



## Department of Anesthesiology

### Carbamylated Erythropoietin-FC Fusion Protein During Porcine Aortic Balloon Occlusion-induced Kidney Ischemia/Reperfusion Injury

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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 (I/R). 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 defence mechanisms, the cellular energy metabolism and the activity of the mitochondrial respiratory chain.

Aortic cross-clamping during surgery for abdominal aortic aneurysm repair is a typical clinical example of I/R injury, the most vulnerable organs being the kidneys. Recombinant human erythropoietin (rhEPO) was demonstrated to protect against I/R injury but has several undesired side effects that are attributed to the activation of a homodimeric receptor complex (EPO-R/EPO-R). The organ-protective properties are referred to the activation of an alternative receptor complex consisting of the EPO-R and the common  $\beta$  receptor, and the stimulation of this EPO-R/ $\beta$ cR alone is devoid of the undesired side effects. Carbamylated Epo derivatives (cEPO) only bind to the EPO-R/ $\beta$ cR and thus may be an alternative to rhEPO. 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 kidney dysfunction. Therefore, our group focuses on the clinical potential of a newly developed carbamylated EPO-FC fusion protein in a porcine model of thoracic aortic balloon occlusion-induced I/R injury. In order to mimic the clinical scenario we use animals with familial hypercholesterinemia that, due to a special diet, develop the typical symptoms of a “metabolic syndrome” that causes ubiquitous vascular sclerosis and ultimately results in chronic renal dysfunction and histopathological alterations of the



Student analyzing an immune histochemistry staining of the kidney for the neutrophil gelatinase-associated lipocalin.

kidney tissue. The present data suggest that in contrast to the existing literature, the therapeutic efficacy of even high doses of cEPO derivatives is much less pronounced under conditions of pre-existing kidney disease and is most likely due to the minor effect on tissue inflammation and apoptosis.

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#### Selected Publications:

- 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.
- Baumgart K, Wagner F, Gröger M, Weber S, Barth E, Vot JA, Wachter U, Huber-Lang M, Knöferl MW, Albuszies G, Georgieff M, Asfar P, Szabó C, Calzia E, Radermacher P, Simkova S (2010) Cardiac and metabolic effects of hypothermia and inhaled H<sub>2</sub>S in anesthetized and ventilated mice, *Crit Care Med* 38, 588-95.
- Gröger M, Öter S, Simkova V, Bolten M, Koch A, Warninghoff V, Georgieff M, Muth CM, Speit G, Radermacher P (2009) DNA damage after long-term repetitive hyperbaric oxygen exposure, *J Appl Physiol* 106, 311-5.
- Simon F, Giudici R, Scheuerle A, Gröger M, Asfar P, Vogt JA, Wachter U, Ploner F, Georgieff M, Möller P, Laporte R, Radermacher P, Calzia E, Hauser B (2009) Comparison of cardiac, hepatic and renal effects of arginine vasopressin and noradrenaline during porcine fecal peritonitis: a randomized, controlled trial, *Crit Care* 13, R113.
- Barth E, Bassi G, Maybauer DM, Simon F, Gröger M, Öter S, Speit G, Nguyen CD, Hasel C, Möller P, Wachter U, Vogt JA, Matejovic M, Radermacher P, Calzia E (2008) Effects of ventilation with 100% oxygen during early hyperdynamic porcine fecal peritonitis, *Crit Care Med* 36, 495-503.