Pathomechanism and therapeutic possibilities of microcirculatory and mitochondrial dysfunction in sepsis (2015-2020)

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Sepsis is defined as a potentially life-threatening condition caused by a dysregulated host response to an infection – according to the newest definition (Singer 2016). It propagates to septic shock with persisting hypotension-requiring vasopressors to maintain blood pressure despite adequate volume resuscitation. The mortality of severe sepsis is still very high which necessitates additional investigations to map novel routes in order to achieve more efficient therapeutic results. According to current knowledge, the key problem in sepsis is oxygen extraction deficit which can originate either from an insufficient oxygen delivery to the cells, or the inability of the cells to utilize oxygen. On one side, the poorly functioning microvasculature results in insufficient oxygen delivery to the tissue, hence the persisting microcirculatory dysfunction becomes one of the major factors leading to the organ failure. On the other side, mitochondria are unable to use oxygen efficiently, and the switch to anaerobic pathways causes energy deficit and eventual cell death. These processes are interlinked and the host–pathogen interactions finally leading to combined microcirculatory and mitochondrial distress syndrome. In our research plane, we hypothesize that a successful therapy should target the microcirculatory, endothelial and mitochondrial components of the inflammatory process/activation simultaneously - to ameliorate the outcome of sepsis.
With this theoretical background, the major goal of our study was to find optimal, clinically applicable manoeuvres for microcirculatory recruitment and mitochondrial resuscitation to minimize the energy deficit of vital organs during the septic response.

As an initial step of our research program, we summarised the pathophysiological background of the oxygen extraction deficit as the key problem in sepsis according to our current knowledge in a review article. Moreover, this paper gives an overview of the therapeutic possibilities of the protection of glycocalyx layer and the microcirculatory - mitochondrial resuscitation maneuvers (2).

In the first half of our research program, we made significant efforts to develop appropriate, clinically compatible animal models to achieve our goals for sepsis therapy. Animal models should have significant impact on clinical sepsis management. Although different animal models do not completely mimic human septic conditions and rodent reactions are markedly differing from the human with respect to the immune response, or susceptibility to inflammatory insults, we agree with the researchers who say that rodent research is an essential step of translation of results from the laboratory to the bedside.

1. Development of clinically compatible animal models for sepsis research

1.1. Characterisation of nonocclusive mesenteric ischemia (NOMI) induced sepsis in rodent

In this line, we have developed an antigen-independent nonocclusive mesenteric ischemia (NOMI) induced hyperdynamic sepsis model on rodent (with a duration of 36 hours) in our research project. In this reliable *in vivo* in rat model of NOMI we investigate the major components of local and systemic circulatory reactions in a clinically relevant time frame. A long run septic process was induced by partial aortic occlusion (PAO)-caused transient mesenteric hypoperfusion. The mean arterial pressure of the splanchnic area was kept on 40 mmHg by 60 minutes of PAO in anesthetized male rats. At 24 hours after PAO hyperdynamic circulation and elevated plasma levels of inflammatory biomarkers (HMGB-1, ET-1, TNF-alfa) were observed in re-anesthetized animal, while the intestinal intramural microcirculation was significantly impaired compared to control group (3, 4).

1.2. Development of fecal peritonitis induced polymicrobial rodent and porcine models according to new definitions

Two major events have defined the direction of sepsis research over the last four years: the Third International Consensus Conference for Sepsis and Septic Shock Definitions (Sepsis-3 in 2016) and a development of consensus-based guideline for strengthen the translational value of pre-clinical sepsis modelling (Osuchowski 2017). The previous event determined the clinical criteria of human sepsis and highlighted the importance of organ failure evaluation based on the sequential organ failure assessment (SOFA) scoring systems in human patients. The latter one, published as the Minimum Quality Threshold in Preclinical Sepsis Studies (MQTiPSS) criteria clearly outline an evidence-based scheme for the design of rodent experiments and propos the elaboration of a species-specific scoring system for evaluation of the sepsis induced organ dysfunctions. Therefore, in our research program we followed the suggestions of new guidelines to development fecal peritonitis induced polymicrobial rodent and porcine models according to the new definitions. For both of our models, we placed great emphasis on monitoring the progression of sepsis by determining the extent of organ failures by using of a species-specific scoring system and the microbiological characterization of triggering polymicrobial infection.

1.2.1 Characterisation of a porcine model of fecal peritonitis induced sepsis

During our research program, we significantly improved our previous sepsis model on pig. Currently we described a 24 hrs long porcine model of polymicrobial, intraabdominal sepsis with clinically relevant hemodynamic responses, laboratory profile, inflammatory biomarkers and bacteraemia, with mixt advantages of the conscious and anesthetized models. The host responses were quantified by modified human SOFA-like basic and complete porcine specific SOFA (ps-SOFA) scoring systems. The basic ps-SOFA scoring is suitable for evaluation of the cardiovascular, pulmonary and renal dysfunctions online without laboratory testing, while complete ps-SOFA score (with the assessment of coagulation and hepatic dysfunction parameters) provides an alternative endpoint instead of mortality and improves reproducibility. Processes of sepsis and septic shock can be distinguished with using of both ps-SOFA scoring system. Sepsis severity showed strong correlation with that of germ count in the induction inoculum and blood culture and organ failure determined with ps-SOFA scores. This large animal model of sepsis is suitable for clinically relevant investigation of new therapeutic strategies and it could contributes to the standardization of preclinical studies and reducing the gap between preclinical and clinical outcomes (24).

1.2.2 Characterisation of a rodent model of fecal peritonitis induced sepsis

We characterized a relatively long (24-72 hrs) polymicrobial fecal peritonitis rat models, in which the septic insult could be accurately standardized with pre-defined amounts of intra-abdominal fecal inoculum. Invasive monitoring was started after 12, 24, 48 and 72 hours to calculate the components of rat organ failure assessment (ROFA) scoring system, based on the measurements of PaO_2/FiO_2 ratio, mean arterial pressure, urea, AST/ALT ratio and lactate levels. Blood and tissue samples were taken to characterize the immune response and mitochondrial oxygen consumption as the function of time. Transmission of pathogen microorganisms was traced with mapping the variability of the inducer inoculum, ascitic fluid and blood culture. Sepsis was evidenced by multiorgan dysfunction that peaked after 24 hours, but the symptoms were relieved after 48 hr, which was also reflected in inflammatory parameters and mitochondrial function. Our experimental model showed 20% mortality, which was highly associated with monoculture content of E.coli in the inducer inoculum. Significant correlation was found between the dose of the inducer inoculum and ROFA scores, but it was limited to 24 hrs of progression, due to species-specific compensation mechanisms starting after

48 hours. We conclude that microbiological profile plays a significant role in the outcome of sepsis, which limits the model adequacy to 24-hour progression in the rat. Monitoring the temporal translocation of infection may clarify the randomness of symptoms in experimental sepsis (20, 22, 23).

2. Targeting the oxygen supply-dependent component in sepsis

2.1. Mapping of inflammation induced microcirculatory dysfunction in different organs.

First, a review article summarized the key methods and findings focusing on the microcirculatory reactions in different clinically relevant experimental models (6). In addition, we have performed *in vivo* experiments that are tangentially linked to our project, to study microcirculatory dysfunctions induced by different inflammatory processes in different organs as urinary bladder, hind limb and mandibular periosteum (7, 8, 15).

2.2. Modulation of the effects of sepsis biomarkers in association with microcirculatory disturbances

2.2.1. Examination the relationship between inflammatory plasma biomarkers changes and oxygen supply in fecal peritonitis-induced sepsis in pigs

In our pig model, we investigated the potential association between the changes of VO_2-DO_2 (oxygen consumption - oxygen delivery) ratio, the peripheral microcirculatory alterations, and the early predictive changes of systemic inflammatory mediators [(TNF-α, IL-10, big endothelin, and high mobility group box protein1 (HMGB1)] to the late onset of organ damage characterized by the ps-SOFA score. Fecal peritonitis resulted in SOFA score-independent sublingual microcirculatory failure. Early detection of plasma TNF-α, HMGB1 and big endothelin monitors appropriately the onset of organ dysfunction leading to late severe damage, and therefore these markers are of potential predictive importance in experimental sepsis (5, 18, 24)

2.2.2. Role of the oxidative and nitrosative stress components to inflammation induced microcirculatory dysfunction in different segments of the gastrointestinal tract.

We studied the relationship between microcirculatory dysfunctions and nitrosative stress under an antigen-independent inflammatory process in the gastrointestinal tract. We have found evidence for region specific differences in the intestinal microperfusion and the tissue xanthine oxidoreductase (XOR) activities in response to a standard mesenteric artery occlusion. XOR can catalyse the reduction of nitrite to NO under hypoxic conditions in a pH-, nitrite-, and oxygen-dependent manner. Segment-specific differences in XOR activation governed the onset of nitrosative stress in transiently ischemic or hypoxic tissues. With segment-specific microcirculatory alterations, the risk of evoke of nitrosative stress is highest in transiently hypoxic tissues with high endogenous XOR activities. In this scenario, the risk of nitrosative stress is highest in the duodenum and lowest in the large intestine (11).
In addition, we investigated the role of neuronal NO synthase (nNOS) in ischemic preconditioning (IPC)-induced protection after mesenteric ischemia-reperfusion (IR). Neuronal NOS is a dominant isoform of NOS in the gastrointestinal tract. Our study is the first to show that neuronal NOS plays a pivotal role in a more rapid microcirculatory recovery and in IPC-linked tissue protection by inhibiting an IR-related acute inflammatory response (16).

2.3. Examination of the early elimination of the inflammatory mediators in septic shock patients

We have investigated the effect of extracorporeal cytokine removal (CytoSorb®) treatment on organ dysfunction and cytokine storm within the first 48 hours of human septic patients in a prospective randomized clinical study. Patients fulfilling septic shock criteria were randomized

into Control (n=10) and CytoSorb groups (n=10), in the latter CytoSorb treatment was applied for 24 h in the early stage of septic shock. Overall SOFA scores did not differ between the groups, but in the CytoSorb-group norepinephrine requirements, procalcitonin (PCT) and Big ET-1 concentration decreased significantly compared to control group. Moreover, plasma levels of IL-1a, IL-1ra, IL-8 and IL-10 showed a decreasing tendency at 48 hr within the CytoSorb group. To our best knowledge, this is the first study, in which extracorporeal cytokine adsorption treatment was tested on its own, and not combined with other extracorporeal renal replacement therapies in a controlled trial. According to our results, CytoSorb therapy proved to be safe, and we found that one single treatment already showed some benefits within the first 48 hours of septic shock without any therapy-related adverse events (13).

2.4. Pharmacological modulation of sepsis biomarker levels and associated oxygen supply - targeting the microcirculatory resuscitation

It has been published that antisense homology box-derived peptides can represent a novel pharmacological tool to design highly specific biologically active peptides to eliminate or inactivate mediators with deleterious effects (Baranyi 1995, 1998). In our research program, we tested the effects of two of these types of peptides (complement C5a and ET-1 antagonists) on septic process-induced oxygen supply deficiency, microcirculatory dysfunction, and inflammatory mediator levels.

2.4.1. "Microcirculatory resuscitation" using complement C5a antagonist compound

Since circumstantial evidence suggests that complement activation plays important role in sepsis, we set out to investigate the long-term effects of treatment with a complement C5a antagonist in a rat model of NOMI induced hyperdynamic sepsis. C5a inhibitor acetyl-peptide-A (AcPepA) or vehicle administration was initiated at the 45th minute of partial aortic occlusion (PAO). The AcPepA treatment not only reduced the elevated leukocyte infiltration and plasma levels of inflammatory mediators as HMGB1 or endothelin-1, but also significantly improved the intestinal microcirculation. C5a inhibition is of promise for use in NOMI associated septic situations (3, 4).

Besides rat model, we have investigated the effects of the specific complement C5a antagonist compound AcPepA on microcirculatory changes and inflammatory activation in a clinically relevant long-term porcine model of abdominal sepsis. Oxygen dynamics of septic animals were characterized with elevated DO_2 and VO_2, but low oxygen extraction ratio, while the sublingual microcirculation was deteriorated, as compared with the baseline. The AcPepA post-treatment (at 20^{th} hr of sepsis) increased significantly the DO_2 and VO_2 values, and the VO_2-DO_2 ratio and the perfusion rate of sublingual microcirculation increased as well. Our data shows that the inhibition of complement cascade components has beneficial effects on the oxygen extraction and microcirculation in experimental sepsis. The C5a antagonist treatment could be a novel therapeutic opportunity to ameliorate the hypoxic consequences of septic inflammation (manuscript in preparation).

2.4.2. "Microcirculatory resuscitation" using agonist and/or antagonist component of the endothelin (ET) system

The hypoxia-sensitive ET release has an important role on the development of tissue hypoxia in sepsis. ET peptides have explicit vasoconstrictor effects through the ET_A and the ET-B_2 receptors (ET_A-R, ET_B-R, respectively) and vasodilator effect through the ET-$_{B1}$ receptors. We developed a "microcirculatory resuscitation therapy" by specific treatments based on ET_A-R antagonist and ET_B-R agonist. The ET_A-R antagonist treatment decreased significantly the ET-1 plasma level, maintained microcirculation and oxygen dynamics, while the selective ET_B-R agonist treatment countervailed the sepsis-induced hypotension. The combined ET_A-R

antagonist–ET_{B1}-R agonist therapy reduced the plasma ET-1 and Il-6 levels, and significantly improved the intestinal microcirculation. Our results suggest that if microcirculatory failure occurs, the specific inactivation of vasoconstrictor ET_A-Rs can amplify the vasomodulator effects of circulating ET-1 through the ET_B-Rs, leading to a potentially beneficial outcome at the subcellular level. On the other hand, direct activation of ET_B-Rs can improve the capillary perfusion rate due to its local vasodilator effect or possibly through the increased microcirculatory driving pressure gradient as well (19).

2.4.3. "Microcirculatory resuscitation" using kynurenic acid, an endogenous inhibitor of N-methyl-D-aspartate receptors

Another, potential route of modulation of inflammatory mediator release and oxygen supply in sepsis is the kynurenic acid (KYNA), a metabolite of the tryptophan–L-kynurenine pathway. KYNA has a high affinity for the glycine co-agonist site on N-methyl-D-aspartate receptors (NMDA-R), binds to orphan G protein-coupled receptor GPR35 and aryl hydrocarbon receptor. Increased expression and activation of NMDA-R has been observed in sepsis, leading to complex intracellular damage, oxidative-nitrosative stress, and microcirculatory disorder. Therefore, we investigated the modulator effects of KYNA and its synthetic analogue SZR-72 on microcirculatory disturbances and the levels of inflammatory mediators (ET-1, IL-6, nitrotyrosine levels and XOR activity) in our rat sepsis model. Both NMDA-R antagonist treatments significantly reduced the severity of oxidative-nitrosative stress. The microcirculatory parameters of ileac serosa microcirculation (perfusion rate, perfusion heterogeneity, determined by intravital videomicroscopy imaging) were normalized by KYNA treatment, but not following SZR-72 administration. The differences observed between the effects of KYNA and SZR-72 treatments are presumably due to differences in molecular structure and receptor connections (22).

2.5. Therapeutic possibilities for preservation and regeneration of the endothelial glycocalyx integrity - impact of fluid resuscitation in sepsis.

2.5.1. Investigation of the reliability of hemodynamic parameters to monitor the efficacy of fluid resuscitation

As optimal fluid therapy is an essential element of organ supportive care in sepsis, we compare stroke volume (SVI) to cardiac index (CI) guided volume resuscitation in a bleeding-resuscitation experiment on pigs. Our results indicate that CI-based goal-directed resuscitation may result in residual hypovolaemia, without restoring adequate SVI. As the SVI-guided approach normalized most hemodynamic variables, we recommend using SVI instead of CI as the primary goal of resuscitation (1).

Despite of the increasing doubts, several guidelines recommend to maintain the mean arterial pressure (MAP) >65 mmHg as the most frequent indication of fluid therapy. In a pig study we investigate the effects of a MAP-guided management in a bleeding-resuscitation animal experiment. Animals were bled till the initial stroke volume index dropped by 50% (t0). Fluid replacement was performed in 4 equivalent steps (t1-4) with balanced crystalloid solution to reach the baseline values of MAP. In the current experiment bleeding led to haemorrhagic shock, while MAP remained higher than 65 mmHg. Furthermore, MAP was unable to indicate the normalization of stroke volume index and cardiac index that resulted in unnecessary fluid administration. Our data give further evidence that MAP may be an inappropriate parameter to follow during fluid resuscitation (12).

2.5.2. In vivo examination of the endothelial glycocalyx layer (EGL)

Shedding of the glycocalyx layer (GX) critically impairs the integrity of capillaries, causing plasma leakage and endothelial activation, which may contribute to the development of vascular

pathologies and sepsis-induced multi-organ dysfunction. The assessment of GX or its degradation products requires different approaches in experimental and clinical settings. Therefore, we developed a reproducible approach to detect GX thickness changes using intravital microscopy with specific image analysis. This off-line analysis included the elimination of the motion artefacts by interlinking the images, definition of the boundary area of the EGL using intensity curves and area-based measurement of EGL. In this setup, tracer exclusion technique was employed with higher and lower molecular-weight fluorescence dyes (FITC 2000: fluorescein isothiocyanate-dextran 2000 kDa and TR 70: Texas-red-dextran 70 kDa, respectively). Control and endotoxin-treated mice were compared and the data were validated with standard measures of GX degradation (syndecan-1 concentrations in the plasma). A marked reduction in GX size was observed in LPS-treated animals as compared to the controls, which changes were paralleled by significant increases in plasma syndecan-1 concentrations. Our results demonstrate that the degree and kinetics of GX damage can accurately be given, and suggest that the effectiveness of salvage therapies may be numerically expressed under experimental circumstances (21).

2.5.3. The impact of fluid resuscitation on glycocalyx integrity in vivo

Adequate fluid resuscitation is the cornerstone of maintaining and correcting oxygen delivery. However, the volume-replacement ratio may be affected by the degradation of the EGL, as was found often in the critically ill patients. We have examined the EGL degradation and the volume-replacement ratio of different resuscitation fluids (crystalloids and colloids) as the function of time in moderate bleeding-resuscitation porcine model. EGL degradation was determined by measurement of the plasma levels of its degradation markers as syndecan-1 and glypican using sandwich ELISA technique. Our results showed that the volume-replacement ratio for crystalloid and colloid followed the Starling's principle since the glycocalyx remained intact (10).

2.5.4. The impact of goal-directed crystalloid vs. colloid fluid therapy on microcirculation during free flap surgery

Adequate fluid resuscitation is the cornerstone of maintaining and correcting oxygen delivery. In our human study, we compare the effects of crystalloids and colloids on the microcirculation during free flap surgery when management was guided by detailed haemodynamic assessment. Hypovolaemia was treated with Ringerfundin or HES fluid boluses, respectively. The microcirculatory effects were assessed by laser-Doppler flowmetry (PeriFlux 5000 LDPM), with the probe placed on the flap and on a control area. Our results showed that when fluid management was applied by detailed haemodynamic assessment, more crystalloid than colloid was needed to maintain haemodynamic stability, but there was no difference between the effects of crystalloids and colloids on the microcirculation (14).

3. Targeting the oxygen utilisation-dependent component of the septic process

3.1. Examination of mitochondrial respiratory function and ROS production

Mitochondrial-derived reactive oxygen species have been deemed an important contributor in sepsis pathogenesis. In international cooperation, we investigated whether two mitochondria-targeted antioxidants (SkQ1 and MitoTEMPO) improved long-term outcome, lessened inflammation, and improved organ homeostasis in polymicrobial murine sepsis. Surprisingly, none of the tested antioxidants demonstrated any benefits, while SkQ1 markedly increased CLP mortality. Our study can be also considered as cautionary; it suggests that in certain severe inflammatory states, scavenging of the mitochondrial-derived reactive oxygen species can be therapeutically inefficient and/or deleterious (9).

3.2. Development of a new method for the detection of extramitochondrial calcium movement with high-resolution fluorespirometry

Mitochondria are main controller units of calcium (Ca^{2+}) homeostasis of the eukaryotic cell. Various channels, transmembrane proteins and receptors have been identified in the regulation of mitochondrial Ca^{2+} influx, efflux and storage, and the net result of these processes fundamentally influences the activity of intracellular regulatory systems. In low micromolar concentration range (~0.1–10 μM) Ca^{2+} fine-tunes oxidative phosphorylation and ATP synthesis, and the electron transport system can be either stimulated or depressed. Higher concentrations (~50 μM) however, lead to the opening of the mitochondrial permeability transition pore (mPTP), with non-selective Ca^{2+} efflux, collapse of mitochondrial membrane potential and apoptosis-mediated cell death. Despite the importance of the process, there is no laboratory test method for the simultaneous, dynamic determination of Ca^{2+} and oxygen movements. Therefore, our aim was to design a method, where the respiratory chain activity and mPTP opening can be detected together with extramitochondrial Ca^{2+} concentrations. Using high-resolution fluorespirometry, we also tested whether mitochondrial mPTP inhibition or anoxia affects the mitochondrial Ca^{2+} flux. Ca^{2+} movement evoked by $CaCl_2$ or anoxia was assessed with CaGreen-5N dye using blue-fluorescence-sensor in isolated liver mitochondria, liver homogenates and duodenal biopsies. Exogenous Ca^{2+} resulted in an abrupt elevation in CaGreen-5N fluorescence followed by a decrease (Ca^{2+} uptake) with simultaneous elevation in O_2 consumption in liver preparations. This was followed by a rapid increase in the fluorescence signal, reaching a higher intensity (Ca^{2+} efflux) than that of the exogenous Ca^{2+}-induced elevation. After pre-incubation with cyclosporin A, a marked delay in Ca^{2+} movement was observed, not only in isolated liver mitochondria, but also in tissue homogenates. In all samples, the transition to anoxia resulted in immediate increase in the level of extramitochondrial Ca^{2+}. Our results demonstrate that the CaGreen-5N method is suitable to monitor simultaneous O_2 and Ca^{2+} fluxes, and the opening of mPTP in various biological samples. In this system, the duration of stimulated Ca^{2+} fluxes may provide a novel parameter to evaluate the efficacy of mPTP blocker compounds (17). Hopefully, our method may also give a tool for the examination of mitochondrial Ca^{2+} disturbances resulting from sepsis induced tissue hypoxemia.

3.3. "Mitochondrial resuscitation" with combined ET_B-R agonist-ET_A-R antagonist therapy in rat sepsis

We developed a "mitochondrial resuscitation therapy" by a combined ET_A-R antagonist and ET_B-R agonist treatments, which increased oxygen consumption and oxygen extraction, and resulted in a significant increase in complex II-linked oxidative phosphorylation and respiratory control ratio in septic rats. The microcirculatory and mitochondrial functions are closely linked under physiological circumstances, since the capillary-mitochondrial oxygen gradient may be a decisive factor in mitochondrial function in sepsis. Therefore, ET receptors could indirectly influence mitochondrial function through the mechanism of tissue perfusion and restoration of the intracellular oxygen supply. Our study is the first, which highlight that additive effects of a combined ET_A-R–ET_{B1}-R-targeted therapy may offer a tool for a novel microcirculatory and mitochondrial resuscitation strategy in experimental sepsis (19).

3.4. Mitochondrial "resuscitation" using the endogenous NMDA-R antagonist kynurenic acid and its synthetic analogue

It has been evidenced the presence of the N-methyl-D-aspartate receptor (NMDA-R) on the mitochondrial membrane of the nervous system and heart. Moreover, NMDA-R-mediated increase in intracellular calcium (Ca^{2+}) level is major regulator of mitochondrial Ca^{2+} uptake and Ca^{2+} overload. Therefore, we investigated the effects of the endogenous NMDA receptor antagonist KYNA and its synthetic analogue SZR-72 on the mitochondrial respiratory function,

mitochondrial membrane potential (ΔΨmt) and mitochondrial Ca^{2+} flux in a rodent model of peritonitis-induced sepsis. Treatment with KYNA or SZR-72 (160 μmol/kg, i.p., in both treated groups) was performed 16 and 22 hrs after sepsis induction. Mitochondrial respiratory function linked to complex I- and complex II-driven oxidative phosphorylation was assessed from liver homogenates using high-resolution respirometry. Safranin T and Calcium Green-5N fluorescent dyes using Fluorescence Sensor Blue connected to oxygraph monitored mitochondrial membrane potential and mitochondrial Ca^{2+} influx /efflux. We have observed divergent effects of KYNA and SZR-72 on mitochondrial respiration. Administration of SZR-72 may directly affects directly electron transport system and ATP synthesis through the regulation of calcium-influx/efflux. Increased calcium storage capacity can be associated with the inhibition of mitochondrial permeability transition pore and delayed ΔΨmt depolarization that can ultimately contribute to the preservation of mitochondrial function in sepsis (22).

Publications 2015-2021 - K116689

1. Táncos K, Németh M, Trásy D, László I, Palágyi P, Szabó Z, Varga G, Kaszaki J: Goal-directed resuscitation aiming cardiac index masks residual hypovolemia: an animal experiment. BioMed Research International, Volume 2015, Article ID 160979; **IF 2.134 Q2**;
2. Kaszaki J, László I, Juhász L. Szabó A: Sepsis - from the microcirculation to the mitochondial function. Aneszteziológia és Intenzív Terápia 47(1):15-21, 2016. (in Hungarian) **IF 0;**
3. Érces D, Nógrády M, Varga G, Szűcs S, Mészáros AT, Fischer-Szatmári T, Chun Cao, Okada N, Okada H, Boros M, Kaszaki J: Complement C5a inhibition improves late hemodynamic and inflammatory changes in a rat model of nonocclusive mesenteric ischemia. Surgery 159:960-971, 2016. **IF 3.904 Q1**
4. Nógrády M, Varga G, Szűcs S, Kaszaki J, Boros M, Érces D: Komplement C5a-antagonista-terápia hatása nem okklúzív mesenterialis ischaemia állatmodelljeiben. Effects of complement C5a inhibitor therapy in animal models of non-occlusive mesenteric ischemia. Magyar Sebészet 2017; 70(3) 221–231. DOI: 10.1556/1046.70.2017.3. **IF 0**
5. Srour R, Halcsik R, Juhász L, Poles MZ, Érces D, Boros M, Kaszaki J: Prognostic importance of plasma biomarkers in experimental sepsis. J Crit Care 40: 325. (2017). http://dx.doi.org/10.1016/j.jcrc.2017.07.007
6. Szabó A, Janovszky Á, Pócs L, Boros M: The periosteal microcirculation in health and disease: An update on clinical significance. Microvascular Research (2017) 110: 5–13. **IF: 2.465 Q2;**
7. Járomi P, Garab D, Hartmann P, Bodnár D, Nyíri S, Sántha P, Boros M, Jancsó G, Szabó A: Capsaicin-induced rapid neutrophil leukocyte activation in the rat urinary bladder microcirculatory bed. Neurourology and Urodynamics 2017; 1–9. **IF 2.927 Q1**
8. Pócs L, Janovszky Á, Garab D, Terhes G, Ocsovszki I, Kaszak J, Boros M, Piffkó J, Szabó A: Estrogen-dependent efficacy of limb ischemic preconditioning in female rats. J Orthopaedic Research 2017. DOI 10.1002/jor.23621. **IF 1.695 Q1**
9. Rademann P, Weidinger A, Drechsler S, Mészáros A, Zipperle J, Jafarmadar M, Dumitrescu S, Hacobian A, Ungelenk L, Röstel F, Kaszaki J, Szabó A, Skulachev VP, Bauer M, Bahrami S, Weis S, Kozlov AV, Osuchowski MF: Mitochondria-targeted antioxidants SkQ1 and mitoTEMPO failed to exert a long-term beneficial effect in murine polymicrobial

sepsis. Oxidative Medicine and Cellular Longevity Volume 2017, Article ID 6412682; **IF 4.836 Q1**; https://doi.org/10.1155/2017/6412682.

10. László I, Demeter G, Öveges N, Érces D, Kaszaki J, Tánczos K, Molnár Z: Volume-replacement ratio for crystalloids and colloids during bleeding and resuscitation: an animal experiment. Intensive Care Medicine Experimental (2017) 5:52; DOI 10.1186/s40635-017-0165-y. **IF: 0**
11. Poles M.Z, Bódi N, Bagyánszk, M, Fekete É, Mészáros A.T, Varga G, Szűcs S, Nászai A, Kiss L, Kozlov A.V, Boros M, Kaszaki J. Reduction of nitrosative stress by methane: Neuroprotection through xanthine oxidoreductase inhibition in a rat model of mesenteric ischemia-reperfusion. Free Radical Biology and Medicine 2018. 120: 160-169. **IF: 5.657 Q1**
12. Öveges N, László I, Tánczos K, Németh M, Lebák G, Tudor-Drobjewski B-A, Érces D, Kaszaki J, Rudas L, Huber W, Molnár Z: Mean arterial pressure targeted fluid resuscitation may lead to fluid overload: A bleeding-resuscitation animal experiment. PLOS ONE 2018.| https://doi.org/10.1371/journal.pone.0196188. **IF: 2.776 Q1**
13. Hawchar F, László I, Öveges N, Trásy D, Ondrik Z, Molnar Z: Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study. Journal of Critical Care 2019. 49:172-178. doi: 10.1016/j.jcrc.2018.11.003 **IF: 2.83 Q1**
14. László I, Janovszky Á, Lovas A, Vargan V, Öveges N, Tánczos T, Mikor A, Trásy D, Loderer Z, Piffko J, Szabo A, Molnar Z: Effects of goal-directed crystalloid vs. colloid fluid therapy on microcirculation during free flap surgery. A prospective randomised clinical trial. Eur J Anaesthesiol 2019; 36:1–14. **IF: 3.902 Q1**
15. Pócs L, Janovszky Á, Ocsovszki I, Kaszaki J, Piffkó J, Szabó A: Microcirculatory consequences of limb ischemia/reperfusion in ovariectomized rats treated with zoledronic acid. Journal of Orthopaedic Surgery and Research 2019. 14:95 https://doi.org/10.1186/s13018-019-1117-x **IF:1.907 Q2**
16. Varga S, Juhász L, Gál P, Bogáts G, Boros M, Palásthy Z, Szabo A, Kaszaki J: Neuronal nitric oxide mediates the anti-inflammatory effects of intestinal ischemic preconditioning. Journal of Surgical Research 2019. 244:241-250. **IF: 1.872 Q1**
17. Nászai A, Terhes E, Kaszaki J, Boros M, Juhász L: $Ca^{(2+)}$N It Be Measured? Detection of Extramitochondrial Calcium Movement with High Rresolution FluoRespirometry. Scientific Reports 2019. 17;9(1):19229. doi: 10.1038/s41598-019-55618-5. **IF 4.12 Q1;**
18. Kaszaki J, Rutai A, Fejes R, Tallósy S.P, Poles M.Z, Érces D, Boros M, Szabó A: Investigation of the relationship between organ damage, microcirculatory dysfunction and reactive oxygen intermedier formation in experimental sepsis. Critical Care 2019. 23 (Suppl 2): p4.
19. Rutai A, Fejes R, Juhász L, Tallósy SZP, Poles MZ, Földesi I, Mészáros A, Szabó A, Boros M, Kaszaki J: Endothelin A and B receptors: potential targets for microcirculatory-mitochondrial therapy in experimental sepsis. Shock 2020. 54:87-95; doi: 10.1097/SHK.0000000000001414 **IF: 2.54 Q1**
20. Tallósy SP, Rutai A, Juhász L, Poles MZ, Burián K, Érces D, Szabó A, Boros M, Kaszaki J: Translational value of the microbial profile in experimental sepsis studies. Critical Care 2020. 24(Suppl 1): p187.

21. László I, Csákány L, Veres A, Németh M, Poles M, Kaszaki J, Molnár Z, Szabó A: Az endotheliális glycocalyx megjelenítése és vastagságának meghatározása intravitalis mikroszkópiával. Aneszteziológia és Intenzív Terápia, 2020 (accepted for publication) **IF 0;**
22. Juhász L, Rutai A, Fejes R, Tallósy SZP, Poles MZ, Szabó A, Szatmári I, Fülöp F, Vécsei L, Boros M, Kaszaki J: Divergent effects of the N-methyl D-aspartate receptor antagonist kynurenic acid and the synthetic analogue SZR-72 on microcirculatory and mitochondrial dysfunction in experimental sepsis. Frontiers in Medicine - Intensive Care Medicine and Anesthesiology; 2020. Vol 7; Article 566582; doi: 10.3389/fmed.2020.566582; **IF: 3.421; Q1**;
23. Tallósy S.P, Poles M.Z, Rutai A, Fejes R, Juhász L, Burián K, Sóki J, Szabó A, Boros M, Kaszaki J: The initial microbiology predicts the outcome of fecal peritonitis in the rat. 2021. Shock (under review).
24. Rutai A, Zsikai B, Bizánc L, Nagy E, Tallósy S.P, Érces D, Poles M, Juhász L, Földesi I, Burián K, Szabó A, Boros M, Kaszaki J: Prediction of severity with selected biomarkers in a clinically-relevant pig model of sepsis. 2021. Shock (under submission).