Therapeutic strategies for the protection of renal oxygenation in experimental models of acute kidney injury
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Citation for published version (APA):
“The art of medicine consists in amusing the patient while nature cures the disease.”

Voltaire

THESIS OUTLINE
The research presented in this thesis has been conducted at the Department of Translational Physiology of the Academic Medical Center of the University of Amsterdam. The main aim of this department is to ‘translate’ clinical scenarios into (patho)physiological concepts (and vice versa) and to develop therapeutic strategies based on insights obtained in the clinic and in the lab.

As discussed in the General Introduction, the concept of microcirculation and its essential role in both health and disease became evident in the last decennia. In this view, new treatment modalities are being developed which are aiming to prevent and/or treat impairments of microcirculatory oxygenation. The main emphasis of our lab research is particularly on the renal microcirculation and function. The kidney is highly sensitive to hypoxia and acute renal failure occurs frequently following compromised cardiovascular conditions in the critically ill. Acute renal failure has been shown to worsen clinical outcome in patients with shock. We focus on several clinically-relevant models of renal ischemia/reperfusion injury, hemorrhagic shock, and endotoxemic shock. In this thesis, which covers a wide range of pathophysiological models and therapeutic strategies, we have investigated the effects of blood transfusion, fluid resuscitation, and adjuvant drug therapies to protect the kidney from hypoxia and injury.

The first step in this thesis, Chapter 1, was to gain more detailed insights into why blood transfusions using aged cells are not effective in restoring microcirculatory oxygenation as has been shown in earlier studies by our group. Therefore we investigated whether prolonged storage of RBCs would lead to alterations in nitrite reductase activity, hence in altered hypoxia-induced nitric oxide (NO) and methemoglobin formation. Subsequently, in Chapter 2, we tested whether fluid therapy could be used in order to resuscitate microcirculatory oxygenation. More specifically, we aimed to investigate the acute effects of acetate-balanced colloid and crystalloid resuscitation on renal oxygenation in a rat model of hemorrhagic shock. We hypothesized that acetate-balanced solutions would be superior in correcting impaired renal perfusion and oxygenation after severe hemorrhage compared to unbalanced solutions. In Chapter 3, we realized that in more complex scenarios, such as in sepsis, adjuvant therapies in addition to fluid resuscitation could be used and we decided to test the only clinically available drug which was approved for sepsis: recombinant human activated protein C (APC). We aimed to test whether continuous APC administration would be able to protect renal oxygenation and function during endotoxemia. In order to understand the pathophysiology of AKI better, in Chapter 4 we aimed to investigate whether a somewhat simpler model for induction of AKI, i.e., renal ischemia/reperfusion (I/R), leads to inducible NO synthase (iNOS)-dependent changes in renal oxygenation and we tested the potential benefit of iNOS inhibitors as a potential
renoprotective strategy. The underlying rationale behind this is that renal oxygenation depends on a balance between oxygen supply and consumption, with the nitric oxide (NO) as a major regulator of microvascular oxygen supply and oxygen consumption. And finally, in Chapter 5, we aimed to test another potential renoprotective agent in the context of renal I/R injury: the organic vanadium salt bis maltolato oxovanadium (BMOV). We tested its effects on renal oxygenation and renal function in the acute phase of reperfusion.