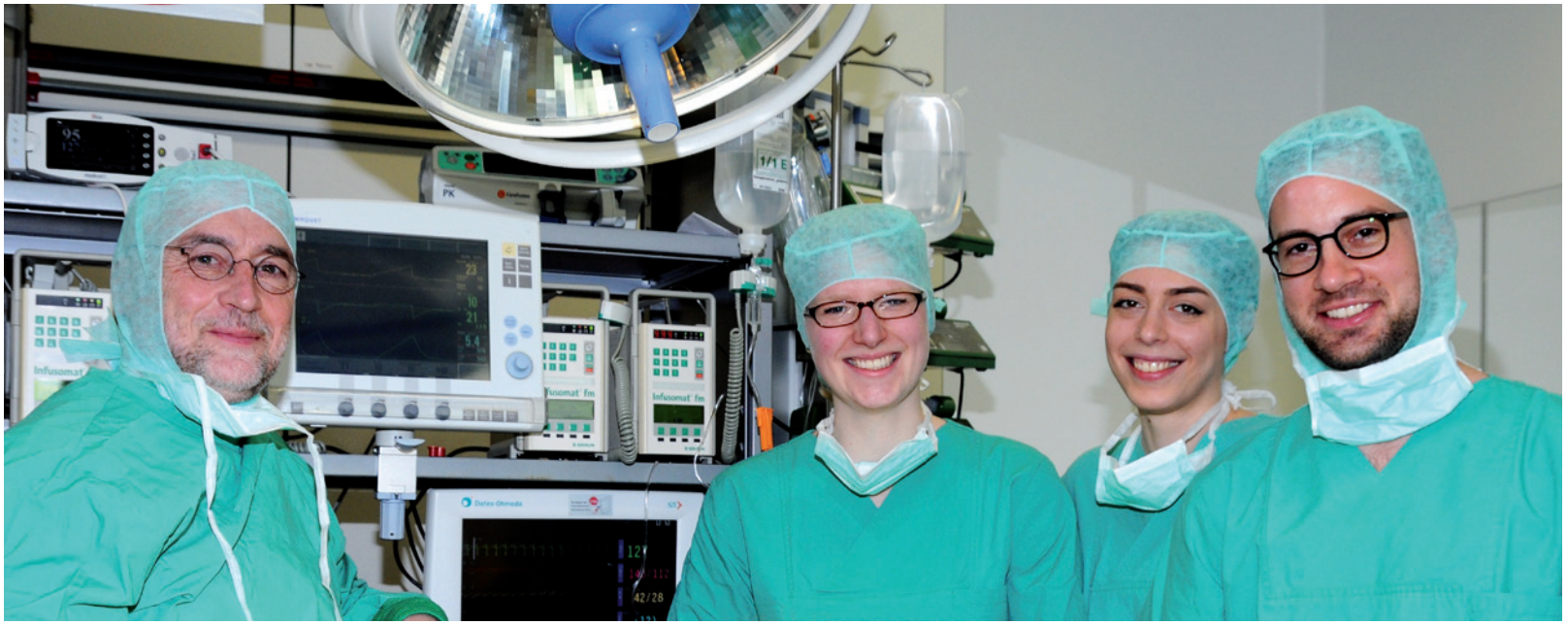

Department of Anesthesiology

Effects of the PPAR-β/δ Agonist GW0742 During Resuscitated Porcine Septic Shock

Head: Michael Georgieff

The scientific focus of the department is the development of new strategies to prevent multiple organ failure after circulatory shock resulting from trauma and hemorrhage, sepsis or ischemia/reperfusion-injury. Particular attention is paid to the clinical relevance of the protocol design, i.e. the integration of standard intensive care measures (e.g. mechanical ventilation, invasive hemodynamic monitoring, circulatory support etc.) into experimental setup in order to mimic the clinical scenario as far as possible. Innovative interventions studied target the systemic inflammatory response, the interplay of oxidative and nitrosative stress as well as antioxidant defense mechanisms, the cellular energy metabolism and the activity of the mitochondrial respiratory chain.

The Team:
Head of Department: M. Georgieff
Professors: P. Radermacher, M. Schneider
Group Leaders/Postdocs: E. Calzia, K. Föhr, J. Vogt, M. Weiss
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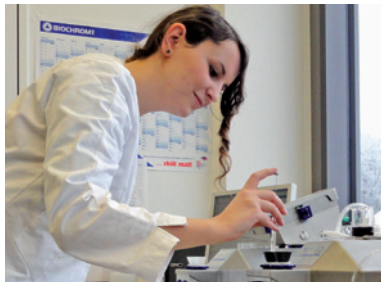
Study Programme Experimental Medicine Students: M. Reize, S. Riedesser
Additional Members of Thesis Advisory Committees: E. Calzia (Ulm), M. Huber-Lang (Ulm)

In unresuscitated rodent models of septic shock activation of the peroxisome proliferator activator, receptor-β/δ (PPAR-β/δ) improved visceral organ function. All the existing data, however, originate from rodent models, which did not integrate standard therapy aimed at maintaining adequate systemic hemodynamics. In addition, all these experiments were performed in young and healthy animals, which is in sharp contrast to the clinical scenario of patients with pre-existing co-morbidities such as atherosclerosis and/or chronic obstructive pulmonary disease. Therefore, our group focuses on the clinical potential of the newly PPAR-β/δ agonist GW0742 in a porcine model of long-term, fully resuscitated, fecal peritonitis-induced septic shock. In order to mimic the clinical scenario we use animals with familial hypercholesterinemia, which, due to a special diet, develop the typical symptoms of a "metabolic syndrome" that causes ubiquitous vascular atherosclerosis and ultimately results in chronic renal dysfunction and histopathological alterations of the kidney tissue. The present data suggest that in contrast to the existing literature, the therapeutic efficacy of exogenous PPAR-β/δ agonists is nearly completely blunted under conditions of pre-existing kidney disease, most likely due to the markedly reduced tissue PPAR-β/δ-receptor expression associated with the increased oxidative stress and reduced endogenous nitric oxide production which is typical for this disease.

Student analyzing an immune histochemistry staining of the kidney for the PPAR-β/δ-receptor expression.



Student performing the measurement of the mitochondrial activity of kidney parenchyma cells using "high resolution respirometry."

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Selected Publications:

- *Bracht H, Scheuerle A, Gröger M, Hauser B, Matallo J, McCook O, Seifritz A, Wachter U, Vogt JA, Asfar P, Matejovic M, Möller P, Calzia E, Szabó C, Stahl W, Hoppe K, Stahl B, Lampl L, Georgieff M, Wagner F, Radermacher P, Simon F (2012): Effects of intravenous sulfide during resuscitated porcine hemorrhagic shock. Crit Care Med. 40:2157-67.*
- *Gröger M, Matallo J, McCook O, Wagner F, Wachter U, Bastian O, Gierer S, Reich V, Stahl B, Huber-Lang M, Szabó C, Georgieff M, Radermacher P, Calzia E, Wagner K (2012): Temperature and cell-type dependency of sulfide-effects on mitochondrial respiration. Shock. 38:367-74.*
- *Simon F, Scheuerle A, Gröger M, Stahl B, Wachter U, Vogt J, Speit G, Hauser B, Möller P, Calzia E, Szabó C, Schelzig H, Georgieff M, Radermacher P, Wagner F (2011): Effects of intravenous sulfide during porcine aortic occlusion-induced kidney ischemia/reperfusion injury. Shock. 35:156-63.*
- *Wagner F, Wagner K, Weber S, Stahl B, Knöferl MW, Huber-Lang M, Seitz DH, Asfar P, Calzia E, Senftleben U, Gebhard F, Georgieff M, Radermacher P, Hysa V (2011): Inflammatory effects of hypothermia and inhaled H2S during resuscitated, hyperdynamic murine septic shock. Shock. 35:396-402.*
- *Simon F, Scheuerle A, Gröger M, Vcelar B, Möller P, Georgieff M, Calzia E, Radermacher P, Schelzig H (2011): Comparison of carbamylated erythropoietin-FC fusion protein and recombinant human erythropoietin during porcine aortic balloon occlusion-induced spinal cord ischemia/reperfusion injury. Intensive Care Med. 37:1525-33.*
- *Wagner F, Scheuerle A, Weber S, Stahl B, McCook O, Knöferl MW, Huber-Lang M, Thomas J, Asfar P, Szabó C, Möller P, Gebhard F, Georgieff M, Calzia E, Radermacher P, Wagner K (2011): Cardiopulmonary, histological and inflammatory effects of intravenous H2S after blunt chest trauma-induced lung contusion in mice. J Trauma. 71:1659-67.*