Selected Abstracts from the
31th International Vicenza Course on Critical Care Nephrology

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Abstracts

1 A Safety Evaluation of a Randomised Double Blind Controlled Trial of Lipocalin-Directed Sodium Bicarbonate Infusion for Renal Protection in At-Risk Critically Ill Patients

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Background: Urine alkalinisation with sodium bicarbonate decreases renal oxidative stress and might attenuate sepsis-associated acute kidney injury (s-AKI). Its safety and feasibility in patients at risk of s-AKI has never been tested.

Methods: We randomly assigned patients at risk of s-AKI [systemic inflammatory response syndrome (SIRS), oliguria and elevated (≥150 μg/l) serum neutrophil gelatinase-associated lipocalin (NGAL) concentration] to receive a 0.5 mmol/kg bolus followed by a 0.2 mmol/kg/hr infusion of either sodium bicarbonate (treatment group) or sodium chloride (placebo group).

Results: Among 50 patients with SIRS and oliguria, 25 (50%) had an elevated serum NGAL concentration. Of these, 13 were randomized to receive sodium bicarbonate and 12 to receive sodium chloride infusion. Study drugs were infused on average for a period of 25.9 ± 10.0 hours. Severe electrolyte abnormalities occurred in seven (28.0%) patients [four (30.8%) in treatment group vs. three (25%) in placebo group]. These abnormalities resulted in early protocol cessation in six (24.0%) patients and study drug suspension in one (4.0%). This adverse event rate was judged to be unacceptable and the study terminated early. There was no difference between the two groups in NGAL concentration over time, occurrence of AKI, requirement for renal replacement therapy, hospital length of stay and mortality.

Conclusion: Administration of sodium bicarbonate and sodium chloride solutions in patients risk of s-AKI was associated with frequent major electrolyte abnormalities and early protocol cessation. The tested protocol does not appear safe or feasible.

Clinical Trial Registration: NCT00706771.

2 Contrast-Enhanced Ultrasound to Evaluate Changes in Renal Cortical Perfusion Around Cardiac Surgery: A Pilot Study

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Introduction: Contrast-enhanced ultrasound (CEUS) is a new technique that might enable portable and non-invasive organ perfusion quantification at the bedside. However, it has not yet been tested in critically ill patients. We sought to establish CEUS’s feasibility, safety, reproducibility and potential diagnostic value in the assessment of renal cortical perfusion in the peri-operative period in cardiac surgery patients.

Methods: We recruited twelve patients deemed at risk of acute kidney injury planned for elective cardiac surgery. We performed renal CEUS with destruction-replenishment sequences before the operation, on intensive care unit (ICU) arrival and the day following the admission. Enhancement was obtained with Sonovue® (Bracco, Milano, Italy) at an infusion rate of 1 ml/min. We collected hemodynamic parameters before, during and after contrast agent infusion. At each study time, we obtained five video sequences, which were analysed using dedicated software by two independent radiologists blinded to patient and time. The main output was a perfusion index (PI), corresponding to the ratio of relative blood volume (RBV) over mean transit time (mTT).

Results: All 36 renal CEUS studies, including 24 in the immediate post-operative period could be performed and were well tolerated. Correlation between readers for PI was excellent (R² = 0.96, p < 0.0001). Compared with baseline, there was no overall difference in median PI’s on ICU admission. However, the day after surgery, median PI’s had decreased by 50% (p < 0.01) [22% decrease in RBV (p = 0.09); 48% increase in mTT (p = 0.04), both suggestive of decreased perfusion]. These differences persisted after correction for haemoglobin; vasopressors use and mean arterial pressure.

Four patients developed AKI in the post-operative period. There was no correlation between post-operative changes in creatinine levels and changes in PI’s.

Conclusions: CEUS appears feasible and well tolerated in patients undergoing cardiac surgery even immediately after ICU admission. CEUS derived parameters suggest a decrease in renal perfusion occurring within 24 hours of surgery.
Electronic Bed Weighing vs. Daily Fluid Balance Changes after Cardiac Surgery

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Objectives: To establish the validity and reliability of measuring weight in critically ill patients with electronic weighing beds.

Design: Prospective observational trial.

Setting: Private intensive care unit (ICU) affiliated to university hospital.

Patients: All patients admitted to ICU after cardiac surgery with an intended length of stay >48 hours.

Interventions: None

Measurements and Main Results: We weighed all eligible patients on ICU admission whenever possible and then twice daily (1200 and 2400 hrs) using electronic weighing beds (Hill-Rom® Batesville, USA). For each measurement, non-removable items were recorded and an average value deducted from the measured weight. We compared differences in body weights (BW) between two consecutive twelve hours periods with the corresponding fluid balance (FB). Additionally, we compared weights obtained with electronic-weighing beds to those obtained with a regular calibrated scale on ICU discharge. We obtained data in 103 consecutive patients in 414/548 (75.5%) of all possible BW measurements. On average, we identified a total of 3.5 kg (SD 1.4) of non-removable items on patients’ beds at time of weighing. The correlation between 12 hourly changes in BW and FB was weak (r = 0.28, 95% CI 0.16–0.38) and when only values obtained in intubated patients were taken into account (r = 0.34, 95% CI 0.16–0.49). Similarly, limits of agreement were wide (95% CI: −3.3 to 3.5 kg). There was also poor agreement between weights obtained on electronic beds and those obtained on the regular scale on ICU discharge (95% CI: −7.6 to 7.6 kg).

Conclusion: Body weight measured by electronic weighing beds does not seem sufficiently robust or accurate to replace daily fluid balance in ICU. The clinical value of equipping ICU’s with such beds remains uncertain.

Hemofiltration in Children with Biventricular Heart Insufficiency After Cardiac Surgery

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In recent years, considerable growth of opportunities in the field of cardiovascular surgery alongside with increased severity of illnesses in the cohort of patients requiring surgical correction of complex heart diseases have both contributed to significant expansion of the use of ECMO procedure. In most cases application of ECMO is conditioned by the development of biventricular and respiratory insufficiency. Development of severe metabolic disorders and water-electrolyte disbalance can be attributed to the same, which often demands parallel to ECMO introduction of CRRT in the course of treatment of these patients.

Aim of Study: To assess the safety and effectiveness of combined ECMO and CRRT procedure in patients with critical low cardiac output and developed multiorgan failure after cardiac surgery.

Materials and Methods: Within the period from January, 2010 to February, 2013 we monitored 53 patient (babies from 0–12 months – 27, children from 1–3 years – 12, older than 3 years – 14) after cardiac interventions aimed at the correction of congenital heart diseases. Postoperative period of these patients was complicated by biventricular heart failure (EFLV ≤ 10–12%, PLa 28–30 mmHg, CVP 20–24 mmHg), which required connection of ECMO system in order to support blood circulation and provide correction of respiratory disorders. In all patients progressing cardiac and respiratory failure were accompanied by acute kidney injury together with anuria, continuing growth of water-electrolyte imbalance and vivid metabolic disorders. To perform hemofiltration, to ECMO extracorporeal circuit CRRT system was introduced. To avoid the “stealing” of oxygenized blood and to decrease recirculation degree, the CRRT system was connected via connectors in venous blood lines (before and after ECMO pump) located at most remote points. ECMO was performed with “Biopump” device with the use of Medtronic (USA) and “Medos” (Germany) oxygenators. Duration of the therapy comprised from 3 to 15 days. Volumetric perfusion rate was maintained on the 100% level with gradual reduction to 50% when cardiac contractility recovery was observed. Hemofiltration was performed with the use of AVpause or AV400 hemofilters (Fresenius, Germany). Replacement solution Duosol containing 2 and 4 μmol/L of K⁺ (B/Braun, Germany) was infused with infusion pump into the central venous catheter. Hemofiltration “dose” was 20–40 ml/kg/h. For precise control of ultrafiltration rate and volume, an infusion pump was also installed on the ultrafiltration line. Duration of the therapy comprised 15 days. System anticoagulation in the ECMO circuit was performed using heparin supporting the activated coagulation time at the level of 180–220 s.

Results: Combined extracorporeal therapy resulted into calculated water exchange volume of 20–40 ml/kg/h. Required hemofiltration volume was calculated on the basis of blood volume level separately in each case. CRRT circuits were not in use for more than 48 hours, when the filter and extracorporeal circuit were replaced. All CRRT procedures were carried out with no complications. Recovery of water-electrolyte balance was documented on the first day of CRRT and the balance of volemic load (CVP 8–12 mmHg, PLa 10–14 mmHg) could then be maintained. During CRRT, lowering of azotemia, correction of metabolic and water-electrolyte balance disorders were documented.

Conclusion: Inclusion of CRRT into ECMO extracorporeal circuit has proved to be safe and can be effectively used for the treatment of patients with critical low cardiac output and AKI syndrome after cardiac surgery.
Effect of Dialysate Flow Direction on Solute Clearances During Continuous Renal Replacement Therapy

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Introduction: Continuous renal replacement therapy (CRRT) is commonly used in critically ill patients with acute kidney injury (AKI). During CRRT, dialysate can be used to increase solute removal by diffusion.

The connection of the dialysate fluid to the filter is usually applied such that dialysate fluid (Qd) flows in the opposite direction (counter-current) of blood to guarantee the maximum solute clearance by diffusion. However, there is no evidence about the superiority of counter-current on co-current configuration in CRRT. Here, we performed a clinical study to investigate the effect of the direction of Qd on urea and creatinine removal. A computational fluid dynamic analysis was also done to provide quantitative insight into the solute removal in both configurations.

Materials and Methods: We conducted a prospective crossover study on adult patients admitted in ICU requiring CRRT in the period between September 2012 and March 2013. CRRT was performed with Multifiltrate (Fresenius Medical Care, Bad Homburg, Germany) using a hemofilter (CUREFLO- ACF-130W, Asahi-Kasei, Tokyo, Japan). The CVVHDF were randomly initiated with co-or counter-current configuration for the first 50 min until it was switched to CVVHD. At this point ultrafiltration rate was set as zero and Qd was set as 2000 ml/h. After 15 min, paired sampling of blood and effluent was obtained (T1) and direction of Qd was reversed. After 15 minutes paired sampling of blood and effluent was repeated (T1:15) and the original CVVHDF was resumed. At 230 min it was switched again to CVVHD with Qd of 2000 ml/h and without ultrafiltration. At 240 min we repeated paired samples as done previously (T4) and then we reversed Qd. After 15 min of run period paired sample were repeated (T4:15) and treatment returned to original CVVHDF in counter-current configuration. Urea (UCl) and creatinine (CrCl) clearance were calculated using the following formula: Qd (Cdi-Cdo)/Cbi. Moreover, Effluent/Plasma (E/P) ratio was also calculated.

Results: Median values of UCl and CrCl were for the first patient, 27 ml/min and 24.6, respectively in co-current configuration while 33.7 ml/min and 33.6, respectively in counter-current configuration. Urea and creatinine E/P were 0.81 and 0.79 in co-current configuration and 1.0 for both urea and creatinine in counter-current configuration. Computer simulation result showed the saturation profiles of urea and creatinine along the length of hemofilter for co-current and counter-current dialysate flow configurations, which also showed different equilibrium points as observed in clinical trial.

Conclusion: Counter-current dialysate flow configuration during CRRT provides a higher solute clearance. However, advantages of each configuration should be balanced against the overall performance of the treatment and its simplicity in terms of treatment delivery and circuit handling procedures. More data including electrolytes dialysances are necessary to find optimal clinical indications for dialysate flow configurations.

First World Application of Carpediem (Miniaturized CRRT Equipment for Infants): A Technical Evaluation

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Acute kidney injury (AKI) is an independent risk factor for morbidity and mortality in critical ill children. Renal replacement therapy (RRT) is a cornerstone of therapy to correct uremia and...
fluid overload. Provision of maintenance hemodialysis to neonatal and infants implicate many challenges: blood flow rate, UF settings and accuracy, catheter size and length, extracorporeal circuit volume, circuit functional survival and the anticoagulation strategy.

**Aim:** We evaluated the technical aspects of the first world in-vivo treatment with the new cardio renal paediatric dialysis machine (CaRPeDiEM) specifically designed for infants.

**Material and Methods:** Patients weighting 3.2 Kg admitted at the PICU, was treated with the CaRPeDiEM in CVVH pre dilution. Fluid overload was the main reason for RRT initiation. The extracorporeal circuit included a D50 hemofilter (polysulfone, 0.075 m²) totalizing 27 ml of priming volume (10% of total circulating blood volume). A 4.5 FR dual lumen catheter length 3.9 inch was placed in the femoral veins. Heparin was continuously infused of 10 U/kg/hr. Haemoglobin was 10 g/dL.

**Results:** A total number of 61 hours was done with 4 circuits. Arterial, Venus, Drop and PreFilter Pressures were stable during all treatment (see figure 1 for the first circuit, 16 h).

**Discussion:** Despite the negative data in literature (13.9±8.6 h with 6.5 FR catheter for patients weighting < 3Kg or circuit life < 20 h with 5 FR catheter, ppCRRT) our circuit life was quite long (17.5±6.24 h). In addition the reasons for downtime were clinical. Limitation on flow through a tube described by Poiseuille law and the need of laminar flow dictated by Raynolds, suggest the right blood flowneed to optimize the circuit survival, in particular with small catheter. The Carpediem blood pump allows a wide and appropriate range (5–50 ml/min) of flows. Fluid balance safety is moreover assured by a very high sensitivity, 1 g, scale.

**Conclusion:** The data of the first in vivo treatment, suggest that CRRT with Carpediem is safe and effective in neonates and infants weighting less than 10 Kg. Prolonged circuit survival with small catheter due to equipped features, allows to explore all potential benefits of CRRT in infants without technical and clinical complications.

**Management of AKI in Newborn with Miniaturized Equipment for CRRT (Carpediem): First World Case Report**

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**Background:** Continuous renal replacement therapy (CRRT) is becoming the treatment of choice for supporting critically ill pediatrics patients with AKI, fluid overload (FO) and hemodynamic instability. Such therapy is usually performed with machines designed for adults. In these patients mortality is strongly associated with the presence of MODS, patient weight, and the severity of fluid overload.

We report the first patient treated with the Carpediem (Cardio Renal Pediatric Dialysis Emergency Machine, a newly designed miniaturized equipment specifically designed for neonates): this is a case of an infant with severe FO who received renal replacement therapy primarily to remove fluid excess.

**Case Report:** Patient 38 week-old male infant (weight 3.2 kg) was transferred from a community hospital and admitted to the PICU with sepsis and acute lung injury due to severe combined immunodeficiency syndrome. Medications include 2 inotropes and almost one potential nephrotoxic agent (aminoglicosid). He was sedated and intubated 10 hours after admission. Adequate diuresis was always maintained with continuous infusion of diuretics. The degree of FO was 24% of body weight on the Day 4 (Fig. 1), with pRIFLE R, increasing to 30% before RRT initiation (pRIFLE R). Concomitant with bone marrow transplantation on Day 6, fluid intake fall to 709 ml/die (see fig1), and patient had...
a further decline in renal function, reaching pRIFLE I on Day 9. Urine output decreased (Fig 1) and to reduce the degree of fluid overload, a total of 500 ml/day was removed with CRRT. To avoid common complications such as: temperature, vascular access, excess of extracorporeal priming volume (filter and lines), the CaRPeDiEM was utilized. Pre-dilution CVVH was performed for 61 hours without significant hemodynamic disturbance, technical complications or need for more inotropic agents. Heparin was continuously infused. Blood pressure was stable, particularly around the time of CRRT initiation (figure 2), without any hypotension episode for all the entire duration of CRRT. No clotting occurred in the extracorporeal circuit thanks to accurate anticoagulant monitoring. The main reason for CRRT discontinuation was recovery of renal function. Patient died 2 days after for respiratory failure. FO was reduced by 17% over the 61 hours of CRRT.

Conclusions: A critically ill newborn underwent CRRT with CARPEDIEM, showing an improvement of cardiac, pulmonary and hemodynamic parameters, while maintaining optimal fluid and circulatory stability. CARPEDIEM can be an effective CRRT machine for small size infants, avoiding the typical complications and risks deriving from the use of adults machine.

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Echocardiography, Right Ventricular Function and Pulmonary Hypertension in NKF Stage III Chronic Kidney Disease: Preliminary Data from Multicentric Study
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Background: Chronic kidney disease is characterized by signs and symptoms of right heart failure. On echocardiographic evaluation TAPSE measurement is well known parameter of right heart sisto-diastolic function. Low TAPSE means reduced cranio-caudal excursion of tricuspidal annulus, sign of both reduced ejection fraction and reduced distensibility of right ventricle. Low TAPSE index often present together with enlarged right chambers size and pulmonary hypertension; it could be good prognostic index for cardiac mortality risk in CHF patients, adding significant prognostic information to NYHA stadiation.

Patients and Methods: Our study was designed to evaluate right ventricle function and TAPSE on 380 patients (185 males and 195 females with mean age of 64 ± 4.4 years) affected by moderate chronic renal failure (mean EPI eGFR 44 ± 8 ml/min), free from overt pulmonary hypertension. TAPSE, PAPs, right chambers diameters, classical Framingham factors were recorded. Data were collected from three nephrology units and all echocardiographic tests were performed by certified echocardiography nephrologists working with standard methods.

Results: TAPSE was reduced (<23 mm) in 43% of patients enrolled, while dilated right chambers were present in 24%. PAPs exceeded 30 mmHg in 29% of patients. Echocardiographic signs of left ventricular hypertrophy were found in 36% of patients. The ejection fraction was normal in all patients. Statistical analysis
showed a significant indirect correlation between TAPSE and PAPs and between TAPSE and tele-diastolic diameters and volumes of the right ventricle, while a direct correlation was observed between TAPSE and Framingham score. TAPSE showed a bimodal distribution, with a subpopulation “low TAPSE - high PAPs”, next to a population characterized by normal values for both parameters.

Conclusions: A reduction in compliance and systolic function of the right heart chambers is quite early and frequent in course of CKD. Nephrologists should take into due consideration, managing blood volume or planning vascular access for hemodialysis.

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Hydrodynamic Performance Evaluation of the Miniaturized Hemofilter Unit for a Wearable Ultrafiltration Device
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A small wearable hemofiltration device could allow heart failure or kidney diseases patients the possibility of eliminating acute hemodynamic changes and the freedom from spending many hours attached to large stationary treatment system. We developed a miniaturized hemofilter for a vest-type wearable ultrafiltration device for the treatment of overhydration and congestive heart failure (WAKMAN, RanD S.r.l., Medolla, Italy). In this study, we investigated the performance of the miniaturized hemofilter unit based on dynamic CT imaging study using contrast media and in vitro evaluation of hydrodynamic properties. The dynamic CT imaging technique showed development of uniform blood flow distribution and effective bubble removal in the hemofilter the treatment condition (Qb = 50 ml/min, no net ultrafiltration). In the intended operating ranges of blood flow (50–60 ml/min) and ultrafiltration rate (5–6 ml/min) of the wearable ultrafiltration device, pressure drop in blood compartment and TMP linearly increased with blood flow rate and the calculated ultrafiltration coefficients were 30.03 and 3.17 ml/h/mmHg for normal saline and semi-skimmed bovine milk, respectively. In conclusion, the newly developed miniaturized hemofilter for a wearable ultrafiltration device meets the technical requirements of wearable medical devices and its structural design develops uniform blood flow distribution and stable hydrodynamics during the operation. Performance test with whole blood is required to provide information on coagulation properties for the long treatment (~12 hours/day) for overhydration and congestive heart failure.

10
Comparison of Bisphenol A Elution in Hollow-Fiber Hemodialyzers
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Introduction: Bisphenol A (BPA) is environmental hormones or endocrine disrupting molecular compound (molecular weight = 228.3 kDa). BPA is used for the polymerization of some plastic materials applied in hemodialyzer for extracorporeal dialysis like polycarbonate (PC) of the housing and polysulfone (PSu) of the membranes.

Aim of the Study: We compare BPA elution from among 3 different hemodialyzers.

Materials and Methods: We evaluated the BPA elution from 3 different dialyzers: Nipro Elisio 17H (Polypropylene housing and Polynephron© membranes), B-Braun Diacap (PC housing and PSu membranes) and Nipro Elisio 170H (PC housing and Polynephron© membranes).

We circulated 600 ml of cell culture media (RPMI) for 240 minutes through dialysis circuit. We measured the BPA concentration before and after the treatment through Enzyme-Linked Immuno-Sorbent Assay (ELISA) method and we calculated the BPA mass eluted. We also incubated monocyte cell line (U937) for 24 hours in medium samples taken before and after the treatments and we evaluated the differences between viability, necrosis and apoptosis of the cells by Annexin V-FITC kit in the 3 different dialyzers. The analysis was performed by Navios Flow Cytometer.

Results: The results (N=2) are summarized in the following table (Median[IQR]).

Conclusion: Polypropylene housing and modification of membrane materials for hemodialyzer could elute less BPA into the circuit during hemodialysis. This can be confirmed by viability, necrosis and apoptosis of monocytes incubated with circulating medium for 24 hours.

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How to Perform CRRT without Anticoagulation

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Frequent clotting applying continuous renal replacement therapy (CRRT) can make treatment ‘dose’ inadequate, increases cost, and requires a deal of nursing time with new circuit preparation. There are also frustrating interruptions to other nursing care routines to remove and re-establish the treatment. In addition, this failure or ‘off time’ may be associated with a progressive positive fluid balance making greater demands on the effective treatment ‘on time’. Although prescribed as ‘continuous’, actual circuit function time is highly variable in the ICU setting with data from large randomized controlled CRRT trials indicating that about 21 hrs (median) is a common time for continuous function in the ICU. Single centre reports, with frequent use of anticoagulation report median circuit function time greater than 50 hrs. However when data related to specific subgroups is considered, a median circuit life of 9 hrs may be reported and is a clinical challenge with considerable ‘off time’; e.g. ARF associated with liver failure.

Patency of the extracorporeal circuit (EC) is commonly achieved using anticoagulants such as heparin or citrate. Although these methods can be very effective, many patients cannot safely be given anticoagulation; e.g. major and vascular or neuro surgery and liver failure management. When anticoagulants are not used, or clotting occurs within a few hours despite anticoagulation, blood flow failure and mechanical flow blood factors within the CRRT circuit are of greater importance.

Performing CRRT without anticoagulation, and for optimal use irrespective of context, requires; large Fg access catheter with side-by-side lumen profile, pre and post membrane substitution fluids administration, longer bubble trap blood inlet design, reliable blood pump flow, nurse training and troubleshooting ability for alarms response, and an audit routine to quickly know circuit ‘life’ in your ICU.

References:

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<td>Medullary perfusion (BPU)</td>
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one third. During sepsis (table 1), cortical perfusion did not change significantly while cortical tissue pO2 increased. In contrast, both medullary perfusion and tissue pO2 decreased.

Conclusions: This is the first study to measure intrarenal perfusion and oxygenation in hyperdynamic sepsis in a non-anaesthetized large mammal. We reproduced severe sepsis with hypotension and AKI with features similar to those of human sepsis and we showed decreased medullary perfusion and oxygenation, possibly due to mismatched local perfusion and oxygen consumption.

13 Intraoperative Cell-Saver: What Are We Saving?
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Background: Increased awareness of the potential hazards of homologous transfusions has led to an emphasis on blood conservation during cardiac surgery. Several modalities including intraoperative cell-saver have emerged as alternatives to avoid the immunomodulatory effects. In particular, cell-savage devices are routinely used to process mediastinal shed and stagnant blood in the mediastinal and pleural cavity. Mediastinal shed blood is known to have high inflammatory properties. Several researches focused on quality of red blood cell (RBCs) saved, on quality of the saved product in term of reduction of inflammatory biomarkers and on the inflammatory response after reinfusion of the cell-saver (CS) product. The aim of this study was to investigate the effect of cell-saved product on human monocyte cell line. The secondary objective was to analyze in vitro inflammatory markers and oxidative stress following incubation with Cell-Saver (CS) product.

Materials and Methods: In January 2013 we collected blood samples from 14 patient underwent on-pump cardiac surgery. An intraoperative CS device was used in each patient. We collected two EDTA blood samples for each patient (one at the end of cardiopulmonary by-pass (CPB) from the venous reservoir and one from the CS treated blood pack). Plasma were immediately separated from the blood cells and stored at –80°C until use. For each patient, plasma from CPB and from CS were incubated with monocytes cell line (U937) for 24h in standard condition and, subsequently, apoptosis and necrosis was evaluated by cytofluorometric assay. In addition, quantitative determination of inflammatory parameters (TNF-α, IL-6 and NGAL) and oxidative stress (Endogenous Peroxidase Activity-EPA; Myeloperoxidase-MPO) was performed in CPB and CS plasma samples.

Results: A quantitative analysis of apoptosis showed significantly higher apoptosis rates in monocytes incubated with CS plasma compared to CPB group 19.1%, (IQR 14.07–21.05) vs 3.10%, (IQR 1.22–3.65) with a significant delta apoptosis between the samples from the same patient (14.7±4.63) (p < 0.01). The necrosis rates in monocytes incubated with CS plasma compared to CPB group (19.1%, (IQR 19.85–20.78) vs 3.4%, (IQR, 1.4–4.45 ) was significantly increased with a significant delta necrosis between the samples from the same patient (15.3±5.15) (p < 0.001).

IL-6 (136.3 (IQR, 75.34–375.28) vs 24.81(IQR, 19.73–29.23), TNF-α (28.55 (IQR, 26.23–31.26) vs 33.41(IQR, 33.17–35.33) and NGAL (110 (IQR, 82.25–189) vs 39 (IQR, 26.5–75.5) levels were lower in CS product (all for p < 0.05). An increase of oxidative stress was observed in CS plasma: EPA values were increased in all CS samples (60.5 (IQR, 55.4–71.4) vs 49.5 (IQR, 31.5–57.4), p < 0.05). MPO levels was higher in 4/14 CS samples, although, no statistically significant different between CPB and CS was observed for this marker.

Conclusion: Quantitative analysis of cell viability indicate that CS product induce monocyte activation, mobilization, and recruitment resulting in apoptosis and necrosis. In particular, the Cell-Saver product is able to induce a strong damage on monocytes. We have demonstrated induction of kinase mediated immunomodulatory effects of CS product using a human monocyte cell line.

14 New Approach to Study the Phenotype Changes in Cardiomyocytes Due to Uremic Serum
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Cardiorenal syndrome (CRS) is defined as a condition characterized by the initiation and/or progression of renal failure due to heart failure and vice versa. Traditional cardiovascular risk factors play an important role in the incidence of cardiovascular mortality in Chronic Kidney Disease (CKD) patients. However, these factors explain only partially the high incidence of cardiovascular events in CKD. Other mechanisms may be oxidative stress, inflammation, apoptosis and disregulation of calcium signaling. In our dialysis center we have 160 CKD patients with high incidence of cardiovascular disease and mortality. The aim of this study is develop a model to better understand the effect of uremic serum as a potential cause of cardiovascular disease. The project was developed into following phases: 1. Enrollment of CKD patients and healthy controls in which we collected serum and ultrafiltrate samples during RRT; 2. Analysis of general biochemistry of the all samples; 3. Isolation and culture of neonatal rats cardiomyocytes; 4. Cell incubation with different collected samples (10%, 30% and 60% of CKD and healthy serum and ultrafiltrate) and 5. Cell count, evaluation of cell morphology and apoptotic assays (Gaspare 3/ Troponin/DAPI Immunofluorescence, Tunel, etc). It has been observed that when the uremic serum and ultrafiltrate concentration increases in the culture medium we identified an increased cell death and apoptosis. In conclusion, this phenomenon was particu-
larly evident with CKD serum, suggesting that the best concentration of serum is 30% because 60% is too toxic to maintain the cells in culture for more than 24 hours; that is the minimum time to obtain an effect on the phenotype.

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Aphthous and Necrotic Effects of P-Cresol in Renal Tubular Epithelial Cells
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Introduction and Aims: Uremic syndrome is characterized by a deterioration of kidney function due to the accumulation of uremic toxins. Uremic toxins are particularly difficult to remove by conventional dialysis treatments and are the major causes of mortality in CKD patients. One of the uremic toxin is p-cresol, a fenol protein-bound lipofile. The effects of p-cresol is well known in different type of cells. Many studies have revealed dual effect of uremic retention solutes on leukocyte function: blunting upon stimulation and basal activation linked to microinflammation, malnutrition, and atherosclerosis. Granulocyte function is depressed by a longer incubation with p-cresol, p-cresol inhibits both cytokine-induced expression of endothelial adhesion molecules and stimulates monocyte adhesion to endothelial cells. Moreover, p-cresol inhibits endothelial cells proliferation and wound repair in vitro, and it may be involved in increase in endothelial permeability in CKD patients. Despite the presence of many studies on p-cresol effects in different cell lines, it’s still poorly understand what determines in epithelial renal cells, considering that kidney is the principal organ involved in uremic syndrome. Our aim is to evaluate in vitro effect of p-cresol on renal tubular epithelial cell line (LOC), in terms of apoptosis and necrosis, to better understand the pathophysiological impact of this toxin.

Methods: We incubated LOC for 24 hours in medium with scalar concentration of p-cresol, from 40 mg/L (up level in uremic patient) to 2.5 mg/l. We used untreated LOC as negative controls. We perform a qualitative analysis of cellular viability in treated LOC by detection of DNA ladder showing the typical apoptotic DNA fragmentation we perform also a quantitative analysis of cell viability in term of apoptosis and necrosis by Annexin V/Propidium Iodide Cytofluorimetric assay. In addition, we evaluated Caspase-3 concentration by Enzyme-Linked Immuno Sorbent Assay (ELISA). All experiments were performed 5 times.

Results: We observed a strong DNA fragmentations in cells treated with low concentration of p-cresol. At increasing concentration of toxin, we noticed a decreasing DNA Ladder because the necrosis is almost the only type of cell death. We confirmed the presence of apoptotic and necrotic pathways by quantitative analysis. Cytofluorimetric determinations showed that p-cresol concentrations ≥20 mg/L cause the necrosis of >60% of cells; instead at concentration ≤5 mg/L, the percentage of necrosis was comparable to control (Fig.1). We detected a positive trend, but no significant relationship between Caspase-3 levels and p-cresol concentrations. We may better understand the pathophysiology of this phenomenon increasing the number of experiments.

Conclusions: In conclusion, p-cresol caused cellular death in renal tubular cells, determining necrosis in almost total cultured cells at the maximal concentration. At lower concentration, p-cresol determined cell death through apoptosis. This data was confirmed by Caspase-3 activation. This results were consistent with the clinical studies showing a link between high concentrations of plasma-free p-cresol and haemodialysis patients outcomes, as hospitalization rates for infection disease and cardiovascular events. These results highlight the necessity of developing new therapeutic and dialytic strategies to increase p-cresol removal in CKD patients.

Fig 1. Percentage of cell necrosis at different p-cresol concentrations. **Statistically different from baseline (p < 0.05).
Impact of Lactate in Substitution Fluids on Acid-Base Balance and Lactatemia in Septic Shock Patients Treated by Continuous Veno-Venous Hemofiltration

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Background: Septic shock patients usually exhibit or present metabolic acidosis and hyperlactatemia. When acute kidney injury (AKI) occurs, they are treated by continuous veno-venous hemofiltration (CVVH) with bicarbonate based substitution fluids. While some fluids contain 3 mmol of lactate per litre for acid-base stabilisation, others use chlohydric acid. We studied the impact of these different solutions on acid-base balance and lactatemia.

Subjects and Methods: This study is a post-hoc analysis from IVOIRE trial (multicentre randomised controlled trial) that compared high volume hemofiltration (HV = 70 ml/kg/h) versus standard volume (SV = 35 ml/kg/h) during 96 hours in septic shock patients with AKI. During the study, in two centres (Bordeaux and Libourne), substitution fluids were switched from AccusolTM (Baxter) containing chlohydric acid (11/2005 to 07/2008) to PrismasolTM (Gambo) containing lactate (08/2008 to 12/2009) due to market change. Eighty-two patients were included, 41 treated with AccusolTM (HCl) and 41 with PrismasolTM (Lac). We compared the two groups at inclusion (before the start of hemofiltration) and after the 96 hours of treatment by hemofiltration in term of demographic data, lactatemia, acid-base balance, SOFA, SAPS II, liver dysfunction, group of randomisation and outcome. We performed univariate and multivariate logistic regression analysis. The statistical analysis included Wilcoxon test for quantitative variables and Chi² or Fisher exact test for qualitative variables respectively.

Results: The two groups, respectively (HCl) and (Lac), were comparable at inclusion for demographic data or all studied parameters: Lactate 6.1 mmol/l vs 4.5 mmol/l (p = 0.98), SAPSII 69 vs 68 (p = 0.77), SOFA 12 vs 12 (p = 0.87), ASAT 439 UI/l vs 527 UI/l (p = 0.63), group of randomisation: HV 51% vs 49% (p = 0.82). At 96h, there was no difference between the two groups respectively (HCl) and (Lac): Lactate 2.3 mmol/l vs 2.4 mmol/l (p = 0.6), patients with lactate > 2 mmol/l 43% vs 48% (p = 0.7), SAPSII 51 vs 43 (p = 0.42), SOFA 11 vs 10 (p = 0.85), ASAT 90 UI/l vs 86 UI/l (p = 0.37), mortality 22% vs 29% (p = 0.45) and other parameters (pH, bicarbonates, hepatic dysfunction, etc…). The relative risk (RR) to present hyperlactatemia with substitution fluids with lactate was RR = 1.12 (0.63–1.97). The univariate logistic regression found that only SOFA and SAPSII were associated with hyperlactatemia and not the group of substitution fluids, odds ratio = 1.23 (0.41–3.64) (p = 0.7). In multivariate logistic regression only SAPSII at inclusion remains associated with hyperlactatemia at 96h.

Conclusion: This study shows that substitution fluids with 3 mmol/l of lactate have no impact on acid-base balance, lactatemia or risk of hyperlactatemia or any other parameters and was comparable with fluids without lactate. The use of this type of substitution fluids for septic shock patients with AKI does not seem to be associated with a higher risk of hyperlactatemia even with high volume hemofiltration and may be used safely. This study is a before/after study and the results should be confirmed with a large prospective randomised study.

Acidosis and Mortality in Intensive Care Unit (ICU) Patient’s on Continuous Renal Replacement Therapies (CRRT): Classical vs. Stewart’s Approach

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Background: Acid-base disorders are common indications for CRRT in ICU. If unrecognized they may result in poor outcomes. Stewart approach may be superior for acid-base analysis in the critically ill.

Aim: Assessment of Classical and Stewart approaches for the analysis of acid-base disturbances during CRRT and mortality risk at 30 days.

Methods: We enrolled 40 consecutive adult patients on CVVH and mechanical ventilation. All patients received a 35 ml/Kg/h infusion of a standard buffer [5 Liters (mmol/L): [HCO₃⁻]35, [Na⁺]140, [K⁺]2, [Ca²⁺]1,75, [Mg⁺]0.5, pH 7.4]. We calculated [pH] and SBE with the Henderson-Hasselbach and Siggaard-Andersen equations. Physicochemical analysis was performed using the Stewart equations modified by Figge et al. Apparent strong ion difference (SIDa) was calculated as: SIDa, mEq/L = [Na⁺]+[K⁺]+[Mg⁺]+[Ca²⁺]-[Cl⁻]-[lactate]. Effective SID (SIDe) was calculated as: SIDe, mEq/L = 1000x2.46x10⁻¹¹xPaCO₂/(10⁻pH)+[albumin×0.123×pH-0.631]+[PO₄⁻×0.309×pH-0.469]. Acidosis was defined by SBE < -5mEq/l, pH < 7.35, SIDa < 40mEq/l or SIDe < 38mEq/l.

Results: The prevalence of acidosis, assessed by pH, SBE, SIDa or SIDe, was significantly different (P < 0.001) at each step. At 0.6,12 and 24h from start of CVVH, pH < 7.35 was present in 63,30,20% of patients; SBE < -5mEq/l in 35,10,5% and 5%; SIDa < 38mEq/l in 100,88,65 and 88%; SIDe < 40mEq/l in 73,60,48 and 43% respectively. 58% of patients (n = 23) died within 1 month from ICU admission. The risk of death was significantly higher for reduction of SIDA (P < 0.01), SDE (P < 0.05) but not pH (P = NS), independently to APACHE II score and gender. 16 of 17 patients (94%) with SIDa < 40mEq/l at 24h died within 1 month from ICU admission (the relative risk of death was 3.1).

Conclusions: Stewart approach seems to be more sensitive for detection of acidosis in ICU patients on CRRT and has a greater impact to mortality than Classical approach.
Stroke Volume Variation (SVV) and Oxygenation Index (OI) Are Risk Factors for Acute Kidney Injury (AKI) in Abdominal Aortic Aneurysm (AAA) Surgery

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**Background:** AAA surgery patients are at high risk for AKI. Hemodynamic instability, hypovolemia, haemorrhage and reduced cardiac output may play a key role in AKI. SVV predicts volume responsiveness in mechanically ventilated patients; elevated levels of Oxygenation Index (OI) are linked to fluid overload and associate to poor outcome in critical ill patients but little is known about their role in AKI. We aimed to assess if patients with wide changes of SVV or OI at clamping and declamping time of the aorta are associated with high risk of AKI development.

**Methods:** We enrolled 21 consecutive hypertensive patients undergoing elective AAA surgery with supra-renal clamping. Patients were all on volume-control mechanical ventilation (8 ml/kg) and positive end expiratory pressure of 4 cmH2O. Patients with arrhythmias, spontaneous ventilations, and those extubated before 12h post-operative were excluded. SVV was measured with the FlowTrack/Vigileo (Edwards Lifesciences®) device every 3 minutes during the procedure and for 24h after surgery. OI was calculated as = mean airway pressure/(PaO2/FiO2)x100. Patients received 70ml/kg/h of crystalloids; fluid boluses and transfusions were given if needed. Data were compared with ANOVA.

**Results:** 9 patients (43%) developed AKI, defined as RIFLE Risk category. SVV and OI were significantly higher at aortic clamping (p < 0.0001) and declamping time (p < 0.0001 and p < 0.01 respectively) (fig. 1).

**Conclusions:** High SVV and OI during and after suprarenal AAA surgery are associated with high risk of AKI.

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Bioimpedance and Fluid Overload in Patients Admitted to the Intensive Care Unit for Sepsis Syndromes

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**Introduction:** The mainstay of treatment for sepsis is the early initiation of both antibiotics and fluid resuscitation. Treatment guidelines call for administration of IV fluid until central venous pressure is >8 mmHg. Ultimately the goal is to maintain tissue perfusion. Bioimpedance vector analysis (BIVA) is a noninvasive technique that utilizes the principle that the body acts as an electrical circuit with a measurable resistance (opposition to electrical current) and reactance (ability to store energy). BIVA can accurately quantify total body water and is comparable to the gold standard of deuterium dilution (r>0.99).

**Methods:** In this ongoing, prospective, observational study we included patients >18 years of age admitted to the intensive care unit (ICU) with the diagnosis of sepsis, severe sepsis, or septic shock (based on the Society of Critical Care Medicine definitions). BIVA (using EFG Diagnostics Cardio EFG analyzer) was used to measure total body water. Patients with end stage liver or kidney disease (requiring dialysis) were excluded. Demographics, co-morbid conditions, vital signs, fluids received, urine output, laboratory values, and bioelectric impedance values were collected prospectively.

**Results:** We have enrolled 8 patients to date. Mean age was 73 years (range 61–85), 4 (50%) were female, mean BMI was 28, 4 (50%) had diabetes mellitus, 7 (88%) had hypertension, 2 (25%) had impaired left ventricular function, 6 (75%) were current or former smokers, mean length of ICU stay was 3.75 days (range 1–6). Three (37.8%) had sepsis, 4 (50%) had severe sepsis, and 1 (12%) had septic shock. Mean initial glomerular filtration rate was 40 mL/min/1.73m2 (range 9–67). Mean percent total body water on day 1 was 82.4%, day 2 89.8%, day 3 90.0%, day 4 91.1%, day 5 90.1%, and day 6 92.1% (normal <74.3%). On day 1 4 (50%) had...
clinically evident ankle edema. By day 3 all patients remaining in ICU had clinically evident edema. Four (50%) developed radiographic evidence of pulmonary edema. Mean peak fluid overload (pkFO) was 13.1 L (range 5.0–26.2 L).

**Discussion:** All of our patients became fluid overloaded, mean peak pkFO was 13.1 L. Our patients were already fluid overloaded at the time of first measurement, presumably from initial resuscitative efforts. Patients with sepsis suffer from hypotension secondary to a combination of vasodilatation and increased vascular permeability. Treatment requires large volumes of IV fluids. As patients recover, this massive fluid load manifests clinically as edema. Edema can impair tissue oxygenation, obstruct of capillary blood flow, disrupt metabolite clearance, and alter cell-cell interactions. Each liter of 0.9% saline contains 9 grams of sodium. This large salt load must be excreted by the kidney. Patients with impaired renal function are at risk for more severe and longer duration of clinically significant edema.

**Background:** Hemorrhagic fever with renal syndrome (HFRS) is an acute viral disease characterized by fever, hemorrhage and acute renal failure and is caused by closely related zoonotic viruses of genus Hantavirus of the family Bunyaviridae. Infections with Hantaviruses occur through inhalation of aerosol from rodent faeces, urine or saliva. Hantaviruses produce a spectrum of illnesses with specific manifestations depending on the particular virus involved. The aim of our study was to analyze the clinical course and outcome of acute kidney (AKI) in patients with hemorrhagic fever with renal syndrome (HFRS).

**Methods:** We retrospectively analyzed 36 patients (23 males, 3 females) aged from 19 to 64 years treated in our facility from 2006 to 2011.

**Results:** Most of the patients were connected with work at a farm or in a forest. The disease was confirmed serologically with enzyme-linked immunosorbent assay (ELISA). In all of the cases, the disease broke out from May to November. The most frequently expressed clinical signs and symptoms were fever, headache, abdominal pain, severe myalgia, profuse conjunctival hemorrhage and thrombocytopenia. Hypotension, macrohematuria, pulmonary infiltration, pleural effusion, hepatomegaly and positive meningeal sign were present in 16 patients infected with Belgrade serotype virus whilst in other infected patients with less severe disease Hantaan virus was established. All patients had acute kidney injury (AKI), anuric was 45% of them, and treatment with dialysis was necessary in 83%. Platelet count at the admission was the most significant prognostic factor for the development of severe AKI (odds ratio, 26.53; 95% CI, 6.33–94.26; P < 0.0001). We observed favorable effect of “an early di-alysis” to the course of the disease and its outcome. 5 patients (13.8%) died, all infected with Belgrade and the cause of death in 4 patients was cerebral hemorrhage, and shock in one patient. After the convalescent phase we noted a chronic renal failure in 6 patients who had a severe form of the disease and 2 of them progressed to end stage renal disease. All of them had hypovolemic shock, severe ARF, ARDS, visceral haemorrhage and disseminated intravascular coagulation (DIC) through the course of their disease.

**Conclusions:** According to clinical characteristic and syndromes that follow HFRS, most of our patients had severe form of illness. Belgrade virus infection is associated with a more severe disease type and development of chronic renal failure as a sequela of the disease.

**21 Serum and Plasma Neutrophil Gelatinase-Associated Lipocalin (NGAL) Levels Are Not Equivalent in Patients Admitted to Intensive Care**

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**Background:** Neutrophil gelatinase-associated lipocalin (NGAL) is proposed as a biomarker of acute kidney injury (1). NGAL has been studied in a range of body fluids including serum and EDTA-plasma (2,3). The aim of the present study was to investigate whether measurements of NGAL concentrations in serum and EDTA-plasma are directly comparable in patients admitted to intensive care units.

**Methods:** NGAL was measured in 40 paired samples of serum and EDTA plasma from 25 patients admitted to intensive care with a commercial particle-enhanced turbidimetric immunoassay (The NGAL Test®, BioPorto Diagnostics A/S) on a Roche Hitachi 917 (Roche-Hitachi Inc., Tokyo, Japan) analyzer.

**Results:** Serum NGAL concentrations ranged from 26.8 to 1808 ng/mL (median 281 ng/mL, interquartile range (IQR) 453 ng/mL). EDTA-plasma NGAL concentrations ranged from 25.7 to 1752 ng/mL (median 225 ng/mL, IQR 352 ng/mL). The difference in NGAL concentrations in paired serum and EDTA-plasma samples (serum – plasma) ranged from –13.8 to 321 ng/mL (median 79 ng/mL, IQR 116 ng/mL; difference from 0, p < 0.0001, Wilcoxon’s signed rank test). Although serum and EDTA-plasma values were correlated (Spearman’s r = 0.95, p < 0.0001), Deming regression analysis showed a slope of 1.1 that was not significantly different from unity (95% confidence interval (CI) 1.0–1.1) but a highly significant intercept of 67.9 ng/mL with a wide confidence interval (95% CI 29.8–106).

**Conclusion:** NGAL concentration values measured in serum and EDTA plasma cannot be directly compared and should not be
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High-Volume Hemofiltration Pulse to Treat Refractory Shock in Septic Acute Kidney Injury: Experience of Two Academic Hospitals in Bogota, Colombia

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Background: The use of high volume hemofiltration (HVHF), and more recently, intermittent pulsed dosing, is a strategy implemented in AKI patients when septic shock is refractory, and hemodynamic instability demands progressive high doses of vasopressors. Until now the precise definition of these strategies remain unclear with different schemes across studies. Until now the precise definition of these refractory, and hemodynamic instability demands progressive high doses of vasopressors. Until now the precise definition of these strategies remain unclear with different schemes across studies.

Methods: This is a retrospective observational study, including 7 patients with refractory septic shock, severe hemodynamic instability and AKI, requiring onset of continuous renal replacement therapy (CRRT) in two academic hospitals in Bogota, Colombia. CRRT was initiated as a pulse of HVHF (dose of 60 ml/kg/hour for the first 6 hours and then 35 ml/kg/hour as maintenance dose). We describe demographic, clinical and bio-

References:

Conflict of interest statement: TSI, MHB and JU: None declared. KB and LOU: Hold positions at BioPorto Diagnostics A/S which manufactures The NGAL Test™ and are the inventors of patents and patent applications relating to the diagnostic use of NGAL determination. PHC: Hold a position at Dako A/S which manufactures Cystatin C ImmunoParticles. BioPorto Diagnostics A/S provided reagents for NGAL analysis. Dako A/S provided reagents for cystatin C analysis. TSI and MB had full access to all data.

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Hydration Status Evaluation by BIVA in Patients Requiring CRRT

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Background: Disorder of fluid balance is an important risk factor for morbidity and mortality in critically ill patients. Total body fluid status is particularly important, but it has been poorly studied in patients requiring CRRT.

The aim of the study was to evaluate the variation of hydration status, measured by Bioelectric Impedance Analysis (BIVA), in critically ill patients at the beginning of CRRT, in the following days and at the discontinuation of treatment.

Methods: This is a prospective cohort study in adult critically ill patients requiring CRRT. 89 BIVA measurements were performed at beginning and during treatment every day for 5 days in 21 patients under the treatment for at least 48 h. Patients were considered normohydrated if BIVA was between 72.7% and 74.3% of body water, fluid overloaded if BIVA > 74.3% and dehydrated if BIVA < 72.7%.
**Results:** The most common indication for CRRT has been the state of fluid overload with oliguria (in 13 of 21 pts), followed by sepsis (in 11 of 21 pts).

The variation of the degree of body hydration status measured by BIVA showed a gradual increase in body hydration with a median 6% higher at fifth day than the day of beginning of the treatment despite removal of fluids through CRRT.

At discontinuation of CRRT, that was performed for recovery diuresis and improvement of renal function or for resolution of the state of shock, patients had however a state of over-hydration with a median of 87.2% of total body water.

There were no statistically significant difference in survival between patients with overhydration and normohydrated, probably due to the limited sample number and a fair degree of fluid overload in all patients.

**Conclusion:** In conclusion, a fluid overload is common in critically ill patients in CRRT, and this condition persists during treatment. This suggests an inadequacy of the protocols of fluid balance probably related hemodynamic instability of patients requiring CRRT. BIVA may, therefore, is a valuable additional diagnostic method to monitor the hydration status in critically ill patients in intensive care unit.

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**The Importance of Rifle Criteria in Postoperative Cardiac Surgery Patients with Acute Kidney Injury**

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**Background:** Acute Kidney Injury (AKI) is a major postoperative complication in heart surgery and is associated with a poor prognosis, being an independent predictor of mortality. The incidence of AKI post operatively varies from 2% to 15% with an associated mortality of 40–80%. There is limited data regarding the appropriate time to initiate continuous veno-venous hemofiltration (CVVH) in postoperative cardiac surgery patients with AKI. The aim of this retrospective study is to highlight the need of the RIFLE criteria in determining the initiation time of CVVH in open heart surgery patients with AKI.

**Methods:** We studied 600 patients, who underwent coronary artery by-pass. Surgery was performed by the normothermic technique and the composition of the prim of the cardiopulmonary bypass was the same in all patients. Twenty one patients (3.33%) required renal replacement therapy (RRT) post-operatively. CVVH was performed via a central double lumen vein catheter (11.5 F, Medcomp USA). A four pump Prisma Machine (Hospal) was used. Filtration was achieved through a polysulphone filter with surface of 1.0m². Blood flow rate of 220 ml/min was set in all patients. Replacement fluid rate of 35ml/h/kg was used in predilution mode. The classical approach in our unit for CVVH treatment initiation is when two of the following conditions were met: i) creatinine levels ≥ 4mg/dl or increase of creatinine >1mg/dl/24h, ii) urea levels ≥ 240 mg/dl, iii) potassium levels ≥ 6 mEq/L, iv) metabolic acidosis, v) pulmonary pressure ≥ 60 mmHg and vi) urine output less than 15 ml/h for 12 hours. We reevaluated the patients, taking in consideration the RIFLE criteria and we were able to assign patients in two groups: Group-1 (9 patients) received CVVH treatment in Stage Injury (stage I) and Group-2 (12 patients) CVVH treatment started in Stage Risk (stage R). Statistical analysis was performed using the SPSS software version 13.0, and p < 0.05 was considered as statistically significant.

**Results:** Using the classical approach it was difficult to group patients in order to indentify the best appropriate time for these patients to start CVVH. According to RIFLE criteria survival was significantly better in Group-2 (4 deaths /12 patients) compared to Group-1 (6 deaths /9 patients). Infections (mainly pulmonary infections) were more in Group-1 (80%) compared to Group-2 (50%) but not statistically significant. Mean duration of CVVH treatment was significantly less in Group-2 (5 days versus 8 days in Group-1). Group-2 patients stayed in ICU for a mean time of 10 days while patients in Group-1 stayed 17 days (p < 0.05).

**Discussion-Conclusions:** The use of RIFLE criteria in the septic intensive care patients with AKI is well established. It seems that the use of RIFLE criteria is also important in the postoperative cardiac surgery patients with AKI, giving the opportunity to specify particular groups of patients and probably guidelines for the management of AKI in these patients. Despite the limitations due to the small number of patients studied, our data suggest that early initiation of CVVH treatment (even in the stage of R of the RIFLE criteria) improves hospitalization of postoperative cardiac surgery patients with AKI and decreases mortality.

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**Diagnosis of AKI: How Do We Combine Biomarker Results and Risk Prediction Models?**

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Accurate acute kidney injury (AKI) biomarkers could allow interventions to be targeted to patients early enough to benefit from treatment or serve as surrogate clinical endpoints for AKI prevention. Performance of novel AKI biomarkers is usually defined as ability to predict occurrence of creatinine and urine output consensus diagnostic criteria, and is quantified as the area under the curve (AUC) of the receiver operating characteristic (ROC). ROC analysis is effective at identifying statistical risk factors for AKI diagnosis in populations, but does not reliably inform on clinical utility to identify individuals at risk of AKI, which is dependent on the cut-off chosen to define high risk of AKI, its associated likelihood ratio (pre- to post-test odds of AKI), and the population incidence of AKI.

Consequently, investigators have sort to examine the ability of biomarkers to refine diagnosis of AKI adding them to clinical risk prediction models alone or in combination with other biomarkers. There are two distinct goals of these analyses. Firstly to assess whether a novel biomarkers an independent population risk factor for AKI when added to existing clinical information and/or other biomark-
ers (statistical significance). Secondly, to assess if addition of a new biomarker meaningfully adds to the ability of risk prediction models and existing biomarkers to define individuals at highest risk of developing AKI (clinical utility). Presence of statistical significance can provide useful biological information, even in the absence of clinical utility, for instance by suggesting that two markers assess different aspects of the pathogenesis of AKI, rather than providing redundant information on the same process.

There is much debate regarding the most appropriate methods to combine biomarkers and risk prediction models, and how best to assess these combinations. Two or more predictors can be combined in multivariable logistic regression analysis or as weighted linear combinations of predictor variables. Enhancement of risk prediction can then be assessed by reclassification calibration statistics or statistical comparison of AUCs. The degree to which models are enhanced by addition of a novel biomarker can be further assessed by calculation of novel metrics, the net reclassification index (NRI) and the integrated discrimination improvement (IDI) that assess correct direction and magnitude of change in assessed risk, respectively. These parameters can be overly sensitive and require careful interpretation; a reclassification table and separate assessment of positive and negative risk reclassification is necessary to achieve this.

Finally all forms of AKI risk prediction are intrinsically limited by the indirect and imprecise relationship between standard AKI diagnostics and actual renal pathology, potentially causing clinically accurate predictions to be dismissed. Optimal assessment of novel biomarkers may require calibration against other AKI-associated events, both short-term physiological changes and longer-term, patient-centred outcomes, such as development of chronic kidney disease.

In septic shock fluids and vasopressors are titrated to varied goals, including mean arterial blood pressure (MAP), cardiac output, oxygen delivery or organ function. Kidney function is often targeted, as acute kidney injury (AKI) is both a sensitive indicator of illness severity and an independent contributor to the pathogenesis of multi-organ dysfunction.

Plasma fluid extravasation, venodilation, and myocardial depression can decrease cardiac performance in sepsis, so fluid therapy is often targeted to cardiac output and organ perfusion. However fluid responsiveness in sepsis can be unpredictable, while increased capillary permeability means the effects of plasma volume will be short-lived. Venous congestion and tissue oedema are thus common consequences of fluid resuscitation and, importantly, are associated with organ dysfunction, in particular, worse outcomes in AKI. An ideal fluid strategy in sepsis would maintain organ perfusion while minimising fluid overload; in the first six hours of septic shock strategies including fluid administration aimed at measures of oxygen delivery (central venous saturation or arterial lactate) have shown benefit, including decreased occurrence of AKI. Significantly, overall fluid administration doesn’t appear to be greater using these early, goal directed approaches, possibly due to more rapid shock reversal. Conversely, prolonged targeting of elevated oxygen delivery in the ICU appears harmful. Thus, beyond the initial resuscitation period, intensivists are faced with a philosophical choice between minimising fluid administration, requiring earlier recourse to organ support and vasoactive drugs, or maintenance of venous return and stroke volume resulting in progressive fluid overload. In the absence of data for prospective clinical trials, balancing these conflicting goals remains a matter of clinical judgement.

In septic shock, vasopressor therapy is commonly titrated to MAP. The intent is to counter global vasodilation, diverting blood flow to vital organs such as the kidney, but not to reduce cardiac output and organ perfusion by excessive vasoconstriction. While MAP targets are commonly individualized to patient and clinical context, considerable experimental and clinical evidence suggests that increasing MAP to 75 mmHg with vasopressors, increases both renal blood flow and glomerular filtration; as increased renal perfusion pressure and reduction of renal sympathetic tone outweigh any increase in renal vascular resistance, while predominantly post-glomerular vasoconstriction augments filtration pressure. Whether targeting a higher MAP with vasopressors actually results in better renal or patient outcomes in septic shock is currently unknown. Forthcoming results of clinical trials may provide more data to guide clinicians.
Patients and Methods: Forty patients with chronic kidney disease (stage III B-IVK/DOQI 2003) with clinical symptoms suggestive of APN were recruited. Both CEUS (Siemens Sequoia 512) and MRI (Achieva 1.5 T, Philips) were performed in a blinded manner by two different operators. Sensitivity, specificity, positive and negative predictive values were calculated.

Results: In 32 patients (80%) CEUS detected poorly parenchymal renal areas, while MRI findings were suggestive of APN in 33 patients (82.5%). In six patients (15%) there were no ultrasonographic signs of APN and these findings were confirmed by MRI. Sensitivity was 96.9 %, specificity 100%, positive predictive value 100%, negative predictive value 87.5%.

Conclusions: The present study suggests that CEUS is an accurate technique for detecting parenchymal changes in case of APN, and it represents a useful diagnostic tool in patients with CKD where iodinated or paramagnetic contrast medium use is limited.

28 Usefulness of a Venovenous Extracorporeal CO₂ Removal Device (PROLUNG) in Severe Pneumonia Complicated by Refractory Bronchospasm

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We will report on the case of a 68 year-old woman, smoker, admitted to our ICU after an AAA reparation surgery. Her post-operative course was complicated by right bilobar pneumonia; she failed NIV and needed invasive ventilation. Her oxygenation was seriously impaired despite the use of high FiO2 and adequate ventilator settings; moreover, she developed a severe bronchospasm, refractory to maximal medical therapy. Her blood gas analysis showed a remarkable respiratory acidosis with high CO₂ values (>100 mmHg). After a discussion with the consultant Nephrologist, a novel form of extracorporeal CO₂ removal (Prolung, ESTOR, MI) was considered. A double lumen 14 Fr catheter was placed in the right femoral vein, the treatment was started with a continuous infusion of eparine; there were no signs of haemodynamic impairment or complications. The initial parameters (Qb 380 ml/min, O₂ flow 14 L/min) allowed a rapid and reliable reduction in the value of PaCO₂ (from 105 mmHg to 55 mmHg), as shown in serial Blood gas analysis and through the continuous EtCO₂ monitoring. This treatment was continued during the complex acute phase of pneumonia (the patient needed 5 cycles of pronation – 12h/12h- for her severely compromised oxygenation) and was progressively reduced following the gradual recovery of the lung function. After 7 days, the patient was weaned from the ventilator and successfully extubated to NIV. The treatment with low-flows was continued for some hours after the extubation, in order to manage and protect the patient during a potentially stressful time. It was possible to focus our ventilatory support on the impaired oxygenation, while Prolung solved the respiratory acidosis and its possible consequences. Systemic complications of extra-corporeal support were not observed and hemodynamic stability was fully preserved. There were no significant episodes of bleeding or thrombosis. The treatment was instituted very soon after the prescription and the double-lumen catheter allowed the requested blood-flow without any complication. In conclusion, PROLUNG proved effective in solving a severe, refractory hypercapnia. The extracorporeal support allowed a more protective ventilation, preventing barotrauma/volutrauma and subsequent iatrogenic damage to lung parenchyma.