The microcirculatory response during cardiac surgery
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General discussion
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An optimal match between cellular oxygen demand and oxygen delivery in microvascular exchange vessels by preservation of microcirculatory perfusion and oxygenation is essential for normal organ function. During cardiac surgery, microcirculatory function is however affected by the hemodynamic and metabolic changes associated with extracorporeal circulation or cardiac positioning. Under normal physiological circumstances, alterations in microvascular perfusion and oxygenation can easily be corrected, for instance by volume loading, vasoactive substances or red blood cell transfusion. However, in case of severe derangement of systemic hemodynamics, microcirculatory function may be deteriorated, thereby contributing to abnormal organ function and patient outcome.

Proof of the thesis
The aim of this thesis was to identify the responses of the microcirculation to extracorporeal circulation and cardiac displacement during cardiac surgery. Integrative monitoring using sublingual visualization of the microcirculation by Sidestream Dark Field (SDF) imaging, combined with reflectance spectrophotometry analysis of sublingual hemoglobin oxygen saturation, enabled us to identify the behavior of the microcirculation during acute hemodynamic and metabolic changes.

We showed that acute, macrocirculatory alterations are reflected by specific microcirculatory responses. These responses were however different between on-pump and off-pump cardiac surgery. We have identified functional shunting of oxygen in on-pump patients as a consequence of convective limitations in the microcirculation in relation to cardiopulmonary bypass. In off-pump patients functional shunting was a result of diffusional limitations in relation to cardiac positioning maneuvers. A correction of the oxygen carrying capacity and hematocrit of blood by red blood cell transfusion improved microcirculatory perfusion and oxygenation.

Long-term effects of deterioration of microcirculatory function
The present thesis shows that different modalities of cardiac surgery are associated with distinct microcirculatory changes. However, these changes are reversible and could be corrected by simple interventions. The studies presented in this thesis only focused on acute, perioperative changes in microcirculatory perfusion and oxygenation, while microcirculatory responses to surgery may be continued in the early postoperative period. Whether these microcirculatory responses may have affected organ function and patient outcome cannot be
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answered with the present findings, especially since our studies only included low-risk patients undergoing coronary artery bypass graft surgery.

In addition to the perioperative setting, sublingual microcirculatory perfusion and oxygenation has frequently been studies in patients with sepsis. In 2002, Ince et al. suggested that the microcirculation should be considered as the canary of the septic syndrome, as it reflects the state of disease in patients.\textsuperscript{1} De Backer et al. showed that sepsis is associated with a reduction in microcirculatory perfusion, which is not improved by a correction of overall system hemodynamics.\textsuperscript{2} More interestingly, they showed that the severity of microcirculatory depression is closely related to lactate levels, organ failure and patient outcome.\textsuperscript{1,2} From these findings it may be suggested that normal microcirculatory perfusion and oxygenation after cardiac surgery may be indicative for good patient recovery. The lack of studies focusing on long-term benefits of preservation of microcirculatory function during acute changes in system hemodynamics, like cardiac surgery, however warrants further investigation.

\textbf{The coupling of system hemodynamics with microcirculatory perfusion}

Elbers and colleagues visualized the sublingual microcirculation in cardiac surgery using SDF imaging, and concluded a dichotomy between macrocirculatory behavior and microcirculation function.\textsuperscript{3,4} They concluded that optimization of systemic hemodynamics by vasopressor therapy does not necessarily lead to adequate microvessel perfusion and optimal oxygen delivery to the cells, regardless of oxygen availability in the microcirculation.\textsuperscript{3} We recently showed that restoration of pulsatile flow during extracorporeal circulation preserves microcirculatory perfusion during and after cardiac surgery.\textsuperscript{5} In contrast, laminar flow during aortic cross-clamping reduces microcirculatory perfusion, which is not yet restored in the early postoperative period. Interestingly, systemic hemodynamic parameters, including mean arterial pressure and cardiac index, were comparable for pulsatile and laminar flow groups. These findings suggest that, in case of extracorporeal circulation, systemic hemodynamics and microcirculatory perfusion is uncoupled,\textsuperscript{5} which confirms the lack of microcirculatory responses during vasopressor therapy. However, these findings should be evaluated in light of the blood pressure level of our patients. Despite the reduction in blood pressure during pulsatile or laminar flow cardiopulmonary bypass, the mean arterial pressure did not decrease below 60 mmHg. Boerma et al. earlier described the relation between macrocirculatory and microcirculatory alterations, and stated that a correction of blood pressure may not be reflected by microcirculatory perfusion if the mean arterial pressure is above 65 mmHg.\textsuperscript{6} The absent coupling of macrocirculatory and microcirculatory
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hemodynamics in the physiological blood pressure range warrants further establishment of clinical monitoring devices that enable the measurement of microcirculatory function in order to be able to use the alarm function of the microcirculation in disease states to guide therapy.

Microcirculatory shunting as disease feature

Microcirculatory shunting of oxygen in the microcirculation leads eventually to an abnormal cellular respiration due to hypoxia. The relation of high lactate, which is an end product of anaerobic respiration, with microcirculatory disturbances as observed in sepsis, support this notion. In septic patients, disturbed microcirculatory flow occurs more severely in the smallest vessels. The flow in larger microvessels is more or less unaffected, and this provides direct support for the idea that shunting of oxygen in the microcirculation is a prominent feature in sepsis. These results also provide an explanation why changes in systemic hemodynamic variables are a poor reflection of the hemodynamic properties of the microcirculation.

Postoperative complications after surgery, such as a systemic inflammatory response, may be prevented by perioperative preservation of microcirculatory function. In other words, minimizing the initial level of pathophysiological injury, by a reduction of extracorporeal bypass time or optimization of system hemodynamics to support microcirculatory function, may reduce the risk for the microcirculatory and mitochondrial distress syndrome, could improve patient outcome by a lower magnitude of pathophysiologic sequelae and generally lead to a better microcirculatory function during cardiac surgery.

Treatments that may optimize microcirculatory perfusion and oxygenation

Changes in systemic blood pressure above a mean arterial pressure above 65 mmHg seem to be less associated with microcirculatory perfusion deteriorations, probably due to sufficient post arteriolar pressure for capillary entry of red blood cells. Below this systemic blood pressure, this pressure-driven mechanism is inadequate for capillary perfusion, most likely due to the arteriolar vasoconstriction to sustain pressure in larger arteries of vital organs. A wide pharmacologic range of vasoactive agents may be used to regulate perioperative systemic blood pressure, but these substances may not be effective with respect to improvement of microcirculatory perfusion. From this concept, blood pressure therapy should not only target for an adequate macrocirculatory pressure, but also for preservation of microcirculatory flow by keeping the blood pressure preferably at least above 60.
Blood viscosity, associated with low hematocrit values, is a linear function of flow currency as described in Poiseille law. However, the relation between hematocrit (x-axis) and capillary perfusion (y-axis) in experimental studies is described by an S-shaped curve. In a small cohort of Jehovah’s witnesses undergoing on-pump cardiac surgery with higher hematocrit (28-30) we found a larger number of perfused capillaries when compared to patients undergoing conventional on-pump cardiac surgery with hematocrit levels of 20-24 (unpublished data). Moreover, less hemodilution by reducing the volume of the prime solution in the heart-lung machine may further contribute to a decreased risk for red blood cell transfusion and preservation of microcirculatory perfusion and oxygenation. This is currently deployed by the use of mini-bypass system, that lead to a reduction of prime volume and improvement of blood hematocrit and viscosity. The beneficial effects of mini-bypass systems for microcirculatory function remain to be investigated.

Hypothermia during cardiopulmonary bypass is known to preserve myocardial cellular function. However, experimental studies in sheep using a temperature of 34 °C have shown a reduction of ventricular function, oxygen extraction and microvascular flow when compared to normothermic animals. This suggests that maintenance of normothermia during on-pump cardiac surgery may contribute to preservation of microcirculatory function, which is the case in off-pump surgery. Our current findings are inconclusive for therapeutic recommendation with regard to the effects of temperature on microvascular perfusion and oxygenation, since we did not compare the effects of different temperature levels during cardiopulmonary bypass, and further investigation is warranted.

The old twist: on-pump versus off-pump cardiac surgery

Off-pump cardiac surgery is superior to on-pump procedures with respect to secondary endpoints like blood loss and inflammation, but not with regard to graft patency. Although off-pump is an alternative for low-risk coronary bypass surgery, it is still not available for cardiac valve surgery. Our findings show that off-pump is less associated with alterations in microcirculatory perfusion and oxygenation, and only during the period of cardiac displacement. Although the microcirculatory changes associated with cardiac displacement are reversible, our findings suggest that the severe hemodynamic changes associated with luxation of the heart should be avoided or prevented in order to preserve microcirculatory flow. Our findings show that the assumption that off-pump surgery is less associated with microvascular derangements is not true, and off-pump surgery as alternative for on-pump
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surgery should only be considered in patients who are not at high risk for microcirculatory deterioration.

REFERENCES