Functional heterogeneity of oxygen supply with blood and hemoglobin-based oxygen carriers in porcine models of hemorrhagic shock
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**OUTLINE OF THE THESIS**

In this thesis, we investigated the heterogeneity of regional oxygenation between and within the gut and heart during hemorrhagic shock and resuscitation with autologous blood and with HBOCs. We used cross-linked (DCLHb) and a polymerized HBOC (polyHbX), believed to differ in vasoactivity. Quantitatively measured microvascular oxygen ($\mu$PO$_2$) was measured by the Pd-porphyrin phosphorescence technique, using a multi-fiber system. Furthermore, the behavior of $\mu$PO$_2$ was compared with other global and regional hemodynamic and oxygenation parameters. Hemorrhage was achieved by a controlled withdrawal of a fixed volume of circulating blood, and this model was created in anesthetized pigs.

The aim of Chapter 1 was to investigate the relationship between microvascular and venous oxygen pressures in the pig intestine during hemorrhagic shock and resuscitation. Microvascular pO$_2$ ($\mu$PO$_2$) was measured using the Pd-porphyrin phosphorescence quenching technique. In addition, mesenteric venous blood gasses, blood flow, ilial CO$_2$ production and global hemodynamics were measured. The pigs were subjected to controlled moderate (25 ml/kg blood withdrawal) or severe (40 ml/kg blood withdrawal) hemorrhagic shock and resuscitation was performed with either a crystalloid solution or with the withdrawn blood.

In Chapter 2, we reviewed the regional heterogeneity of the oxygen supply-consumption ratio within the heart. We describe the results obtained using direct, non-invasive indicators of the balance between oxygen supply and consumption, including NADH videofluorimetry (mitochondrial energy state) and microvascular PO$_2$ measurement by the Pd-porphyrin phosphorescence technique.

In Chapter 3, we investigated macro- and microcirculatory parameters, not only in the gut but also in the heart, during hemorrhage and resuscitation with the withdrawn blood. We hypothesized that the microcirculation in the gut would follow the macrocirculation in the acute phase of hemorrhagic shock and isovolemic autologous whole blood resuscitation but that the microcirculation in the heart would be preserved, even under conditions of macrocirculatory depression. The pigs were subjected to controlled hemorrhagic shock (30 ml/kg blood withdrawal) and to isovolemic resuscitation with autologous blood. Quantitative measurement of microvascular oxygen pressure ($\mu$PO$_2$) was performed by simultaneous phosphorimetry on the gut and heart.

As an alternative to allogeneic blood, hemoglobin-based oxygen carriers (HBOCs) have been developed. In Chapter 4, we review the mechanisms of oxygen delivery
by these HBOCs, the modifications to the hemoglobin molecules made to reduce the adverse effects associated with HBOCs, and their effects on vascular autoregulation and on blood rheology. In addition, we describe the effects of HBOCs at the microcirculatory level in several organs.

In Chapter 5, we investigated in pigs the efficacy of resuscitation with polyHbXL (a polymerized cross-linked hemoglobin solution), which is believed to have limited vasoactivity. We investigated whether vasoconstriction changes regional tissue perfusion and oxygenation and affects cardiac function. The pigs were anesthetized and subjected to controlled hemorrhagic shock (25 ml/kg blood withdrawal), followed by isovolemic resuscitation with either autologous blood or polyHbXL. Systemic hemodynamics and systemic and cardiac oxygenation parameters were determined, and in addition, catecholamines, high cardiac energy phosphates, and regional blood flow were measured, the latter with radioactive microspheres.

In Chapter 6, we investigated the influence of a very low dose of DCLHb (a di-aspirin cross-linked hemoglobin solution), believed to have marked vasoactivity, on gut microvascular oxygen pressure ($\mu$PO$_2$) in hemorrhaged pigs. The values of gut $\mu$PO$_2$ were studied in correlation with regional intestinal parameters, as well as with global metabolic and circulatory parameters. Controlled hemorrhagic shock (40 ml/kg blood withdrawal) was followed by resuscitation with either a low dose (5 ml/kg) of DCLHb or a combination of lactated Ringer’s solution and modified gelatin.

Finally, in Chapter 7, the hypothesis was tested that resuscitation with HBOCs affects the oxygenation of the microcirculation differently between and within organs. To this end, we tested the influence of increasing doses of DCLHb on the microcirculatory oxygenation of the heart and gut serosa and mucosa in a porcine model of hemorrhage. The pigs were subjected to controlled hemorrhage (30 ml/kg blood withdrawal), which was followed by resuscitation with 10, 20, or 30 ml/kg of DCL-Hb or by isovolemic resuscitation with 6% hydroxyethyl starch solution (HAES). The measurements included systemic and regional hemodynamic and oxygenation parameters. The microvascular oxygen pressures ($\mu$PO$_2$) of the epicardium and of the serosa and mucosa of the ileum were measured simultaneously using the palladium-porphyrin phosphorescence technique.