Summary

Knowledge of the cerebral perfusion pressure (CPP) and its components are important in understanding and treating patients in the perioperative period. Unfortunately, traditional methods of intracranial pressure measurement are invasive and require the placement of an intracranial catheter. The ability to estimate cerebral perfusion pressure less invasively has thus tremendous potential for use in the management of patients with impaired (auto)regulation of cerebral blood flow, head injuries, intracranial hypertension, or ischemia.

The aim of this thesis was to investigate important determinants of the cerebral perfusion pressure regulation and subsequently to provide recommendations on how to keep adequate cerebral perfusion in the perioperative setting.

The **Introduction** chapter explains the purpose of the thesis and describes the current scientific situation and the practical relevance of the research. Commonly, the cerebral perfusion pressure is described as difference between the mean arterial pressure and the intracranial pressure ('classical model' CPP = MAP – ICP). However, this 'classical model' has limitations. As perfusion pressure is reduced, there will be a point where transmural pressure will not be sufficient to counteract the active tension imposed by the smooth muscle layer. Then, the vessel will collapse. At this point blood flow will cease and the corresponding arterial pressure is the critical closing pressure or *zero flow pressure* (ZFP). The *effective cerebral perfusion pressure* (CPPe) is thus better defined by the difference between mean arterial pressure (MAP) and cerebral ZFP ('alternative model' CPPe = MAP – ZFP). The inverse slope of the pressure-flow plot represents vascular bed resistance and is named *resistance area product* (RAP). However, the ZFP of the cerebral circulation could not be measured directly. Transcranial Doppler sonography (TCD) allows non-invasive, continuous measurements of the flow velocity of the middle cerebral artery (Vmca), which represents 80% of global cerebral blood flow. It has been demonstrated that in vivo pressure-flow velocity relationships are linear for many vascular beds, including the cerebral vessels. The zero flow pressure estimated by regression analysis of the pressure - flow velocity plots derived from complete pressure and flow velocity tracings is supposed to be the most precise method, but requires elaborate computations and perfect synchronization of the pressure and flow velocity curves.

Chapter 1 gives an update on intraoperative hypotension, commonly defined as mean arterial pressure below 65 mmHg, on its cerebrovascular, coronary and renal pathophysiology and their clinical implications. Several retrospective studies on very large patient populations suggest a correlation between the occurrence of intraoperative hypotension, and cardiac, renal, cerebral complications as well as postoperative one-year mortality.

Chapter 2 discusses the results of a method comparison study regarding CPPe estimation. The study results demonstrate that it is possible and safe enough to estimate

CPPe, ZFP and RAP with much simpler formula approaches, which were based on the slope-intercept-form.

Carbon dioxide is a strong vasodilator in the cerebral circulation. In **Chapter 3** it could be shown that variation of $PaCO_2$ (within a range of 30-50 mmHg) induced changes in cerebral blood flow and MCA velocity following an exponential function. The hypocapnia-induced reduction in cerebral blood flow and MCA velocity affected both components of the pressure-flow plot: an increase in ZFP and RAP. The increases of effective cerebrovascular resistance and RAP associated with hypocapnia were concordant. Nevertheless, correlation analysis showed only a weak linear relationship.

Hypocapnia induced by hyperventilation and associated alkalosis have a wide range of physiological effects, including increased cerebrovascular resistance, decreased cerebral blood flow and cerebral oxygen delivery. **Chapter 4** discusses the threshold at which this reduction impairs cerebral metabolism. In the present study it could be demonstrated that moderate hyperventilation ($PaCO_2$ 30 mmHg), when compared to moderate hypoventilation, increased net cerebral lactate efflux and markedly reduced cerebral blood flow and partial pressure of oxygen of the jugular-venous bulb, consistent with partial impairment of cerebral metabolism at clinically relevant levels of hypocapnia.

Chapter 5 underlines that there is no evidence to support the therapeutic or prophylactic use of induced hypocapnia. The benefits of preserving normocapnia for the maintenance of cardiac output and tissue oxygenation and perfusion, as well as for the maintenance of CPPe, cerebral blood flow, and cerebrovascular reactivity, are well defined. Despite routine end-tidal carbon dioxide monitoring, periods of inadvertent hyperventilation occur frequently during mechanical ventilation under general anesthesia. This is associated with unfavorable side effects such as cognitive dysfunction and increased length of hospital stay.

Chapter 6 discusses the effects of the volatile anesthetic Halothane on cerebral blood flow and velocity and their components. Halothane (0.8 vol%, 1 MAC) leads to a reduction in CPPe, RAP and effective cerebrovascular resistance, while ZFP, cerebral blood flow and MCA-velocity were rather unchanged. The cerebrovascular CO_2-reactivity remained unchanged. The decrease in cerebrovascular resistance was mainly related to reduction in mean arterial pressure. It seems that halothane as a "peripheral" vasodilatator rather affects the slope of the pressure flow plot than the vasomotor tone.

Argon belongs to the noble gases and has beneficial neuroprotective and organoprotective properties which have been observed in animal experiments, but rarely in human studies. **Chapter 7** discusses the cerebrovascular and cerebrometabolic effects of argon in humans. Ventilation with an gas mixture of 70% Argon and 30% Oxygen showed no clinically relevant changes of the CPPe and its components. The coupling of cerebral flow and metabolism thus seems to be unchanged during argon exposure and our findings indicate a constant cerebral metabolic rate of oxygen and glucose. These

results confirm the safety of argon inhalation, which may be essential for a possible future clinical application of argon as an organoprotective agent.

Pre-eclampsia (hypertension, proteinuria and edema) complicates 3-5% of pregnancies and is a major cause of maternal and fetal morbidity and mortality. **Chapter 8** describes that women with pre-eclampsia had an increased cerebral perfusion due to a reduced ZFP and increased CPPe despite guideline based treatment with antihypertensive medication (methyldopa or methyldopa/ nifedepine). Future studies on blood pressure control in pre-eclampsia should investigate the effect of reducing CPPe on the risk of cerebral complications in pre-eclampsia.

In the **General discussion** the findings of the presented research are reviewed and weighted. Our studies have shown that it is possible and safe to measure CPPe, ZFP and RAP even with simpler formula approaches and less invasive. Furthermore, we were able to show that the monitoring and normalization of the CPPe of our patients has an important role in the perioperative period.

WHO predicts that by 2030, chronic diseases will affect the lives of around 52 million people in the European region. More than 80% of people aged above 65 years, will thus suffer from chronic diseases, especially of the cardiovascular and neurovascular systems. Hence, a lot of our patients in the future will have a disturbed cerebral autoregulation. In the perioperative period any phase of arterial hypotension and subsequently reduced CPPe should be avoided and directly treated. Treatment of intraoperative hypotension should not be done by means of unreflected use of vasoconstrictors. Interventions should be aimed primarily at the underlying causes, which may include vasoplegia, hypovolemia as well as an impairment of cardiac pump function. Any hyperventilation during the perioperative process should be avoided. The threshold of markedly reduced cerebral blood flow and CPPe consistent with partial impairment of cerebral metabolism is already at $PaCO_2$ 30 mmHg (4 kPa). Hyperventilation exaggerates any other vasoconstrictive drug effect.