Results After exposure with high but not with medium NoA we observed a statistically significant decrease in maximum mitochondrial respiratory capacity (E-state, C 133 (118; 148) vs. high NoA 111 (106; 113), and medium NoA 129 (123; 140), P < 0.05 C vs. high NoA). Both LPS and LPS + high NoA did not affect E-state respiration (LPS: 152 (136; 179), and LPS + NoA 129 (125; 137), but increased routine (R) respiration when compared to control (C 43 (40; 55) vs. LPS 66 (51; 72) and LPS + NoA 65 (55; 68), P < 0.05; high NoA 41 (37; 47), and medium NoA 52 (51; 57), NS).

Conclusion High but not moderate doses of noradrenaline reduced mitochondrial respiration in alveolar macrophages in vitro. Surprisingly, LPS increased routine respiration regardless of simultaneous noradrenaline exposure.

References

P21
Effects of the anti-diabetic imeglimin in hyperglycemic mice with septic shock
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Introduction Shock-related hyperglycemia impairs mitochondrial function and integrity [1], ultimately leading to apoptosis and organ failure [2,3]. Imeglimin is a new anti-diabetic drug with anti-hyperglycemic and anti-apoptotic properties [3]. Therefore we investigated its effects in hyperglycemic mice with septic shock.

Methods Immediately after cecal ligation and puncture, mice randomly received s.c. vehicle (n = 9) or imeglimin (n = 10; 100 μg/g). Fifteen hours later animals were anesthetized, mechanically ventilated and instrumented for a consecutive 6-hour observation period. After a second imeglimin bolus, colloid fluid resuscitation and continuous i.v. noradrenaline were titrated to maintain normotensive and hyperdynamic hemodynamics. Then 2 mg/g/hour glucose was infused to induce hyperglycemia. Glucose oxidation and glucoseogenesis were derived from blood 13C, glucose and mixed expired 13CO2/12CO2 isotope enrichment during continuous insulin infusion. Liver mitochondrial activity was assessed using high-resolution respirometry [4,5], Bax, HO-1 and NF-κB expression by immunoblotting and EMSA. All data are median (quartiles).

Results Imeglimin decreased blood glucose levels (165 (153; 180) vs. 192 (186; 221) mg/dl, P = 0.007) by increasing whole body glucose oxidation (55 (52; 57) vs. 51 (49; 55)% of infused isotope, P = 0.058), which coincided with partial restoration of glucoseogenesis (0.38 (0.34; 0.41) vs. 0.31 (0.27; 0.33) mmol/g/hour, P = 0.032), liver mitochondrial activity (oxidative phosphorylation (136 (134; 160) vs. 116 (97; 122) pmol O2/second/mg tissue, P = 0.003), maximal oxidative capacity (166 (154; 174) vs. 147 (130; 159) pmol O2/second/mg tissue, P = 0.006), Imeglimin increased liver Bax expression and attenuated NF-κB activation (all P < 0.001).

Conclusion Imeglimin improved whole body glucose utilization and glucoseogenesis, a well-established marker of liver metabolic capacity [4,5], and attenuated organ injury, at least in part due to inhibition of the mitochondrial apoptosis pathway.

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References

P22
Adrenomedullin blockade improves catecholamine responsiveness and kidney function in resuscitated murine septic shock
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Introduction The effects of adrenomedullin in circulatory shock states are controversially discussed: while its exogenous supplementation improved organ function and survival [1] in experimental models due to maintenance of hyperdynamic hemodynamics [2] in otherwise hypodynamic conditions, high blood levels were associated with increased mortality in patients with septic shock [3], most likely as a result of excessive vasodilatation [4] and/or impaired systolic heart function [5].

Methods Immediately after cecal ligation and puncture to induce peritonitis, mice randomly received vehicle (n = 11) or the adrenomedullin antibody HAM101 (n = 9; 2 μg/g to achieve antibody concentrations >4 ng/ml). Fifteen hours later animals were anesthetized, mechanically ventilated and instrumented for a consecutive 6-hour observation period. Colloid fluid resuscitation and continuous i.v. noradrenaline were titrated to maintain normotensive (mean blood pressure >60 mmHg) and hyperdynamic hemodynamics. Creatinine blood levels and clearance were assessed as surrogate for glomerular filtration [6,7]. All data are median (quartiles).

Results Adrenomedullin antagonism decreased the noradrenaline requirements needed to achieve target hemodynamics (0.009 (0.009; 0.012) vs. 0.02 (0.015; 0.044) μg/g/hour, P < 0.001), increased total diuresis (2.6 (2.3; 3.9) vs. 0.6 (0.5; 2.7) ml, P = 0.028) resulting in improved fluid balance (0.18 (0.14; 0.2) vs. 0.26 (0.19; 0.27), P = 0.011) and kidney function (creatinine levels at the end of the experiment: 1.3 (1.2; 1.5) vs. 2.0 (1.5; 2.9) μg/ml, P = 0.006; creatinine clearance: 400 (316; 509) vs. 197 (110; 301) ml/minute, P = 0.006).

Conclusion In resuscitated murine septic shock, early modulation of excess adrenomedullin activity via antibody HAM101 improves cardiovascular catecholamine responsiveness, ultimately associated with attenuation of acute kidney injury.

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References

P23
Activated protein C, severe sepsis and 28-day mortality
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Introduction Protein C (PC) deficiency is prevalent in severe sepsis, studies showing that more than 80% of patients with severe sepsis have a baseline PC level below the lower limit of normal [1,2]. The aim of the study was to relate the anticoagulation activity evaluated by PC, with clinical parameters and 28-day mortality.

Methods A cohort study of 150 patients >18 years with severe sepsis according to the Surviving Sepsis Campaign, in an ICU of a university hospital. Demographic, clinical parameters and coagulation markers during the first 24 hours were studied. PC activity was analysed using a haemostasis laboratory analyser (BCS* XP; Siemens). Descriptive and
comparative statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results We analyzed 150 consecutive episodes of severe sepsis (16%) or septic shock (8%) admitted to the ICU. The median age was 64 years old (interquartile range, 48.7 to 71); male: 60%. The beginning of severe sepsis took place in the emergency area in 46% of cases. The main sources of infection were respiratory tract 38% and intra-abdomen 45%; 70.7% had medical pathology. The 28-day mortality was 22.7%. The profile of death patients were men (64.7%, n = 22), with significantly higher average age (63 vs. 57 years; P = 0.049), as well as clinical severity scores, APACHE II (29.8 vs. 24.1; P < 0.001) and SOFA (12.1 vs. 8.9; P < 0.001) and major dysfunction organs (4.6 vs. 3.6; P < 0.001); we observed significantly major consumption of PC (55.2 vs. 7.6, P = 0.001), that improves by combining with PC, AUC 0.83 (95% CI: 0.73 to 0.88, sensitivity: 73.5%; specificity: 76.7%; f = 0.001), that improves by combining with PC, AUC 0.83 (95% CI: 0.75 to 0.90, sensitivity: 77%; specificity: 83%; f = 0.001).

Conclusion This cohort study showed an improvement in the survival in septic patients under a lower consumption of PC. Low levels of PC are associated with more severity in Sepsis, dysfunction organ and poor outcome.

References

P25
Role of mannose-binding lectin on pneumococcal infections
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Introduction The role of mannose-binding lectin (MBL) deficiency (MBL2 AX/AO + O/O genotypes) in host defenses remains controversial. MBL is a pattern recognition molecule that initiates the innate immune response. In healthy individuals, MBL is cleared by the liver, and the serum levels are determined by MBL2 and SPs genes.

Methods We studied 348 patients with pneumococcal community-acquired pneumonia (P-CP) and 1,591 controls. A meta-analysis of MBL genotypes in susceptibility to P-CP and to invasive pneumococcal disease (IPD) was also performed. The extent of LD of MBL2 with SFTP1A, SFTP2A and SFTP3 was analyzed.

Results MBL2 genotypes did not associate with either P-CP or bacteremic P-CP in the case–control study. The MBL-deficient O/O genotype was significantly associated with higher risk of IPD in a meta-analysis, whereas the other MBL-deficient genotype (XA/O) showed a trend towards a protective role. We evidenced the existence of LD between MBL2 and SPs genes.

Conclusion The data do not support a role of MBL deficiency on susceptibility to P-CP or to IPD. LD among MBL2 and SPs genes must be considered in studies on the role of MBL in infectious diseases.

P26
Role of serum biomarkers in the diagnosis of infection in patients undergoing extracorporeal membrane oxygenation
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Introduction Although rates and causal organisms of infections occurring in patients on extracorporeal membrane oxygenation (ECMO) have already been described [1], diagnosis of infection itself is challenging in clinical practice. In addition, a significant heterogeneity in infection surveillance practice patterns among ELSO centers has recently been reported [2]. The aim of the study was to analyze the role of C-reactive protein (CRP) and procalcitonin (PCT) in the diagnosis of bacterial and fungal infection in critically ill patients requiring ECMO, and to assess the difference between venovenous (VV) and venoarterial (VA) ECMO setting.

Methods A case–control study on 27 patients. We analyzed serum values of PCT and CRP according to the presence of infection.

Results Forty-eight percent of patients had infection. Gram-negative bacteria were the predominant pathogens (54%), and Candida was the most frequent isolated microorganism overall (15%). PCT had an AUC of 0.681 (P = 0.0062), for the diagnosis of infection in patients on VA ECMO, but failed to discriminate infection in the VV ECMO group (P = 0.14). The AUC of CRP was 0.707 (P ≤ 0.001) in all ECMO patients. In patients receiving VA ECMO, PCT had good accuracy with 1.89 ng/ml as the cut-off (SE = 87.8%, SP = 50%) and CRP as well with 97.70 mg/l as the cut-off (SE = 85.3%, SP = 41.6%). PCT and CRP tests in parallel had SE = 87.2%, and SP = 25.9%. Four variables were identified as statistically significant predictors of infection: PCT and CRP tests in parallel (OR = 1.184; P = 0.0008), age (OR = 0.980; P ≤ 0.001), presence of infection before ECMO implantation (OR = 1.782; P ≤ 0.001), and the duration of ECMO support (OR = 1.056; P ≤ 0.001).

Conclusion Both traditional and emerging inflammatory biomarkers can help in the diagnosis of infection in patients receiving ECMO. Indeed, we demonstrated for the first time that PCT is a reliable infection marker in patients undergoing VA ECMO. We suggest routine