The microcirculatory response during cardiac surgery
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Summary
In the present dissertation we studied alterations in sublingual microcirculatory perfusion and oxygenation in patients undergoing cardiac surgery with extracorporeal circulation or off-pump coronary artery bypass graft procedures. Microcirculatory perfusion was measured using Sidestream Dark Field (SDF) imaging, whereas local tissue hemoglobin oxygenation was quantified using reflectance spectrophotometry. In one study we combined local, sublingual measurements with regional cerebral hemoglobin oxygenation monitoring using near-infrared spectroscopy (NIRS).

In chapter 1, an introduction to the aim of this study is given, including the study objectives.

Chapter 2 provides an overview of the available literature that focuses on microcirculatory responses during on-pump and off-pump cardiac surgery. A description of the methodology of SDF imaging, reflectance spectrophotometry and NIRS is provided. The most important microcirculatory perfusion and oxygenation parameters are described, including total vessel density, perfused vessel density, microvascular flow index (MFI), space-time diagrams, uHbO₂ and the regional tissue oxygen index (TOI). The review further focuses on distinct effects of hemodynamic and metabolic alterations associated with cardiopulmonary bypass, including hypotension, hemodilution, hypothermia, hyperoxemia, cardiac arrest and laminar flow. In particular, cardiopulmonary bypass is associated with a decrease in hemoglobin concentration and perfused capillary density, whereas the hemoglobin oxygen saturation and red blood cell velocity increase during extracorporeal circulation. In contrast, cardiac displacement during off-pump cardiac surgery reduced hemoglobin oxygen saturation and red blood cell velocity, while the hemoglobin concentration and perfused capillary density increase. The review further emphasizes that integrative monitoring of microcirculatory perfusion and oxygenation, which plays a central role in this thesis, may provide novel insight in microcirculatory function during cardiac surgery.

Chapter 3 is the response to the publication of Maier et al.¹ that emphasizes the importance of systematic quantification of microcirculatory responses based on the recommendations of the Delphi round table conference in order to be able to generalize research findings in the field of microvascular research.² The conclusion of this response is that a failure to adhere to these recommendations may lead to a biased representation of the microcirculation and should therefore be avoided.

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In chapter 4 we describe the effects of a high dose of nitroglycerin on system hemodynamics and sublingual microcirculatory perfusion and oxygenation in two patients using SDF imaging and reflectance spectrophotometry. There is increasing evidence that the pressure-driven microcirculation is not sensitive to blood pressure changes within the normal physiological range. However, in case of severe hypotension induced by nitroglycerin, we observed severe changes in microvascular function. Although the nitroglycerin-induced blood pressure decrease was initially associated with an increase in the arteriolar diameter and microcirculatory flow, this response was followed by a reduction in microvessel blood velocity during the hypotensive phase. Our findings suggest that, despite the beneficial afterload-reducing effects of nitroglycerin, derangement of blood pressure control may have detrimental effects on microcirculatory perfusion.

Chapter 5 describes the comparison of the microcirculatory response in patients undergoing on-pump coronary artery bypass graft surgery with cardiopulmonary bypass with patients that underwent off-pump bypass surgery. The microcirculatory response was studied using sublingual SDF imaging and reflectance spectrophotometry. In the on-pump group, microcirculatory measurements were performed before extracorporeal circulation and 10 minutes after the switch to bypass. In the off-pump group, quantification of the microcirculatory response was performed before and during cardiac displacement. The increase in cardiac output after initiation of cardiopulmonary bypass was associated with a decrease in hematocrit and hemoglobin due to hemodilution. During extracorporeal circulation, venular blood velocity was increased, whereas the functional capillary density and sublingual hemoglobin oxygenation were reduced when compared to baseline. In contrast, cardiac displacement reduced cardiac output, which resulted in a cessation of capillary blood flow and a reduction in the capillary blood velocity, whereas sublingual hemoglobin oxygenation was reduced. Our findings showed that on-pump and off-pump cardiac surgery are characterized by different microcirculatory responses. Moreover, although off-pump cardiac surgery is assumed to be less harmful for systemic hemodynamics than on-pump procedures, cardiac displacement during off-pump surgery is associated with significant alterations in microcirculatory perfusion and oxygenation.

In chapter 6 we focused on the effects of cardiac displacement during off-pump coronary artery bypass graft surgery on systemic and microcirculatory hemodynamics and tissue oxygenation. Microcirculatory and regional tissue oxygenation were measured using
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reflectance spectrophotometry and near-infrared spectroscopy, respectively. The reduction in cardiac output during cardiac displacement was paralleled by decrease in sublingual hemoglobin oxygenation, while functional capillary density as measured by sublingual SDF imaging was unaltered. Moreover, red blood cell velocity significantly decreased when compared to baseline. These microcirculatory changes were associated with a reduction in regional cerebral tissue oxygenation during cardiac positioning. All values returned to baseline after repositioning of the heart to its normal position. These data show that cardiac displacement has significant effects on sublingual microcirculatory perfusion and oxygenation and regional cerebral oxygenation, which may be of consequence in patients who are at risk for cerebral ischemia.

Chapter 7 shows that red blood cell transfusion following cardiac surgery improves blood viscosity, but has no effects in systemic oxygen delivery, uptake and extraction when compared to patients receiving gelatin-based solution or non-resuscitated patients. However, red blood cell transfusion increased medium-sized vascular density, red blood cell delivery and microcirculatory hemoglobin oxygenation as measured by sublingual SDF imaging and reflectance spectrophotometry when compared to pre-transfusion values. These effects were not present in patients receiving gelatin solution or controls. Changes in microvascular hemoglobin and oxygen saturation correlated to the alterations in the systemic hemoglobin concentration. These findings showed that red blood cell transfusion after cardiac surgery improves microcirculatory perfusion and oxygenation, independent of changes in system hemodynamics, volemia and oxygenation.

In chapter 8, the main findings in this thesis are discussed. And finally, in chapter 9, a summary and the main conclusions of this thesis are described.

REFERENCES

Summary and conclusions

Main Conclusions

I. The microcirculatory response during cardiac surgery with cardiopulmonary bypass reflects the cumulative effect of distinct hemodynamic and metabolic alterations.

A combination of sublingual microcirculatory perfusion and oxygenation measurements is useful to distinguish microvascular responses during on-pump and off-pump cardiac surgery. Extracorporeal circulation induces a reduction in the hemoglobin concentration and perfused capillary density. Moreover, the sublingual hemoglobin oxygen saturation and red blood cell velocity increase during cardiopulmonary bypass. These microcirculatory responses reflect the cumulative effect of distinct hemodynamic and metabolic alterations, including hypotension, hemodilution, hypothermia and laminar flow.

II. The microcirculatory response during cardiac surgery leads to functional shunting of oxygen via convective limitations in the microvascular network in on-pump procedures and via diffusive limitations in off-pump cardiac surgery.

In on-pump cardiac surgery, functional shunting of oxygen during cardiopulmonary bypass is characterized by a high red blood cell velocity and low oxygen off-loading capacity. The red blood cell is limited in off-loading the oxygen at high speed in the reduced number of perfused capillaries. This is supported by a low hemoglobin concentration and oxygen saturation in the sublingual microcirculation, which illustrates convective failure.

In off-pump cardiac surgery, cardiac displacement is associated with functional shunting of oxygen and characterized by a low red blood cell velocity and unchanged perfused capillary density. This leads to insufficiency of oxygen delivery as a result of hypoperfusion in the microcirculation. A low hemoglobin concentration and oxygen saturation in the sublingual microcirculation illustrates the diffusive failure in off-pump surgery.

III. Microcirculatory perfusion and oxygenation follow distinct, acute systemic hemodynamic alterations during cardiac surgery, and are reversible.

Changes in systemic hemodynamics, like the increase in cardiac output during extracorporeal circulation, or reduction in cardiac output during cardiac displacement in off-pump procedures are followed by distinct microcirculatory responses. There are indications that the
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association of systemic hemodynamics and the microcirculatory response is loose in case of normal, physiological blood pressure ranges. However, in case of severe derangements of the blood pressure, microcirculatory perfusion and oxygenation is impaired.

IV. A reduction in sublingual microcirculatory oxygenation during a drop in cardiac output is associated with a reduction in frontal regional cerebral hemoglobin oxygenation.

Cardiac displacement during off-pump procedures is associated with a sudden decrease of systemic blood pressure and cardiac output, followed by a reduction in sublingual tissue hemoglobin saturation and red blood cell velocity. These local changes in tissue oxygenation are associated with a reduction in regional cerebral hemoglobin oxygenation, suggesting that the sublingual microcirculation and regional cerebral tissue response are similar in their reactivity to a reduction in cardiac output.

V. Blood transfusion compared to gelatin infusion improves some microcirculatory parameters, independently of systemic parameters.

Cardiac surgery with extracorporeal circulation is associated with hemodilution, which reduces the oxygen-carrying capacity of blood due to the relative reduction of red blood cells, and decreases blood viscosity. A lower blood viscosity is associated with a difficulty of red blood cells to enter high resistance vessels. An increase in blood viscosity by a red blood cell transfusion subsequently improves the medium-sized vascular density, red blood cell content and hemoglobin oxygenation in the sublingual microcirculation, whereas the infusion of a gelatin-based solution had no effect on these parameters. In agreement, others showed an improved sublingual microvessel density after red blood cell transfusion. It is however questioned whether the increased presence of red blood cells, or the improvement of blood viscosity are responsible for the beneficial effects on microcirculatory perfusion and oxygenation after red blood cell transfusion.