Introduction and outline of the thesis

F. Grüne
INTRODUCTION AND OUTLINE OF THE THESIS

When thinking of our brain and its perfusion, it is interesting to consider the cerebral perfusion of a giraffe. Although their necks are about 2.5 m long, they must be able to drink water from the ground level of the oasis and then be able to eat leaves from trees, causing large changes in cerebral perfusion pressure. Fortunately, nature has provided them with several cardiovascular, anatomical and physiological adaptations to enable them to do so without fainting (i.e. adapted high blood pressure, myocardial hypertrophy, hypertrophy of arteriole walls, valves in the jugular venous system, etc.).

In humans, adaptations and mechanisms in order to maintain cerebral perfusion are somewhat different when compared to giraffes. This is important in perioperative setting. In most cases our patients are operated in supine position, but we also have to take care of patients in extreme Trendelenburg positions e.g. for laparoscopic prostate surgery and (semi-) sitting positions for shoulder and cerebellar procedures, which may affect cerebral circulation for hours. Furthermore, we have patients with compromised cerebral blood flow regulation due to pathological conditions, and finally, our anesthetics might affect cerebral circulation, too.

Serious neurological damage after general anesthesia due to global or regional cerebral ischemia is a rare complication: although the incidence of overt stroke in the perioperative setting is below 1% in non-cardiac surgery, perioperative strokes do have a very high mortality which exceeds mortality after stroke in the non-operative setting and a devastating effect on patients’ quality and duration of life. In contrast to the 10-15% mortality rate (30 days) associated with strokes in the nonsurgical setting, mortality from perioperative stroke ranges from 26% after general surgery to 87% in patients who have had a previous stroke.

Moreover, brain magnetic resonance imaging studies suggest that 1 in 10 patients aged above 65 years has a (subclinical) covert perioperative stroke. Consequently, there is considerable risk of cerebral hyper- and hypoperfusion during perioperative care.

Cerebral oxygen delivery and consumption rate are 10 times higher than global body values and there are no oxygen stores in the brain like myoglobin, which stores oxygen in the muscle. Consequently, the rate of oxygen delivery from the blood to brain tissue critically depends on adequate cerebral blood flow (CBF), cerebral perfusion pressure (CPP) and cerebral autoregulation (CA) as well as the vessel-to-tissue oxygen partial pressure (PtiO₂) gradient and the efficiency of oxygen transfer from the capillary bed.

Cerebral perfusion in humans is regulated by two important principles: one is the flow-metabolism coupling, an adaptive mechanism to provide more blood to the more active parts of the brain and vice versa. The other one is cerebral autoregulation, keeping CBF stable within a broad range of CPP. Both of these mechanisms have their limitations and both might be altered under anesthesia.
Cerebral autoregulation (CA) is the essential local regulatory mechanism that keeps CBF relatively constant despite large changes in systemic arterial pressure. Even short-term fluctuations in CPP cause adjustments in cerebrovascular resistance via complex neurogenic and myogenic mechanisms to preserve a stable cerebral blood flow. That is the reason why humans can run, dance, watch TV, read a book or sleep with a nearly unchanged CBF. Even a prolonged handstand during a yoga lesson with great changes of our cerebrovascular pressures will cause rapid adaptation by CA. Despite its importance, the physiology and pathophysiology of CA are still not fully understood.

General anesthesia is a non-physiological state for the patient’s brain: Intravenous anesthetics reduce cerebral electrical activity, CBF, cerebral oxygen delivery and consumption by nearly 30%. Global CBF is subsequently reduced from 50 to less than 40 ml/100g/min by general anesthesia. A temporary reduction of mean arterial pressure < 70 mmHg, or even < 60 mmHg following intravenous induction of anesthesia, is unfortunately a common side-effect, particularly in older patients. The resulting low cerebral perfusion pressure (CPP) can exceed the limits of autoregulation and may cause inadequate cerebral perfusion, because compensation by cerebral vasomotor tone is possibly exhausted.

The classic concept defining cerebrovascular tone is cerebral vascular resistance analogue to Darcy’s law:
1) current (I) = voltage difference (dV) / resistance (R)
2) flow = perfusion pressure (dP) / resistance (R),
3) CBF = CPP / CVR, then
4) CVR = CPP / CBF.

It assumes that perfusion pressure and flow are linearly related. When calculating the CPP, the mean arterial pressure (MAP) has been used as effective upstream pressure (EUP) and the intracranial pressure (ICP) as effective downstream pressure (EDP) of the cerebral circulation, because of a Starling resistor phenomenon located at the level of cerebral veins (‘classical model’ CPP = MAP - ICP). When ICP is elevated by i.e. intracranial bleeding or hydrocephalus, CPP will decrease unless reflex arterial hypertension occurs. If MAP increases less than ICP beyond this point, CBF will decrease (see figure 1, modified from Dewey et al. 1974). However, the “classical model” has limitations. Using solely the ICP as effective downstream pressure (EDP) of the cerebral circulation, would neglect vascular tone properties of cerebral vessels.

In vivo pressure-flow relationships are approximately straight lines in many vascular beds such as the cerebral vessels. Thus, the zero flow pressure (ZFP), the pressure when flow ceases, can be extrapolated by linear regression of instantaneously obtained data pairs of pressure and flow (velocity). The ZFP represents the EDP of the cerebral circulation. The inverse slope of the pressure-flow plot represents vascular bed resistance and is named resistance area product (RAP) due to the fact that blood flow is the product
of velocity and vessel cross-sectional area.\textsuperscript{23} 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, Figure 2).\textsuperscript{15,24}

In a former investigation, \textit{Weyland and colleagues} suggested the hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels (CrCP\textsubscript{art}) and a second (distal) at the level of collapsible cerebral veins (CrCP\textsubscript{ven}). The effective downstream pressure of the cerebral circulation may be determined by CrCP\textsubscript{art}, CrCP\textsubscript{ven} (i.e. ICP), or jugular venous pressure, depending on which one is the highest (Figure 3).\textsuperscript{15,24} In the light of this concept, some researcher have created the term “effective cerebral perfusion pressure”, which was suggested to refer to the difference between MAP and ZFP, considering the tone of the vessels.\textsuperscript{15,24-28}

In routine daily practice, anesthetists rely on systolic and mean arterial blood pressure as the main determinants of cerebral perfusion, which might be less sufficient for patients with impaired cerebral blood flow and cerebral perfusion pressure regulation.

\textbf{Figure 1: Relationship between CBF, MAP and ICP (classical CPP model)}

The cerebral perfusion pressure (CPP) is commonly defined as difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP), ‘classical model’ CPP = MAP - ICP. Patients without cerebrovascular disease are expected to have a normal ICP between 7-15 mmHg in supine position. When ICP is elevated and reflex arterial hypertension occurs, CPP and cerebral blood flow (CBF) will be constant. If MAP increases less than ICP beyond this point, CPP and CBF will decrease. The blue bars show intracranial pressure (ICP). Modified from \textit{Dewey et al. 1974}.\textsuperscript{13}
Unfortunately, traditional methods of intracranial pressure measurements are invasive and require the placement of an arterial line and an intracranial or subarachnoid catheter. The ability to estimate CPP less invasively has thus tremendous potential for use in the management of patients with i.e. head injuries, intracranial hypertension, impaired cerebral autoregulation, subarachnoid hemorrhage, and stroke.

Several methods for non-invasive assessment of the effective downstream pressure of the cerebral perfusion have been described by using sensing tympanic membrane displacement, skull vibrations, otoacoustic emissions, magnetic resonance imaging to estimate intracranial compliance, brain tissue resonance, transcranial time of flight, recordings of visual evoked potentials, optic nerve sheath diameter assessment, venous ophthalmodynamometry, and ultrasound-guided eyeball compression. Most these techniques are more appropriate for one-point assessment of instant value of EDP/CrCP/ZFP/ICP and subsequently CPP rather than continuous monitoring.

**Figure 2: Relationship between CBF, MAP and ZFP (CPPe model)**

Cerebral autoregulation maintains cerebral blood flow (CBF) relatively constant across a wide range of cerebral perfusion pressures (CPP). When pressure becomes excessively low, vascular bed resistance can no longer adjust to decreasing perfusion pressures and CBF falls. In contrast, when pressures become too high, cerebral vessels are forced open by the driving pressure and thus resistance decreases, resulting in an increase in CBF. The blue bars show intracranial pressure (ICP). Green bars show vasomotor tone (ZFP) When starting with a mean arterial pressure (MAP) about 90 mmHg and keeping ICP constant at 5 mm Hg, we see that the effective cerebral perfusion pressure (CPPe = MAP - ZFP) remains constant as the MAP decreases to 55 mmHg, because of compensatory decreases in ZFP. Modified from Dewey et al. 1974.
Sometimes we also measure tissue-oxygenation by Near Infrared Spectroscopy (NIRS)\(^\text{40}\) or electrical activity by anesthesia depth monitoring devices\(^\text{41}\), but all those methods provide only a rough estimate of the adequacy cerebral perfusion. A non-invasive monitoring device that can reliably indicate whether cerebral perfusion is adequate or not during general anesthesia, would be a useful addition of the anesthetists’ monitoring armamentarium.

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.\(^\text{42}\) It is a useful technique for day-to-day bedside assessment of critical conditions including vasospasm in subarachnoid hemorrhage, traumatic brain injury, acute ischemic stroke, and brain stem death. Today, cerebral blood flow velocity of the middle cerebral artery (Vmca) and its indices are routinely used to assess components of cerebral circulation. Although Vmca is not a direct measure of CBF, changes in flow velocity generally correlate well with changes in CBF\(^\text{43}\), except for specific situations, which may affect MCA diameter such as vasospasm, hypercapnia, migraine attacks, nitroglycerine, or other vasoactive agents.\(^\text{44-49}\)

Since the introduction of TCD, a number of methods have been developed to assess cerebral ZFP by pressure-flow velocity relationship analysis.\(^\text{24 25 50-58}\) However, deciding which method is clinically most suitable for ZFP, RAP and CPPe measurements is still unanswered and thus an important subject in current research.

**Figure 3: Cerebral vascular waterfall of the circulation**

Hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels (CrCPart) and a second (distal) at the level of collapsible cerebral veins (CrCPven). The effective downstream pressure of the cerebral circulation may be determined by CrCPart, CrCPven (i.e. ICP), or jugular venous pressure, depending on which one is the highest.\(^\text{24}\)
Scope and relevance of the thesis
This thesis focuses on the importance of cerebral perfusion pressure. The results are relevant to all patients in the perioperative setting, as all health providers will receive practical tools that enable them to better guide patients in cases of deregulated cerebral perfusion.

Problem statement
Maintaining adequate cerebral perfusion in the perioperative setting is an important task for the anesthesiologist. However, this is sometimes difficult to achieve because the cerebral perfusion of the patient is influenced by different factors such as age, cerebrovascular diseases, positioning during surgery, anesthetic and vasoactive drugs, and artificial ventilation. Furthermore, cerebrovascular physiology and pathophysiology are still not fully understood as stated above.

Aim of the thesis
The aim of this thesis is to investigate important determinants of CPPe regulation and subsequently to provide recommendations on how to maintain adequate cerebral perfusion in the perioperative setting.

OBJECTIVES AND RESEARCH QUESTIONS

Research questions of the thesis are:
- What are important determinants of flow and blood pressure regulation in humans during surgery in the context of intraoperative hypotension?
- Which ZFP, RAP and CPP estimation technique is clinically suitable?
- How does carbon dioxide, known as a strong vasodilator, affect cerebral blood flow, CPPe, ZFP, cerebrovascular resistance, and RAP?
- How does carbon dioxide affect cerebral metabolism?
- Is hyperventilation during general anesthesia potentially hazardous?
- Do volatile anesthetics affect cerebral CO₂ reactivity? Are there interactions regarding CPPe, ZFP, cerebrovascular resistance, and RAP?
- Does argon affect cerebral metabolism, CO₂ reactivity, effective cerebral perfusion, vasomotor tone and cerebrovascular resistance?
- How does treatment of arterial hypertension in patients with pre-eclampsia affect ZFP and CPPe?
1. **What are important factors of flow and blood pressure regulation in humans during surgery in the context of intraoperative hypotension?**

The incidence of intraoperative hypotension (MAP reduction > 20-30% after induction of general anesthesia) is high. Several retrospective studies comprising large patient cohorts demonstrated that intraoperative hypotension is associated with increased 1-year mortality. The hemodynamic significance of intraoperative hypotension is related to the fact, that cerebral, renal and myocardial blood flow and its autoregulation depend on perfusion pressure.

In Chapter 1 we will give an update on intraoperative hypotension and its cerebrovascular, coronary and renal pathophysiology and clinical implications.

2. **Which ZFP, RAP and CPP estimation technique is adequate?**

Since the introduction of TCD, a number of methods have been developed to assess cerebral ZFP by pressure-(flow)velocity relationship analysis. Deciding which method is the most appropriate for ZFP, RAP and CPPe measurements is still unanswered and thus an important subject in current research. We used data from a prospective, controlled, observational clinical study detecting cerebral ischemia caused by short periods of circulatory arrest during internal cardioverter defibrillator device (ICD) implantation and testing.

In a secondary analysis (Chapter 2) we estimated CPPe, ZFP, and RAP by four different methods and compared the results to the reference method.

3. **How does carbon dioxide, known as a strong vasodilator, affect cerebral blood flow, CPPe, cerebrovascular resistance, and RAP?**

Until now, the interrelationship of the partial pressure of carbon dioxide (PaCO₂) induced changes in CBF, Vmca, ZFP, CPPe, CVRe, and RAP is not fully understood. The validity of blood flow velocity measurements as an index of flow is based on the assumption that the cross-sectional area and the flow profile of these vessels remain constant during the period of investigation. Up to now there are no investigations in humans without cerebral diseases that combine measurements of global CBF and Vmca CO₂-reactivity. Recent studies could demonstrate that ZFP varies inversely with changes of PaCO₂. Similarly, reference calculations of CVR, based on quantitative CBF measurements and calculation of CPPe by determination of ZFP have not yet been compared to changes in RAP. Therefore, we investigated the effects of variation in PaCO₂ on CBF, Vmca, CPPe, ZFP, RAP and CVRe in patients under intravenous anesthesia (Chapter 3).

4. **How does carbon dioxide affect cerebral metabolism?**

Hypocapnia induced by hyperventilation and associated alkalosis have a wide range of physiological effects, including increased cerebrovascular resistance (CVR), decreased...
cerebral blood flow (CBF), cerebral oxygen delivery (cDO$_2$) and cerebral metabolism.$^{67}$ In patients with traumatic injury, vascular disorders, or meningitis hyperventilation is associated with impaired aerobic cerebral metabolism, reflected by an increase of net cerebral lactate efflux (CMRL).$^{68-72}$ Despite routine end-tidal PCO$_2$ monitoring, periods of inadvertent hyperventilation occur frequently during mechanical ventilation even in elective patients under general anesthesia, which may be associated with unfavorable side effects such as cognitive dysfunction and increased length of hospital stay.$^{73}$ The anesthetized brain might be less vulnerable to ischemia than the non-anesthetized brain as induction of anesthesia reduces cerebral electric activity, metabolism, and flow.$^{67}$ However, until now there are few studies describing the interrelation between hyperventilation and CMRL in animals and humans without cerebral diseases and their results have been not consistent. The interrelation between moderate variations in PaCO$_2$, CVR, CBF, global cDO$_2$, and cerebral metabolism in patients undergoing intravenous anesthesia is thus not fully understood.

We therefore investigated the effects of arterial PCO$_2$ variation on cerebral hemodynamics and metabolism in 30 cardiac surgical patients undergoing intravenous anesthesia (Chapter 4).

5. Is hyperventilation during general anesthesia potentially hazardous?

Peripheral tissue perfusion and oxygenation depend on various factors, including inspired oxygen concentration, arterial oxygen tension, hemoglobin concentration, cardiac output, vasomotor tone, and the autonomic stress response. Different concentrations of blood and tissue CO$_2$ together with changes in H$^+$ ion blood concentration are known to alter some of these parameters and may influence tissue perfusion and oxygenation.$^{74}$ However, there are various situations, when anesthesiologists accept or clinically tolerate hypocapnia (PaCO$_2$ <36 mmHg) or hypercapnia (PaCO$_2$ >45 mmHg). In Chapter 5 we will summarize the physiological effects, potential harms and consequences of hyperventilation/hypocapnia.

6. Do volatile anesthetics affect cerebral CO$_2$ reactivity?

Cerebral blood flow and cerebral metabolic rate (normally about 3.5 ml O$_2$/ 100g brain/ min) are coupled in the absence of pathology and/or various anesthetic drugs. This means when cerebral metabolic rate increases or decreases so does cerebral blood flow. The flow-metabolism coupling is an adaptive mechanism to provide more blood to the more active parts of the brain and vice versa. It is largely influenced by the type and dosage of anesthesia, including the actions on neural processing, vasoactive signal transmission, and vascular reactivity. Intravenously administered anesthetic drugs such as sufentanil / propofol or fentanyl / midazolam cause simultaneous and proportional
reductions of CBF and CMRO₂. However, volatile anesthetic drugs are known to cause a dose dependent increase in CBF due to vasodilation (Halothane > Desflurane > Isoflurane > Sevoflurane). Although there are indications that the diameter of the cerebral vessels close to the base are not significantly affected by CO₂-induced changes in the cerebral resistance, only a few comparative studies exist on the relationship between TCD based cerebral flow velocity measurements and reference measurements of cerebral blood flow.

The present clinical study (Chapter 6) was conducted to determine the effects of halothane and the influence of a variation in PaCO₂ on the relationship between global cerebral blood flow and blood flow velocity in basal brain arteries.

In a secondary analysis (Chapter 6 / Addendum) we investigated the effects of 1 MAC Halothane (0.8 vol%) under variations in PaCO₂ on CVRe, CPPe, ZFP, and RAP in patients under intravenous anesthesia. Furthermore, we compared reference calculations of CVRe based on quantitative CBF measurements and calculation of CPPe with changes in RAP.

7. Does argon affect cerebral perfusion, CO₂ reactivity and cerebral metabolism?

Argon is the longest known rare gas of the group of noble gases. It has beneficial neuroprotective and organoprotective properties, which have been observed in animal experiments in vitro and in vivo, but rarely in human studies. Up to now the cerebrovascular and cerebrometabolic effects of argon have not been investigated in humans, which may be essential for a possible future clinical application of argon as an organoprotective agent. We performed a larger series of clinical studies using an argon inhalation method for measurements of global cerebral blood flow (CBF), a modification of the Kety-Schmidt technique.

In a prospective, controlled, cross-over study design, we investigated the effects of hyperventilation versus hypoventilation in anesthetized patients on parameters of circulation and cerebral metabolism. In the same group of patients we also investigated the short-term effects of argon inhalation (Chapter 7). We hypothesized that argon has no effects on parameters of cerebral blood flow velocity, effective cerebrovascular perfusion pressure, blood gas analysis, and global cerebral metabolism.

8. How does treatment of arterial hypertension in patients with pre-eclampsia affect ZFP and CPPe?

Pre-eclampsia complicates 3-5% of pregnancies and is a major cause of maternal and fetal morbidity and mortality. The pathophysiology of cerebral damage in preeclampsia is unclear, but studies conducted with TCD and MRI have shown an increased cerebral blood flow in women with preeclampsia, and Belfort et al. reported that women with
severe preeclampsia have an increased cerebral perfusion pressure (CPPe). Currently used drugs in women with preeclampsia, such as labetalol and MgSO₄, tend to lower CPPe, while nimodipine is associated with a mild increase. Furthermore, a randomized study in women with preeclampsia reported that therapy with nimodipine is associated with more frequent eclamptic seizures in comparison with MgSO₄. These findings may be explained by the different effects of these drugs on CPPe.

We investigate whether CPPe is elevated in women with preeclampsia, in whom blood pressure is adequately treated with antihypertensive medication (Chapter 8).

REFERENCES

5. Ng JLW, Chan MTV, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. Anesthesiology 2011; 115:879–90
16. Whittaker SR, Winton FR. The apparent viscosity of blood flowing in the isolated hindlimb of the dog, and its variation with corpuscular concentration. *J Physiol (Lond)* 1933;**78**:339–69
27. Marval PD, Perrin ME, Hancock SM, Mahajan RP. The effects of propofol or sevoflurane on the estimated cerebral perfusion pressure and zero flow pressure. *Anesth Analg* 2005;**100**:835–40


49. Ashina M. Vascular changes have a primary role in migraine. *Cephalalgia* 2012;32:428–30


