfully extubated at day 6 and made an uneventful complete recovery.

Discussion: It can be a difficult challenge to diagnose a DNP intoxication as not all patients readily admit the use of an illicit drug. DNP is not detected in drug fraction of most analytical protocols [5]. Moreover, it is almost impossible to quantify the severity of a DNP-intoxication because of the unavailability and lack of specificity of the methods employed to quantify DNP and its metabolites [4,6]. It’s likely that many mild intoxications remain unrecognized. However, the importance of early recognition of a severe intoxication, as in our case, cannot be overemphasized. Little can be done to reduce the body’s burden of DNP [4]. Any measure (for example gastric lavage with NaHCO_3_ solution) to minimize peak absorption following exposure is likely to fail, unless it takes place immediately following ingestion. Because DNP has a large volume of distribution, it is also not amenable to dialysis or hemoperfusion.

The most important intervention is probably rapid cooling of the body to control the hyperpyrexia. The subsequent need for intravenous sedation, which potentially accelerates the need for intubation due to progressive respiratory failure, should not withhold the physician to initiate this intervention immediately. Dantrolene is likely an important adjunct. Dantrolene counteracts the DNP induced raised free intracellular calcium. The net effect, muscle relaxation, allows for heat dissipation in DNP-related hyperthermia. We believe that our patient survived a life-threatening DNP intoxication because of early recognition followed by immediate aggressive supportive management in which active cooling and possibly dantrolene played a key role.

References

The use of extracorporeal life support as bridge to retransplantation after primary graft failure in two heart transplantation patients

JH Haringman, D van Dijk
Department of Intensive Care, University Medical Centre Utrecht, The Netherlands

Introduction: Primary graft failure is the leading cause of early mortality in heart transplantation (HTx). Heart retransplantation represents 2% of cardiac transplants in adults. As more marginal donors are now accepted because of donor shortage, this proportion is expected to increase. We describe the use of extra corporeal life support (ECLS) as a bridge to retransplantation in 2 patients.

Case A: A 38-year-old female with familiar dilated cardiomyopathy was admitted for HTx. The donor was treated with labetalol for hypertension for a short period of time and the donor heart showed good function. Nevertheless there were only marginal ventricular contractions after implantation of the donor heart, which did not improve despite maximal inotropic support. A venoarterial extracorporeal life support device (ECLS) (Permanent Life Support, Maquet) was implanted. Besides a reexploration because of cardiac tamponade, she was stable on the ECLS and was put on the high urgency waiting list for another HTx. After four days a second cardiac transplantation was performed successfully. Postoperatively there were increasing problems with mechanical ventilation mostly due to reperfusion lung injury. The ECLS was reintroduced, in this situation for providing ventilatory support.

After another six days it was possible to wean her from the ECLS. During her ICU stay she suffered from multiple respiratory and central line infections, was dependent on renal replacement therapy for 53 days and suffered from severe ICU acquired weakness. After 90 days she was discharged from the ICU and she left the hospital for further revalidation 5 months after the initial transplantation.

Case B: A 39-year-old female with a left-ventricular-assist-device (Thoratec Heart Mate II) for progressive dilating cardiomyopathy, was admitted for cardiac transplantation. The total ischemia time was 4 ½ hours. After implantation the donor heart showed contractions and sinus rhythm, but despite maximal inotropic support it was impossible to wean the patient from cardiopulmonary bypass. A central ECLS (Permanent Life Support, Maquet) was implanted and the patient was put on the high urgency heart transplantation waiting list. After two days a second donor heart was successfully implanted with a total ischemia time of 4 hours and 40 minutes and the ECLS could be removed.
After recovery from renal insufficiency she could leave the hospital, 9 weeks after the initial transplantation.

Conclusion: Primary graft failure is a normally lethal complication of HTx. There is growing evidence, however, that immediate application of an ECLS system allows quick and safe stabilisation of these patients. This might result in successful cardiac retransplantation, as demonstrated in these two patients.

Stress induced transient cardiomyopathy due to accidental administration of norepinephrine and atropine instead of neostigmine and atropine

AJR Balthasar1, MA Siemonsma1, S Schalla2, MD Lancé1,2, WNKA van Mook4
1 Department of Anaesthesiology, Maastricht University Medical Centre+, The Netherlands
2 Department of Cardiology, Maastricht University Medical Centre+, The Netherlands
3 Department of Intensive Care Medicine, Maastricht University Medical Centre+, The Netherlands

Introduction: In contemporary medical practice patient safety is increasingly emphasized. Learning from medication errors can contribute to patient safety. A case of transient cardiac failure after accidental administration of 5000 micrograms of norepinephrine combined with an intentional administration of 1000 micrograms of atropine is presented.

Objectives and methods: Publishing causes and consequences of medication errors is important for future prevention and treatment of similar events.

Results: A 48-year-old healthy female patient was scheduled for a right ovariectomy for ovarian cysts by means of a mini laparatomy. Induction and maintenance of anaesthesia as well as the surgical procedure were uneventful. At completion of the operation the relaxation status was checked. A Train Of Four (TOF) of 2 of 4 twitches was scored. The anaesthetic nurse thought to have prepared and injected 2.5 mg of neostigmine and 1 mg of atropine. However, an ampoule of norepinephrine (5000mg/5ml) had been used instead of the ampoule of neostigmine. In the first minutes after injection, blood pressure could not be measured. After 6 minutes a blood pressure of 160/90 mmHg was recorded, heart rate was 120/min. The direct postoperative period was complicated by pulmonary oedema, for which non-invasive mechanical ventilation was initiated in the Intensive Care Unit (ICU). A Trans-Thoracic Echocardiogram (TTE) revealed a Left Ventricular Ejection Fraction (LVEF) of 25% due to global myocardial hypokinesia. ICU discharge was possible the next day. Hospital discharge was a week later with a LVEF of 45% while using acetylsalicylic acid 80mg, atorvastatine 40mg, furosemide 40mg, and candesarten 4mg. One month after discharge, the patient had regained normal exercise tolerance and was asymptomatic. Control TTE showed a completely normalized systolic cardiac function with an LVEF of 65%. Cardiac magnetic resonance imaging MRI revealed no fibrosis formation. Subsequently all cardiac medication was successfully stopped. No rebound heart failure was observed.

Discussion: The pathophysiology of catecholamine-induced cardiomyopathy is presumed multifactorial. Probable mechanisms contributing to cardiomyocyte damage include catecholamine induced coronary vasospasm, elevated intracellular calcium and free radical formation. Also mobilization of free fatty acids from adipose tissue is increased by catecholamines and can result in toxic levels for cardiomyocytes. Finally, a theory of hypercontraction of myofilaments after isoproterenol is described in literature, resulting in a changed structure of myofibrils.

After root cause analysis, the following immediate changes were implemented; all ampoules of 5000 micrograms of norepinephrine were eliminated from all non-cardiac anaesthesia cupboards, the necessity of a double check procedure during medication preparation was again emphasized and made a mandatory hospital policy, and a meeting with the hospital pharmacist was planned to further optimize medication safety in the operation theatre.

Conclusions: This rare case of accidental norepinephrine overdose (combined with atropine) describes the development of an acquired stress cardiomyopathy and pulmonary oedema, and illustrates the potential for complete recovery after temporary support by medical cardiac support.

Resolving of respiratory failure in a patient with diffuse large B lymphoma of the lung

BMF van der Leeuw1, LCJ te Boome2, J de Metz1
1 Department of Intensive Care, University Medical Centre Utrecht, The Netherlands
2 Department of Internal Medicine, University Medical Centre Utrecht, The Netherlands

Abstract: A 49-year-old male with a medical history of coronary artery disease (CAD) and extravaginal teratoma, presented with respiratory failure. Although initially arterial alveolar bleeding was suspected, additional examination confirmed the diagnosis diffuse large B-cell lymphoma. After intubation, patient was treated with immuno-chemotherapy. The leukemic infiltrates resolved and patient could successfully be extubated. Mechanical ventilation and chemotherapy during ICU admission in patients with primary hematological malignancies should therefore be considered, even though prognosis of this category is often limited.

Keywords: Diffuse large B-cell lymphoma, chemotherapy, CHOP.
with a high LDH (>1100 U/L). Bone marrow biopsy conducted to the
diagnosis diffuse large B lymphoma stage IV. Meanwhile, patient became
respiratory insufficient with a progressive hypoxic respiratory acidosis and
was transferred to the ICU for intubation. Since patient was not sedated
during mechanical ventilation the newly diagnosed illness and treatment
options could be discussed with him. After his approval, treatment was
commenced with empirical antibiotics, combined with R-CHOP (rituximab,
cyclophosphamide, doxorubicin, vincristine and prednisolone). Within one
week after this therapy was started, chest X-rays normalized. Subsequently
patient could successfully be extubated. Discharge from the ICU followed
one day later.

7. Rescue Veno-Arterial
Extracorporeal Life Support as a
Bridge to Recovery in Fulminant
Stress-Induced Cardiomyopathy

JWM Holtkamp1, E Pragt1, DW Donker1,2
1 Department of Intensive Care, Maastricht University Medical Center+,
The Netherlands
2 Department of Cardiology, Maastricht University Medical Center+,
The Netherlands

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been
described as rescue therapy in patients with cardiogenic shock refractory
to medical treatment and intra-aortic balloon pump (IABP). Notably, VA-
ECMO is considered a crucial therapeutic element to support myocardial
recovery, as demonstrated in selected cases of reversible cardiac
dysfunction. Still, the benefits of VA-ECMO in acute heart failure remain
to be fully established in order to enhance a more widespread use. We
illustrate the therapeutic potential of VA-ECMO in a unique clinical case of
fulminant cardiogenic shock:

A 45-year-old female in acute distress presented to the emergency
department with clinical signs of shock, necessitating immediate initiation
of mechanical ventilation. Her medical history revealed thrombotic
micro-angiopathy, diabetes mellitus, former cocaine abuse, poorly regu-
lated hypertension complicated by left ventricular (LV) hypertrophy
with preserved LV ejection fraction (EF) (figure, baseline) and chronic
haemodialysis. Initial evaluation by laboratory tests, ECG, chest x-ray and
transthoracic echocardiography were compatible with cardiogenic shock
due to acute coronary syndrome. However, coronary angiography was
unremarkable. Despite tailored volume resuscitation, high-dose inotropic
medication and IABP the clinical condition deteriorated. Importantly, the
regular dialysis session hours before presentation was uneventful. Further
analysis by transesophageal echocardiography (TEE) revealed apical and
mid- LV dilatation (‘ballooning’) accompanied by extensive regional hypo-
alkinemia and preserved wall thickness (LV EF ~55%) (figure, presentation).
A rapidly progressive, potentially reversible, idiopathic cardiomyopathy
was hypothesized. Given the impending risk of acute cardiac arrest, VA-
ECMO was initiated for complete hemodynamic support, resulting instant
stabilization. VA-ECMO support allowed cessation of inotropes and
weaning from IABP within hours, ECG and TEE findings normalized almost
completely within days (figure, recovery). VA-ECMO was discontinued on
day 3, further recovery was prosperous. The patient was discharged home
on day 16.

All clinical findings including the complete and fast cardiac recovery
fit well to the diagnosis of a stress-induced cardiomyopathy. In addition,
toxicological and inflammatory causes were excluded. The available
literature suggests to consider VA-ECMO in cases of cardiogenic shock
refractory to medication and IABP, when facing potentially reversible acute
heart failure. Here, we demonstrate the therapeutic potential of VA-ECMO
as a bridge to full myocardial recovery in an exceptional case of stress-
related cardiomyopathy complicated by refractory cardiogenic shock.

Importantly, VA-ECMO enables early tapering of therapeutic catechola-
 mines. Specifically in stress-induced cardiomyopathy, as holds for acute
heart failure in general, high plasma levels of stress hormones might play
an essential pathophysiological role. In this sense, VA-ECMO might
aid to stop the possible virtuous cycle of high extrinsic (and intrinsic)
catecholamine levels promoting adverse myocardial effects.

In conclusion, we demonstrate the great potential of VA-ECMO in comparison to catecholamine use in (stress-
induced) reversible cardiomyopathies remain to be further elucidated.

8. Hyponatremic hypertensive
syndrome in a child

M IJland1, RJ Eijk1, L Koster-Kamphuis2, J Lemson1
1 Department of Intensive Care Medicine, Radboud University Nijmegen
Medical Centre, The Netherlands
2 Department of Pediatric Nephrology, Radboud University Nijmegen
Medical Centre, The Netherlands

Introduction: The hyponatremic hypertensive syndrome (HHS) represents
a combination of renovascular hypertension and hyponatremia. This is
a rare phenomenon in children. We report a 2-year-old boy having renal
artery stenosis presenting with HHS.

Case report: A 2-year-old boy presented with a 33-day history of
polydypsia, polyuria and anorexia. On physical examination there were
signs of dehydration (weight loss, somnolence, decreased skin turgor, dry
mouth and tachycardia) and malignant hypertension (180/135 mmHg).
He was admitted to the PICU for invasive monitoring and hypertensive
treatment. Blood analysis revealed hyponatremia, hypokalemia, hyper-
reninemia, hyperaldosteronism, high anti-diuretic hormone level and
natriuresis (table 1). Diagnostic evaluation through Doppler-ultrasonography, MAG III-renogram, CTA and renal angiography revealed
a small non-functioning right kidney, with an obstruction at the origin of the
right renal artery (figure 1 and 2). Initial treatment existed of rehydration
with intravenous NaCl (0.45%)-glucose (2.5%) solution. Hyponatraemia
was slowly normalized by means of sodium supplementation within 24
hours. Blood pressure was controlled with intravenous labetalol and
nicardipine. Renal artery angioplasty was impossible due to the complete
obstruction. Therefore, nephrectomy of the right kidney was performed.
After nephrectomy electrolyte alterations normalized and blood pressure
remained stable without medication.

Discussion: HHS is a manifestation of severe hypertension associated
with hyponatremia related to renal ischemia. The pathophysiology of this
phenomenon is complex and principally based on counteracting
mechanisms in both kidneys. Renal artery stenosis activates renine-
angiotensin II-aldosterone system (RAAS) leading to high blood pressure
that subsequently causes pressure natriuresis in the normal contralateral
kidney. Volume depletion and hyponatremia occur, as this mechanism
overrules the sodium reabsorption effects of activated RAAS and
secondary hyperaldosteronism.
Conclusion: HHS secondary to renal artery stenosis is a rare phenomenon in children, but should be suspected if severe hypertension is associated with hyponatremia. Metabolic alterations and hypertension are reversible after treatment of the artery stenosis or nephrectomy.

Table 1. Results of serum laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Reference range</th>
<th>Before nephrectomy</th>
<th>After nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>135-145 mmol/l</td>
<td>122 mmol/l</td>
<td>138 mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-4.7 mmol/l</td>
<td>2.6 mmol/l</td>
<td>4.1 mmol/l</td>
</tr>
<tr>
<td>Renin</td>
<td>5-75 mE/l</td>
<td>23000 mE/l</td>
<td>Not available</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.08-0.69 nmol/l</td>
<td>19.3 nmol/l</td>
<td>Not available</td>
</tr>
<tr>
<td>Anti-diuretic hormone (ADH)</td>
<td>0.2-4.3 pmol/l</td>
<td>43 pmol/l</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Figure 1. Renal angiography showing complete obstruction of the right renal artery

Figure 2. CT angiography showing narrowing of the aortic lumen at the origin of both renal arteries and severe stenosis of the right renal artery

Unobtrusive monitoring in the pre-ICU setting predicts clinical deterioration earlier than clinical observations

DHT Tjan1, B Feddes2, L Gourmelon2, ARH van Zanten1
1 Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands
2 Department of Biomedical Sensor Systems, Philips Research, Eindhoven, The Netherlands

Introduction: The early recognition of imminent critical deterioration of patients in general wards poses serious challenges and may affect patient outcome. Patients at high risk for clinical deterioration show alarm signals hours before a critical level has been reached. Early detection of these signals may improve identification and allow for early intervention. New unobtrusive monitoring systems may improve the early detection of these patients.

We tested a novel Philips Research developed monitor that measures respiratory rate (RR), heart rate (HR) non-invasively using bed-integrated technology.

We performed a prospective clinical blinded observational study in a surgical ward to assess the monitoring capabilities of this monitor. Physicians and nurses were blinded for obtained monitoring results. Observations were not used for clinical management.

We present an illustrative patient that deteriorated in the general ward demonstrating the relevance of early warning signals from an unobtrusive monitoring system.

Case report: A sixty year old male patient underwent left sided hemicolectomy for colon carcinoma. On the third postoperative day (700 am) in the surgical ward patient became more sick with fever (Temperature 39.4°C), rigors and tachypnea. Heart rate increased up to 132 beats/minute and blood pressure dropped to 80/50 mm Hg. Laboratory examination showed: lactate 3.6 mmol/l (0.5-1.7 mmol/l), leukocytes 16.8/ nl (4-11/ nl) with toxic staining, haemoglobin 6.5 mmol/l (8.5-11 mmol/l), CRP 497 mg/l (0-5 mg/l) and PCT >10 ng/ml (< 0.5 ng/ml). Physical examination showed rales and bronchial breath sounds in the right lower lung on auscultation. Extremities were cold and pale as a sign of poor peripheral perfusion. Chest X-ray revealed a right lower lobe pneumonia. At 5.00 PM oxygen 5 L/min was started, fluid therapy (2L bolus / 1 hour ) given and antibiotic therapy commenced with amoxicillin and clavulanic acid for presumed postoperative or aspiration pneumonia.

After initial clinical improvement patient became progressively tachypneic, hypotensive and the ICU outreach team was consulted at 7.00 AM the next day. On arrival patient was somnolent, in respiratory distress, hypotensive with an irregular pulse of 150/min. Patient was immediately transferred to the ICU, intubated and mechanically ventilated. Severe pneumosepsis and septic shock was diagnosed. Rapid volume infusion and vasopressor therapy stabilised the circulation. Despite maximal support patient developed progressive multi-organ dysfunction syndrome and died six days later in the ICU.

In retrospect we analysed the prospectively sampled data in the general ward from the device in this specific patient. Records of respiratory rate are depicted in figure 1. We compared these data with clinical observations.
Seven hours before the ICU team was called for respiratory rate warnings (orange zones) were noted by the system. The duration of green zones dropped, the duration of yellow and orange zones increased and finally red and orange zones were continuously recorded. If the warning signals could have been transferred to responsible nurses and physician ICU interventions could have been started hours earlier.

**Discussion:** This case presents a relatively common postoperative complication of postoperative pneumocephalus with fatal outcome. Although postoperative complications often cannot be prevented completely the clinical course may be influenced through early recognition and therapy. We are convinced that, as demonstrated by this case, patients in the postoperative setting could be monitored by unobtrusive monitoring systems in selected patients early intervention may affect outcome.

We plan a randomised trial to test the hypothesis whether unobtrusive monitoring in general wards may prevent severe clinical deterioration through early intervention compared to regular clinical observations alone.

---

**Figure 1.** Continuous respiratory rate monitoring by unobtrusive monitoring in a surgical patient on a general ward. Colours depict normal (green) range, increased respiratory rate (yellow and orange) and markedly increased respiratory rate (red). Gray zones are episodes that the patient was out of bed or monitoring failed to detect optimal signals.

---

**Acute muscle paralysis, hypotension and respiratory failure after SAB: a case-report of magnesium overdose**

HFEM Willems, AFC Schut, PG Gerritsen, JB Bakker

**Department of Intensive Care, Erasmus Medical Centre, Rotterdam, The Netherlands**

**Abstract:** We present a 51-yr old female patient with muscle paralysis mimicking neurological deterioration, hemodynamic and respiratory failure after subarachnoid hemorrhage (SAH). Our patient was enrolled in a study for supplementation of magnesium sulphate after subarachnoid hemorrhage (SAH). Accidentally her study medication was given intravenously in thirty minutes instead of over a period of twenty-four hours, in total she received 20g. The patient experienced complete neuromuscular paralysis accompanied by extreme hypotension and respiratory collapse. Symptoms improved spontaneously after 10 minutes without neurological sequelae. Additional laboratory results showed increased levels of magnesium. This case illustrates that hypermagnesaemia can mimic neurological symptoms of a rebleed after SAH.

**Introduction:** Supraphysiologic levels of magnesium have shown to be advantageous in prevention of delayed cerebral ischemia after subarachnoid bleeding.[1,4] and is widely used in pregnant women suffering from preeclampsia or eclampsia. However life threatening events after iatrogenic intravenous magnesium overdose have also been published.[2,5] Symptoms of intoxication can be mild: flushing, headache, nausea, to severely life threatening: muscle paralysis, complete heart block and cardiac arrest.[5] We report a case of complete paralysis with hypotension and respiratory failure after accidental magnesium overdosage.

**Case report:** A 51-year-old woman was admitted to our ICU after SAH and clipping of an aneurysm of the communicans posterior artery. Symptoms of the SAH were a sudden onset of headache and nausea, without any neurological sequela and a Glasgow coma scale of 15. Besides a history of tobacco use, her medical history revealed no previous illnesses. According to our hospital protocol she was admitted to ICU for neurological and haemodynamic monitoring after the clipping procedure. Treatment protocol consisted of bedrest, analgesia, thrombosis-prophylaxis, Ca-channel blockers and Triple H-therapy (hypervolemia, hemodilution and hypertension). In addition, she was included in the Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage, (MASH2), trial, which assesses if continuous magnesium administration gives a reduction of delayed cerebral ischaemia compared to placebo. [4] After receiving study-medication mistakenly as a bolus infusion in stead of a slow 24-hour infusion the patient had complaints of feeling flushed and nauseous, shortly hereafter her neurological condition dramatically declined from maximal GCS to E4M1V1. She developed muscle paralysis and became respiratory insufficient with a respiratory acidosis and non-invasive ventilatory support had to be started. Also severe hypotension developed with blood pressure as low as 50/20, corrected only after 300 mcg fenylefrine bolus and additional continuous infusion of 0.8 mcg/kg/hour. Her ECG showed normal sinus rhythm with no apparent conduction disorders. A rebleed was highly suspected but before a head CT-scan could be performed, her condition spontaneously improved: After several minutes she regained muscular strength and was able to breath sufficiently, arterial bloodgas normalized without further support. Strikingly, additional tests showed that magnesium serum level taken right after the incident was 3.21 mmol/l, providing us with a more likely explanation for her sudden clinical decline. Retrospective examination revealed that our patient had received 20 grams of magnesium iv in addition to 60 mg of nimodipine per os, within 30 minutes.

**Discussion:** Magnesium sulphate has shown to be beneficial in treatment of secondary ischaemia after subarachnoid bleeding. [Target levels in a recent study in SAB patients are 2.0–2.5 mmol/l.[6] These values are close to serum levels at which serious complications may occur. [5] In our case after SAH the high level of serum magnesium mimicked symptoms of rebleed. Symptoms of magnesium intoxication can easily be misread for symptoms accompanying rebleed. Magnesium serum levels were not extremely high and as nimodipine and magnesium both act as calciumantagonists, their combination may have aggrevated the hypotensive period observed in our patient.
Ischemic optic neuropathy related to treatment of critically patients: a case report

Bj Snel, GC Adriaal
Department of Intensive Care Unit, Medical Center Haaglanden, The Hague, The Netherlands

Abstract: In the intensive care unit (ICU), ischemic optic neuropathy (ION) is rarely seen. We present a patient, diagnosed with a liver-rupture. He underwent multiple operations and during ICU stay, he developed ischemic optic neuropathy. We reviewed the literature to describe risk factors involved. These are hypotension, prone positioning, high levels of positive end-expiratory pressure (PEEP), massive fluid resuscitation and use of vasopressors.

Introduction: Ischemic optic neuropathy (ION) is a known perioperative complication. In the Intensive care unit (ICU) however, it is rarely seen. We present a patient who developed blindness in the ICU. We reviewed current literature to describe risk factors involved.

Case report: A 33 year old male patient was admitted to the emergency department after a motorcycle accident. He was diagnosed with a liver-rupture. In hypovolemic shock, he underwent an emergency laparotomy, with perihepatic packing and resection of injured segments. He was mechanically ventilated, with a maximum PEEP of 20 mm Hg. Ventilation was performed in prone position for 29 hours. In the first 24 hours, the patient was resuscitated with 21.8 liters of fluids. He was supported with dopamine (maximum dosage of 25 μg · kg⁻¹ · min⁻¹) and dobutamine (maximum dosage of 10.4 μg · kg⁻¹ · min⁻¹). He underwent multiple procedures, including an ileostomy. Eventually the patient complained of blindness and ophthalmologic examination revealed bilateral optic nerve neuropathy. Computed tomography excluded any obvious cerebral pathology. At follow-up, he had no light perception.

Discussion: In 1973, Drance et al. proposed shock-induced ION as a causal factor of glaucoma and visual loss [1]. In 1988, Chelluri was the first to report of visual loss in a patient treated in the ICU, after cardiac arrest [2]. He suggested that high levels of PEEP together with a low systemic filling pressure, are the cause of intraocular pressure build-up and ischemia of the optic nerve.

ION is the most common diagnosis in perioperative visual loss in nonophthalmologic surgery [3,4]. It is particularly associated with spine surgery in the prone position. In the ICU however, blindness is a rare complication. Possible causal factors are suggested in current literature.
Therapeutic use of etomidate in an ICU patient with secondary hypercortisolism.

AJC Roxx1, WA Oranje2, HH van Oijik3, JJ Weenink1,2,3
1 Department of Intensive Care, Twee Steden Hospital, Tilburg-Waalwijk, The Netherlands
2 Department of Internal Medicine, Twee Steden Hospital, Tilburg-Waalwijk, The Netherlands
3 Department of Intensive Care, Spaarneziekenhuis, Hoofddorp, The Netherlands

Introduction: The potential of etomidate to suppress adrenocortical function is well known. We have made use of this property of etomidate to treat a patient with hypercortisolism due to ectopic corticotropin (ACTH) production.

Case: A 66-year old man with a history of chronic diarrhoea and recently diagnosed diabetes mellitus with hypertension was admitted to our Intensive Care Unit for treatment of severe hypokalaemia and alkalosis. His general practitioner had referred him to the cardiologist because of suspicion for decompensated heart failure. Besides edema no other features of heart failure appeared. No stigmata of Cushing’s disease were noted. No diarrohea appeared during admission and the diagnostic workup revealed renal rather than intestinal potassium loss. This prompted us to investigate the possibility of hyperaldosteronism or cortisol excess. ACTH overproduction with hypercortisolism was diagnosed. CT-scan raised the suspicion of ectopic ACTH production from small cell lung carcinoma with hepatic metastases. On the third day of admission intubation had to be performed because of progressive hypoxemia due to atelectasis of the right lower and middle lobes. We used a single dose of 20 mg etomidate followed by a maintenance dose of 12 mg/h as sedative and therapeutic drug for the hypercortisolism. Hydrocortison was started immediately after intubation. Broad antibiotic coverage including prophyaxis with trimethoprim-sulfamethoxazol and fluconazol was started in this immunocompromised patient. Serum levels of both ACTH and cortisol dramatically fell within 8 hours.

A liver biopsy confirmed the suspected metastasized small cell lung carcinoma. After the patient’s condition stabilized he was transferred to a tertiary centre. After substituting ketoconazol for etomidate he was successfully weaned from the ventilator and started palliative chemotheraphy soon afterwards. Unfortunately the patient died from neutropenic sepsis after the first course of chemotherapy.

Conclusion: This case illustrates not only the endocrine emergency of malignant ectopic ACTH production but also the potential of etomidate to suppress adrenocortical function. Both cortisol and ACTH levels dropped markedly shortly after initiation of this therapy as described previously [1]. Although the relevance of this property for daily practice has been debated this case and a recent multicenter randomized controlled trial [2] suggest that significant suppression of cortisol secretion can occur after low and even single doses function.

References

Pneumothorax after bronchoalveolair lavage (on the contralateral side)

RM Wilting
Department of Intensive Care, Maastricht University Medical Center+, The Netherlands

A 49 year old patient was transmitted from another hospital to our Intensive Care Unit. He had a multitrauma after falling from several meters height. Examination and investigation showed diffuse axional injury of his brain, fractures of all the ribs on the left side (flail chest) with a lung contussion, a pneumothorax on both sides and a fracture of his sternum, pelvis and left femur.

Both pneumothoraces were drained immediately (day 0), the ribfractures were stabilized with plates and screws and his fracture of the pelvis and femur also were stabilized with osteosynthesis, all on day 1. His neurological state improved very slow, his respiratory state improved well, his respiratory state improved well, his neurological state improved very slow, his respiratory state improved well, his neurological state improved very slow, his respiratory state improved well, his neurological state improved very slow, his respiratory state improved well.

In our case we think that all of the mentioned factors played a minor role in the development of a pneumothorax, because the pneumothorax was on the contratalateral side. We think that the previous pneumothorax on the contratalateral side of the BAL, must have caused some kind of weak spot and that the high pressure during the BAL caused the pneumothorax. Our advise is that in case of a recent pneumothorax, the decision to do a BAL should be made with cause.
An acutely ill patient who was not comatose despite extreme hypoglycemia

R Sayilir, MW Nijsten
Department of Critical Care, University Medical Center Groningen, The Netherlands

Background: Glucose is an indispensable acute fuel in acute illness. Hypoglycemic symptoms usually develop at glucose levels <3 mmol/L and at glucose levels <1 mmol/L are typically associated with deep coma and death [1]. We present a patient who was awake when he presented to the emergency department with an extremely low glucose. Case description: A 46-year old men presented at the emergency department because progressive malaise. He had lately been suffering from a depression and admitted taking 100g of paracetamol. Physical examination showed an awake patient, hypothermia and normal hemodynamics. Laboratory examination showed a marked lactic acidosis with an arterial pH of 7.05 and a lactate of 25 mmol/L. Ammonia and transaminases were sharply increased as well as the creatinine level. The patient was transferred to the ICU after initiation of acetylcysteine and other supportive therapy. The patient was subsequently transferred to our ICU for potential liver transplantation. Renal replacement therapy was initiated and he successfully underwent a liver transplantation. The post-operative ICU-stay was prolonged due to severe critical illness polyneuropathy and after a long recovery he had sufficiently recovered to be discharged home. Discussion: This patient displayed characteristic time course of biochemical abnormalities observed after severe paracetamol intoxication that causes complete liver failure. A very remarkable aspect is the absence of coma despite an otherwise lethal deep hypoglycemia. Apparently this patient survived hypoglycemia because of the presence of a salvage fuel. In this case only lactate can have served this role. Various studies have demonstrated this role of lactate in other conditions [2]. Conclusion: As also observed under experimental and other pathophysiological conditions, lactate can serve as a salvage fuel during deep hypoglycemia.

This phenomenon may have important relevance for novel therapeutic strategies.

References

Papillary fibroelastoma of the aortic valve: an unusual cause of death

JE de Haan, JB van den Bosch, J Bakker, J Epker
Department of Intensive Care Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

Introduction: Cardiac papillary fibroelastoma is a rare cardiac neoplasm of unknown prevalence. The majority of patients is asymptomatic and diagnosis of papillary fibroelastoma in living patients have been reported sporadically. Albeit considered a benign tumor, severe complications can occur. We describe a catastrophic case of a woman with syncope followed by acute myocardial infarction due to a cardiac papillary fibroelastoma.

Methods: Case report.

Results: A 49-year-old woman was admitted to our hospital after an out-of-hospital cardiac arrest. Her past medical history was unremarkable and she had been well until the evening before admission, when she developed typical chest pain and recurrent syncope. An electrocardiogram, performed by the emergency medical services, revealed acute myocardial ischemia. Shortly thereafter she went into cardiac arrest due to ventricular fibrillation. Cardiopulmonary resuscitation was performed on site and a sinus rhythm was established after 11 minutes. Subsequently she was transported to our hospital for emergency percutaneous coronary intervention. The patient was admitted to our intensive care unit. On examination she was unresponsive to voice or pain stimulus. The temperature was 32.5°C, the blood pressure 99/52 mmHg, the pulse 92 beats per minute, the respiratory rate 12 breaths per minute with mechanical ventilation, and the oxygen saturation 85% while 100% of inspired oxygen was delivered. She was immediately sent for emergency percutaneous coronary intervention. During heart catheterization she again went in to cardiac arrest for which cardiopulmonary resuscitation, including the administration of inotropics and insertion of an intra-aortic balloon pump (IABP), was performed. The angiography showed a right-dominant coronary system and, surprisingly, normal coronary arteries. No gradient over the aortic valve was observed, however the left ventricular function was very poor. An intravascular cooling catheter was inserted in the right femoral vein to facilitate mild hypothermic treatment. The following hours the patient developed a refractory low-output cardiogenic shock despite treatment with inotropics, vasopressors and IABP. She died seven hours after her initial presentation. Informed consent to perform an autopsy was obtained from the family.
Postmortem examination showed a papillary tumor on the left coronary cusp of the aortic valve; the left coronary ostium was obstructed by the tumor (see pictures). There was no evidence of coronary artery disease or other cardiac abnormalities. The lungs appeared congested, resembling pulmonary edema. The remainder of the autopsy, besides minor atherosclerosis of the aorta, was unremarkable. **Conclusion:** In conclusion, this case describes an unusual presentation of a cardiac papillary fibroelastoma located on the aortic valve, which has occluded the left coronary artery, leading to refractory cardiogenic shock caused by ongoing myocardial infarction.

**16. Acute pulmonary oedema following oxytocin administration: 2 cases**

**A Buddeke, REJH Sentjens, ME Sleeswijk**

*Department of Intensive Care, Flevoziekenhuis, Almere, The Netherlands*

**Introduction:** Oxytocin, a posterior pituitary hormone, is commonly used for induction, stimulation or reinforcement of labor, management of incomplete or inevitable abortion and control of post partum bleeding. We describe two cases of pulmonary edema after the administration of iv oxytocin.

**Patient 1:** A 26 year old female was admitted to the emergency room because of shortness of breath and chest pain. Four days before presentation she delivered a healthy child. During her delivery oxytocin (10 units i.m.) was used. On physical examination we saw a moderate dyspnoeic female, RR 160/80 mm HG, heart rate 98 beats/min, saturation 92%, normal heart sounds, bilateral pulmonary diffuse crackels without peripheral oedema. Chest x ray: see figure 1. ECG: sinusrythm, no signs of conduction abnormalities or ischeamia.

Besides hypoxia and respiratory alkalosis their were no other laboratory abnormalities. She was admitted to the ICU and treated with 80 mg furosemide i.v., oxygen and nitroglycerin i.v 2 mg/hrs. After several hours her urine production was 2500cc and the dyspnoe disappeared. An echocardiography was performed shortly after admission and showed normal dimensions, normal systolic and diastolic function and no valve abnormalities.

**Patient 2:** A 27 year old pregnant female was admitted to the emergency room because of abdominal pain and fever. Two days after admittance a cesarean delivery was performed, due to persistent less variable CTG values. Before the cesarean delivery oxytocin 10 units i.m. were administered. Post partum she remained dyspnoeic, with a blood pressure of 110/60, a heart rate of 130 b/min and diuresis of > 40 cc/hour, temperature 39°C and saturation 92%. Chest x-ray: see fig 2. ECG: sinusrythm, no signs of conduction disturbances or ischeamia. The laboratorium results were Hb 5.5 mmol/L, metabolic acidosis and CRP 273 mg/L. After treatment with furosemide and oxygen her dyspnoe disappeared. Echocardiography showed no abnormalities.

**Discussion:** Pulmonary oedema after tocolytic therapy mainly beta 2 agonist is previously described. Pulmonary oedema is probably due to fluid overload, although cardiac dysfunction and increased capillary permeability may also contribute. However in our cases the patients were treated with oxytocin and presented with dyspnoe several hours to days after oxytocin injection. Oxytocin has a similarity to vasopressin, and therefore may reduce the excretion of urine slightly. This is the possible mechanism of pulmonary oedema. Both patients reacted well to the therapy with furosemide and were soon after ICU admittance discharged from the hospital. During a visit at the outpatient clinics of cardiology the patients had no symptoms and there were no signs of heart failure.

**Conclusion:** Oxytocin infusion in pregnancy may induce pulmonary edema within hours until several days. Patients responds well on diuretic treatment and the prognosis is good.

**17. Prone position during Extracorporeal Life Support for H1N1 Pneumonia**

**PB van Pommeren, LC Otterspoor, D van Dijk, J Kesecioglu**

*Department of Intensive Care, University Medical Centre Utrecht, The Netherlands*

**Introduction:** Extra Corporeal Life Support (ECLS) is increasingly being used for patients with severe respiratory collapse. Patients on ECLS are virtually always treated in supine position. We report a patient who was treated with ECLS in the prone position.

**Objective:** To evaluate the risks and benefits of prone positioning during ECLS treatment.

**Case:** A 51-year-old male was admitted to our intensive care unit with severe acute respiratory distress syndrome (ARDS) due to Influenza type A (H1N1). After 7 days, veno-venous ECLS was initiated to provide lung rest. Blood flow of the ECLS was set at 3 L/min and fresh gas flow at 6 L/min, while the ventilator settings were PEEP 20 cmH2O; ΔP 10 cmH2O. With these settings, gas exchange gradually deteriorated. Because a computed tomography (CT) scan of the lungs showed dorsal atelectases, the patient was placed in prone position. Gas exchange immediately improved and prone and supine position were alternated for three days. In prone position sputum drainage was markedly increased and a new CT scan showed reduced dorsal atelectases. The patient was successfully weaned from ECLS after 45 days and later discharged to a rehabilitation center.

**Discussion:** During conventional mechanical ventilation for ARDS, prone positioning is widely used and now considered a simple and safe strategy to reduce atelectasis and improve oxygenation. This case suggests that the same applies to ARDS patients placed on veno-venous ECLS. Turning the patient appeared to be a fairly straightforward and safe procedure. Accidental cannula dislocation did not occur and is in our opinion survivable in case of veno-venous ECLS. A literature search in Pubmed yielded one other report of uneventful ECLS in prone position [1]. We conclude that putting a patient in prone position while on veno-venous ECLS can be carried out safely and may improve sputum drainage and reduce atelectasis.

**Reference:**

1. Mc Cunn, M et al; Extracorporeal support in an adult with severe carbon monoxide poisoning and shock following smoke inhalation. Perfusion 2000;15:169
Cardiac arrest in pregnancy

VH van Waning1, PMLH Vencken2, AJBW Brouwers3, PW de Feiter4
1. Department of internal medicine and intensive care, Sint Franciscus Gasthuis, Rotterdam, The Netherlands
2. Department of gynaecology, Sint Franciscus Gasthuis, Rotterdam
3. Department of surgery and intensive care, Sint Franciscus Gasthuis, Rotterdam, The Netherlands

Introduction: Cardiopulmonary arrest in pregnancy is a rare event. It is important for intensivists to be familiar with the (patho-)physiological changes in pregnancy and the indications for performing a perimortem cesarean section (PMCS). Therefore MOET courses are given [1]. We report 2 cases of perimortem cesarean section performed during CPR.

Hypothesis: It is important to do a PMCS, in the event of maternal cardiac arrest, at an early stage for improving maternal and fetal outcomes.

Cases: The first case, a 37-year-old female, G1P0. Her past medical history included right sided cerebral infarction caused by sinus transversus thrombosis and epilepsy. Her pregnancy was complicated at 30 weeks gestation by a single uncomplicated grandmal seizure as a result of a low depakine level. After the dose of depakine was adjusted and the serum level was adequate no more seizures had occurred. Two days after admission, because of hypertension, at 35 weeks during pregnancy, the nurses found her unresponsive in bed. Basic life support was initiated. Upon arrival of the resuscitation team she had pulseless electrical activity. She was intubated and treated according to the standard advanced cardiac life support protocol. After 8 minutes the patient was still pulseless.

Ultrasound showed fetal heart action. At this time we decided to perform a PMCS. 15 Minutes after start of CPR the PMCS was performed. The patient was transferred to the intensive care unit. Two days later our patient was still unresponsive, E1M1Vtube, papillary and cornea reflex absent. A SEPP showed a severe postanoxic encephalopathy. Because of poor prognosis treatment was withdrawn. She died three days after the CPR.

The male infant, with a birthweight of 2300 grams, had an initial Apgar score of 0/6/7 and had seizures. The baby was resuscitated and intubated. The baby’s 35 weeks gestation survived, and follow-up 12 months after delivery was normal.

The second case, a 35 year old patient, G3 P1, had an uneventful medical history and was referred to the hospital for induction of labour at 41 weeks and 3 days duration of pregnancy. Half an hour after spontaneous rupture of membranes the patient suffered from dyspnea, hypotension, bradycardia and cyanosis. The resuscitation team was alarmed. Upon arrival of the resuscitation team the patient had a cardiopulmonary arrest. CPR was started in left lateral tilt position. Three minutes after cardiopulmonary resuscitation the patient still had no output and the resident started the PMCS resulting in the birth of a girl of 3450 g with Apgar scores of 2/6/7. The patient was transferred to the intensive care unit and uneventful recovery was seen within a few days. Two weeks after the PMCS both mother and daughter were discharged without any neurological or other abnormalities.

Conclusion: Timely use of PMCS is critical for obtaining improved maternal and fetal outcomes.

References

Molecular Absorbent Recirculation System (MARS): An effective bridge to re-transplantation following a prolonged anhepatic phase

VJ Santokhi1,2, J Heidt3, M Reekers4, J van Paasssen3, MS Arbous3
1. Department of Anesthesiology, Leiden University Medical Centre, Leiden, The Netherlands
2. Department of Intensive Care, Leiden University Medical Centre, Leiden, The Netherlands

Background: Liver transplantation remains a final choice for patients with acute liver failure or end-stage liver disease. However, primary non-function (PNF) of the transplant causes the need of urgent re-transplantation. In the condition of no donor liver available, the patient depends on either cell-based or non-cell-based artificial liver systems to survive the anhepatic period. We report our experience with successful bridging of an anhepatic patient for 24 hours to re-transplantation with molecular adsorbents recirculating system (MARS) therapy. MARS therapy utilizes selective hemodiafiltration with countercurrent albumin dialysis aimed at selectively removing both water-soluble and protein bound hepatic toxins in the low and middle molecular-weight range (< 60 KD).

Case report: A 17-year-old patient with primary biliary sclerosis underwent liver transplantation at the Leiden University Medical Center, 20th of August 2010. The implanted liver presented with PNF with severe swelling and the condition of the patient deteriorated rapidly. Subsequently, the liver was resected and a portal-caval shunt was performed. During hepatectomy the patient developed hemodynamic instability and severe coagulopathy. Fourteen units of red blood cells and 12 units of fresh frozen plasma were administered. The patient was admitted to ICU where he increasingly developed a severe inflammatory response, circulatory derangement, renal failure, coagulopathy, and the need of intensive supportive care with vaso-active medication (a continuous infusion of noradrenaline up to 1.4 mcg/kg/min, adrenaline up to 0.06 mcg/kg/min and dobutamine up to 4 mcg/kg/min), mechanical ventilation and transfusion therapy. We instigated MARS therapy within 7 hours of the anhepatic phase. Three hours of MARS therapy resulted in reversion of hemodynamic instability with a decrease of vasopressor therapy, an improvement in renal function, and decrease in ammonia. At the 24th hour of the anhepatic phase re-transplantation was successfully performed. The patient was fully awake and extubated 47 hours after the second liver transplantation. He was discharged from the ICU 96 hours following the second liver transplantation.

Discussion: Our patient presented with PNF after liver transplantation and we needed to bridge an extended anhepatic phase awaiting a new donor liver. Several studies reported different times of anhepatic periods in humans, with the longest reported at 72.5 hours. So far, only a few cases are reported on MARS therapy as a bridge to re-transplantation during an extended anhepatic phase5,6. A few studies suggest there may be benefits of MARS therapy with regard to hepatic encephalopathy for patients with decompensated cirrhosis but its role in the management of acute liver failure is even less clear and awaits controlled trials. We demonstrated that an anhepatic period up to 24 hours can be bridged by the application of MARS besides the usual supportive care. To avoid cerebral edema and partially reverse circulatory derangement by hepatic failure one should consider MARS therapy in anhepatic patients.

Conclusion: Our case report demonstrates that besides intensive supportive care, adjunctional MARS therapy can contribute to a successful bridge to re-transplantation in an anhepatic patient.

Literature
High anion gap metabolic acidosis secondary to pyroglutamic aciduria (5-oxoprolinuria) in an adult receiving antibiotic therapy

H Hussain1, A Tintu1, H de Guus1, B van der Hoven1
1 Department of adult Intensive Care, Erasmus University Medical Centre, Rotterdam, The Netherlands
2 Department of Clinical Chemistry, Erasmus University Medical Centre, Rotterdam, The Netherlands

Introduction: High anion gap metabolic acidosis in adults is a severe metabolic disorder that usually results from accumulation of lactic acid or ketones or from the ingestion of toxic substances such as methanol or ethylene glycol. Another rare but underdiagnosed cause of high anion gap metabolic acidosis in adults is due to accumulation of 5-oxoproline (pyroglutamyl acid).

Case report: A 64-year-old woman, who initially treated with fluoxacinil and rifampicin because of suspicion of aortic stent infection, developed a transient high anion gap metabolic acidosis. Clinically she showed a Kusmaul-like breathing pattern as a compensatory mechanism. After excluding other possibility an analysis of the patient’s urine for organic acids revealed massively increased excretions of 5-oxoproline (68712 μmol /mmol creatinine, normally <100 μmol /mmol creatinine). After discontinuation of rifampicin she made an uneventful recovery, the anion gap normalized and her breathing pattern returned to normal.

Discussion: We think that this patient developed a transient disturbance in γ-glutamyl cycle (figure 1) involving the 5-oxoprolinase step, which resulted in an accumulation of 5-oxoproline that caused a high anion gap metabolic acidosis. The administered rifampicin remains as the only possible causative agent.

Conclusion: Clinicians should consider the possibility of accumulation of 5-oxoproline in critically ill patients with an unexplained high anion gap metabolic acidosis, especially when associated with other conditions, such as renal insufficiency or malnutrition in combination with the use of rifampicin.

Figure 1: Gamma-glutamyl cycle

Acute disseminated encephalomyelitis (ADEM): beneficial effects of a prolonged regime of methylprednisolone and immediate start of plasmapheresis?

AM van der Velden1, M Frank2, H Kerkhoff3
1 Department of Accident and Emergency, Albert Schweitzer Hospital, Dordrecht, The Netherlands
2 Department of Intensive Care, Albert Schweitzer Hospital, Dordrecht, The Netherlands
3 Department of Neurology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

Context: Acute disseminated encephalomyelitis (ADEM) is a demyelinating disease of the central nervous system (CNS), most commonly in children and young adolescents. The estimated incidence is 0.8 per 100 000 population per year, which adds up to about 130 new cases per year in the Netherlands. We present a case of adult ADEM with a favorable outcome. Further studies are needed to show a statistically relevant effect.

Main Lesson: In patients with acute disseminated encephalomyelitis (ADEM), a prolonged i.v. methylprednisolone treatment regime (six days) and a quick start of plasmapheresis (within 24 hours after presentation) might be associated with a favorable outcome. Further studies are needed to show a statistically relevant effect.

References