English summary

In this thesis we aimed to investigate the mechanisms underlying impaired microcirculatory perfusion during cardiac surgery with use of cardiopulmonary bypass. Additionally, we evaluated two treatment strategies in order to protect the microcirculation from harmful stimuli induced by cardiopulmonary bypass: a pulsatile flow modality during cardiopulmonary bypass and the reduction of vascular leakage through a reduction of endothelial permeability.

Chapter 1 provides an introduction on cardiac surgery and describes postoperative morbidity related to the use of cardiopulmonary bypass. Moreover, the microcirculation and its relevance for the perioperative physician are described.

Chapter 2 provides a review of the alterations that occur in the microcirculation during cardiac surgery with or without the use of cardiopulmonary bypass. Microcirculatory monitoring techniques available for the clinician are described. Furthermore, factors that may contribute to disturbances of microcirculatory perfusion during cardiac surgery, including hemodilution, mild hypothermia, use of cardiopulmonary bypass and nonpulsatile flow are discussed.

In chapter 3, we have assessed the perfusion characteristics of the sublingual microcirculation during off-pump cardiac surgery and on-pump cardiac surgery using Sidestream Darkfield (SDF) imaging. Microvascular perfusion was well maintained during and after off-pump surgery, whereas patients undergoing on-pump surgery showed a 20% decrease in the density of perfused capillaries after onset of cardiopulmonary bypass. No recovery of microcirculatory perfusion was observed at intensive care unit admission in the on-pump group, despite normalization of temperature and hematocrit. Interestingly, we found no correlation between microcirculatory and macrocirculatory parameters. We concluded that off-pump surgery was associated with preserved microcirculatory perfusion, whereas on-pump surgery led to a reduction in capillary perfusion which did not recover in the early postoperative phase.

In chapter 4, we compared the use of pulsatile flow with conventional, nonpulsatile flow during cardiopulmonary bypass in patients undergoing on-pump cardiac surgery in a single-blinded randomized trial. It has been demonstrated that pulsatile flow may have a protective effect on the endothelium as compared to nonpulsatile flow and we therefore hypothesized that pulsatile flow during cardiopulmonary bypass preserves capillary perfusion during cardiac surgery. The effects on capillary perfusion were studied using SDF imaging of the sublingual mucosa at multiple time points during surgery and at intensive care unit admission. Pulsatile flow did not prevent the initial decrease of capillary perfusion during cardiopulmonary bypass.
However, recovery of microvascular perfusion after disconnection from cardiopulmonary bypass was improved in the pulsatile flow group when compared to patients exposed to nonpulsatile flow. No difference in plasma inflammatory parameters was observed. Systemic oxygen consumption and oxygen extraction ratio improved during cardiopulmonary bypass only in the group undergoing pulsatile flow, which may indicate a reduction in microvascular shunting. The positive effect of pulsatile flow on capillary perfusion after cardiopulmonary bypass most likely depends on an endothelial cell-mediated effect instead of a direct effect of the pulse, given the delayed recovery of the microcirculation postoperatively.

In chapter 5, the blood flow characteristics in the sublingual microcirculation during on-pump and off-pump cardiac surgery were assessed. We investigated the hypothesis that acute physiological alterations during extracorporeal circulation lead to systemic shunting in the microcirculation. Our data showed that cardiopulmonary bypass is associated with increased microvascular perfusion heterogeneity, and this phenomenon persists postoperatively. Moreover, one-third of the capillaries revealed extremely high red blood cell velocities, incompatible with normal oxygen offloading. In parallel, the arteriovenous oxygen content difference and systemic oxygen consumption decreased, indicating the presence of shunting of blood in the systemic microcirculation during and after cardiopulmonary bypass. We observed no increased microcirculatory heterogeneity or microvascular shunting during off-pump surgery. From these findings we conclude that systemic microvascular shunting is present in patients undergoing cardiac surgery with cardiopulmonary bypass and this is associated with reduced systemic oxygen extraction, while this phenomenon is not present during off-pump surgery.

In chapter 6, we investigated whether cardiopulmonary bypass is associated with loss of endothelial barrier function in an in vitro endothelial cell culture that was exposed to plasma from patients undergoing pulsatile or nonpulsatile cardiopulmonary bypass. Transendothelial resistance was assessed using electric cell-substrate impedance sensing in order to quantify permeability of the endothelial cell monolayer. Plasma sampled after cardiopulmonary bypass led to an increase in endothelial permeability as compared to plasma from baseline. This was paralleled by an increase in endothelial cell activation markers after cardiopulmonary bypass. Hemodilution did not have an effect on endothelial permeability, nor did the use of pulsatile flow as compared to nonpulsatile flow. The current investigation demonstrates that components in patient plasma following on-pump cardiac surgery induce an increased loss of endothelial barrier function in an in vitro model. This effect may be related to the increase in inflammatory and endothelial activation markers.
Chapter 7 describes the relationship between the endothelial glycocalyx and microcirculatory perfusion during cardiac surgery. In patients undergoing off-pump cardiac surgery or on-pump cardiac surgery with pulsatile or nonpulsatile flow, we have investigated endothelial glycocalyx dimensions using a sublingual imaging technique assessing glycocalyx dimensions. In both groups undergoing on-pump cardiac surgery, glycocalyx dimensions decreased after onset of cardiopulmonary bypass, whereas a recovery after disconnection from cardiopulmonary bypass was only observed following pulsatile CPB. Off-pump surgery was not associated with reduced glycocalyx dimensions. Moreover, we found a correlation between glycocalyx dimensions and perfused vessel density in the microcirculation, suggesting that reduced endothelial glycocalyx dimensions are associated with impaired capillary perfusion in patients undergoing cardiac surgery.

In chapter 8, a rat model of cardiopulmonary bypass with a preparation of the cremaster muscle for investigation of microcirculatory perfusion is described. The role of hemodilution in the development of microcirculatory alteration during cardiopulmonary bypass was investigated. Rats underwent either cardiopulmonary bypass, acute hemodilution to a similar hematocrit or a sham procedure. Microcirculatory perfusion remained unaltered in rats undergoing a sham procedure. Onset of cardiopulmonary bypass led to a 40% reduction in perfused capillaries, which showed only a small recovery one hour after disconnection from cardiopulmonary bypass. Acute hemodilution alone led to a minor and temporary decrease in microvascular perfusion. Cardiopulmonary bypass induced increased inflammatory and endothelial activation as compared to hemodilution. Additionally, renal injury as assessed histologically was increased following cardiopulmonary bypass. We concluded that hemodilution cannot fully explain impaired microcirculatory perfusion induced by cardiopulmonary bypass, and may be only a minor and temporary contributor.

In chapter 9, we hypothesized that vascular leakage during cardiopulmonary bypass is a major contributor to disturbed capillary perfusion, and that reduction of vascular leakage preserves microvascular perfusion. Before cardiopulmonary bypass, rats were randomized into treatment with imatinib, known for its protecting effects on the endothelial barrier in septic conditions, or placebo. Cremaster muscle microcirculatory perfusion showed a significant decrease following onset of cardiopulmonary bypass following placebo treatment, whereas imatinib led to preservation of microvascular perfusion. In parallel, vascular leakage decreased in multiple organs under imatinib treatment, and was paralleled by reduced fluid requirements during and after cardiopulmonary bypass. Moreover, markers of renal and pulmonary injury were lower in rats treated by imatinib as compared to placebo. The current results suggest that vascular leakage serves as an important contributor to impaired microvascular perfusion during cardiopulmonary bypass, and that reduction of endothelial
barrier dysfunction improves microcirculatory perfusion and organ injury markers and reduces fluid resuscitation requirements.

In chapter 10 the main results of the current thesis are discussed, as well as the methodological considerations for the studies performed and possible future directions for further research. We proposed a two-hit model for the development of acute microcirculatory perfusion disturbances and impaired tissue oxygenation during cardiac surgery with cardiopulmonary bypass. The inflammatory response generated by the exposure of blood to the extracorporeal circuit leads to endothelial activation and vascular leakage resulting in a reduced number of perfused capillaries. Concomitant hemodilution then further impairs tissue oxygenation through reduced oxygen delivery. We concluded that microcirculatory dysfunction during cardiac surgery with cardiopulmonary bypass is mainly to be attributed to increased vascular leakage due to inflammatory endothelial barrier dysfunction. Both pulsatile flow during cardiopulmonary bypass and imatinib treatment are promising interventions for improvement of microcirculatory perfusion and reduction of acute postoperative organ dysfunction in cardiac surgery with cardiopulmonary bypass.