Introduction and outline of the thesis

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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.).[1-3]

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.[3]

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.[4 5] 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.[4-9]

Moreover, brain magnetic resonance imaging studies suggest that 1 in 10 patients aged above 65 years has a (subclinical) *covert* perioperative stroke.[10] 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 ($PtiO_2$) 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.[11] 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).[12] 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).[13] 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.[13-15]

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.[13 16-22] 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

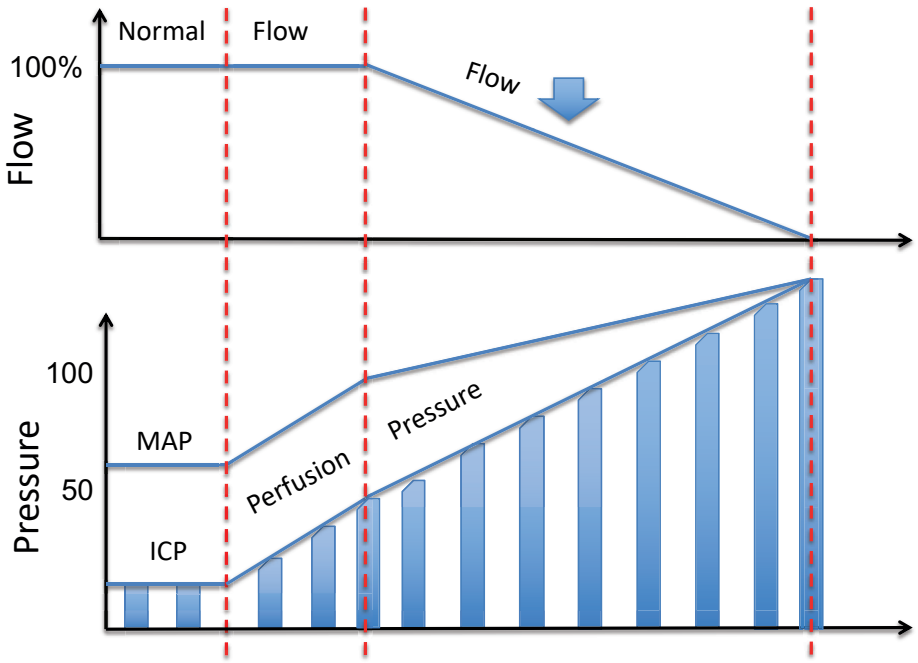

Figure 1: Relationship between CBF, MAP and ICP (classical CPP model)
The cerebral perfusion pressure (CPP) is commonly defined as difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP), 'classical model' CPP = MAP - ICP. Patients without cerebrovascular disease are expected 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 *Dewey et al. 1974*. [13]

of velocity and vessel cross-sectional area.[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).[15 24]

In a former investigation, *Weyland and colleagues* suggested the hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels ($CrCP_{art}$) and a second (distal) at the level of collapsible cerebral veins ($CrCP_{ven}$). 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 (Figure 3).[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.[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.

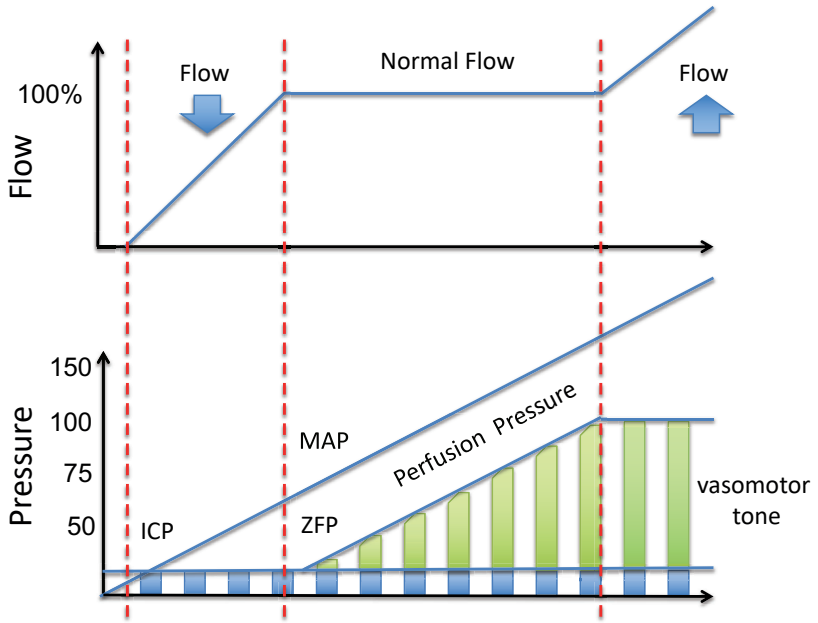

Figure 2: Relationship between CBF, MAP and ZFP (CPPe model)
Cerebral autoregulation maintains cerebral blood flow (CBF) relatively constant across a wide range of cerebral perfusion pressures (CPP). When pressure becomes excessively low, vascular bed resistance can no longer adjust to decreasing perfusion 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.*[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[29], skull vibrations[30], otoacoustic emissions[31], magnetic resonance imaging to estimate intracranial compliance[32], brain tissue resonance[33], transcranial time of flight[34], recordings of visual evoked potentials[35], optic nerve sheath diameter assessment[36], venous ophthalmodynamometry[37], and ultrasound-guided eyeball compression[38]. 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.[39]

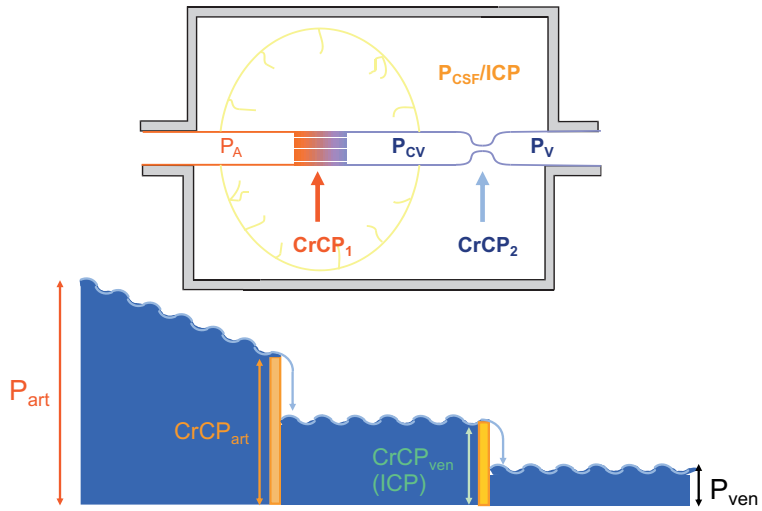

Figure 3: Cerebral vascular waterfall of the circulation
Hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels (CrCPart) and a second (distal) at the level of collapsible cerebral veins (CrCPven). The effective downstream 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.[24]

Sometimes we also measure tissue-oxygenation by Near Infrared Spectroscopy (NIRS)[40] or electrical activity by anesthesia depth monitoring devices[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.[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[43], except for specific situations, which may affect MCA diameter such as vasospasm, hypercapnia, migraine attacks, nitroglycerine, or other vasoactive agents.[44-49]

Since the introduction of TCD, a number of methods have been developed to assess cerebral ZFP by pressure-flow velocity relationship analysis.[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.

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 heath 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 vasodilatator, 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 CO_2 reactivity? Are there interactions regarding CPPe, ZFP, cerebrovascular resistance, and RAP?
- Does argon affect cerebral metabolism, CO_2 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.[59-61] The hemodynamic significance of intraoperative hypotension is related to the fact, that cerebral, renal and myocardial blood flow and it's 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.[24 25 50-58 62] 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.[63]

In a secondary analysis (**Chapter 2**) we estimated CPPe, ZFP, and RAP by four different methods and compared the results to the reference method.[24 53 54 62 64]

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

Until now, the interrelationship of the partial pressure of carbon dioxide ($PaCO_2$) 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.[43 65] Up to now there are no investigations in humans without cerebral diseases that combine measurements of global CBF and Vmca CO_2-reactivity. Recent studies could demonstrate that ZFP varies inversely with changes of $PaCO_2$.[15 24 66] 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 $PaCO_2$ 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 $CMRO_2$. 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 CO_2 -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.[43 75 76]

The present clinical study (**Chapter 6**) was conducted to determine the effects of halothane and the influence of a variation in $PaCO_2$ 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 $PaCO_2$ 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, CO_2 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.[77 78] 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.[79] 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.[80] 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[81 82], and Belfort et al. reported that women with

severe preeclampsia have an increased cerebral perfusion pressure (CPPe).[83] Currently used drugs in women with preeclampsia, such as labetalol and $MgSO_4$, 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 $MgSO_4$.[84] 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

1. Mitchell G, Bobbitt JP, Devries S. Cerebral perfusion pressure in giraffe: modelling the effects of head-raising and -lowering. *J Theor Biol* 2008; **252**:98–108
2. Brøndum E, Hasenkam JM, Secher NH, et al. Jugular venous pooling during lowering of the head affects blood pressure of the anesthetized giraffe. *Am J Physiol Regul Integr Comp Physiol* 2009; **297**:R1058–65
3. Grüne F, Klimek M. Cerebral blood flow and its autoregulation - when will there be some light in the black box? *Br J Anaesth* 2017; **119**:1077–9
4. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology* 2009; **110**: 231–8
5. Ng JLW, Chan MTV, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology* 2011;**115**:879–90
6. Landercasper J, Merz BJ, Cogbill TH, et al. Perioperative stroke risk in 173 consecutive patients with a past history of stroke. *Arch Surg* 1990;**125**:986–9
7. Parikh S, Cohen JR. Perioperative stroke after general surgical procedures. *N Y State J Med* 1993; **93**:162–5
8. El-Saed A, Kuller LH, Newman AB, et al. Geographic variations in stroke incidence and mortality among older populations in four US communities. *Stroke* 2006;**37**:1975–9
9. Buddeke J, van Dis I, Visseren F, Vaartjes I, Bots ML. Hart- en vaatziekten in Nederland 2017 [Internet]. Den Haag: Nederlandse Hartstichting; 2017. p. 1–268
10. Mrkobrada M, Hill MD, Chan MTV, et al. Covert stroke after non-cardiac surgery: a prospective cohort study. *Br J Anaesth* 2016;**117**:191–7
11. Tzeng YC, Ainslie PN. Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur J Appl Physiol* Springer Berlin Heidelberg; 2014;**114**:545–59
12. Luce JM, Huseby JS, Kirk W, Butler J. A Starling resistor regulates cerebral venous outflow in dogs. *J Appl Physiol* 1982;**53**:1496–503
13. Dewey RC, Pieper HP, Hunt WE. Experimental cerebral hemodynamics. Vasomotor tone, critical closing pressure, and vascular bed resistance. *J Neurosurg* 1974;**41**:597–606
14. Carey BJ, Eames PJ, Panerai RB, Potter JF. Carbon dioxide, critical closing pressure and cerebral haemodynamics prior to vasovagal syncope in humans. *Clin Sci* 2001;**101**:351–8
15. Panerai RB. The critical closing pressure of the cerebral circulation. *Med Eng Phys* 2003;**25**:621–32

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
17. Sagawa K, Guyton ACC. Pressure-flow relationships in isolated canine cerebral circulation. *Am J Physiol* 1961;**200**:711–4
18. Early CB, Dewey RC, Pieper HP, Hunt WE. Dynamic pressure-flow relationships of brain blood flow in the monkey. *J Neurosurg* 1974;**41**:590–6
19. Ehrlich W, Baer RW, Bellamy RF, Randazzo R. Instantaneous femoral artery pressure-flow relations in supine anesthetized dogs and the effect of unilateral elevation of femoral venous pressure. *Circ Res* 1980;**47**:88–98
20. Permutt S, Riley RL. Hemodynamics of collapsible vessels with tone: The vascular waterfall. *J Appl Physiol* [Internet] 1963;**18**:924–32
21. Riley RL. A postscript to Circulation of the blood: men and ideas. *Circulation* 1982;**66**:683–8
22. Kazmaier S, Hanekop GG, Grossmann M, et al. Instantaneous diastolic pressure-flow relationship in arterial coronary bypass grafts. *Eur J Anaesthesiol* 2006;**23**:373–9
23. Evans DH, Levene MI, Shortland DB, Archer LN. Resistance index, blood flow velocity, and resistance-area product in the cerebral arteries of very low birth weight infants during the first week of life. *Ultrasound Med Biol* 1988;**14**:103–10
24. Weyland A, Buhre W, Grund S, et al. Cerebrovascular tone rather than intracranial pressure determines the effective downstream pressure of the cerebral circulation in the absence of intracranial hypertension. *J Neurosurg Anesthesiol* 2000;**12**:210–6
25. Hancock SM, Mahajan RP, Athanassiou L. Noninvasive estimation of cerebral perfusion pressure and zero flow pressure in healthy volunteers: The effects of changes in end-tidal carbon dioxide. *Anesth Analg* 2003;**96**:847–51
26. Edouard AR. Non-invasive assessment of cerebral perfusion pressure in brain injured patients with moderate intracranial hypertension. *Br J Anaesth* 2005;**94**:216–21
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
28. Kalmar AF, Dewaele F, Foubert L, et al. Cerebral haemodynamic physiology during steep Trendelenburg position and CO_2 pneumoperitoneum. *Br J Anaesth* 2012;**108**
29. Reid A, Marchbanks RJ, Bateman DE, Martin AM, Brightwell AP, Pickard JD. Mean intracranial pressure monitoring by a non-invasive audiological technique: a pilot study. *J Neurol Neurosurg Psychiatr* 1989;**52**:610–2
30. Ueno T, Ballard RE, Shuer LM, Cantrell JH, Yost WT, Hargens AR. Noninvasive measurement of pulsatile intracranial pressure using ultrasound. *Acta Neurochir Suppl* 1998;**71**:66–9
31. Frank AM, Alexiou C, Hulin P, Janssen T, Arnold W, Trappe AE. Non-invasive measurement of intracranial pressure changes by otoacoustic emissions (OAEs)--a report of preliminary data. *Zentralbl Neurochir* 2000;**61**:177–80
32. Alperin NJ, Lee SH, Loth F, Raksin PB, Lichtor T. MR-Intracranial pressure (ICP): a method to measure intracranial elastance and pressure noninvasively by means of MR imaging: baboon and human study. *Radiology* 2000;**217**:877–85
33. Michaeli D, Rappaport ZH. Tissue resonance analysis; a novel method for noninvasive monitoring of intracranial pressure. Technical note. *J Neurosurg* Journal of Neurosurgery Publishing Group; 2002;**96**:1132–7
34. Ragauskas A, Daubaris G, Ragaisis V, Petkus V. Implementation of non-invasive brain physiological monitoring concepts. *Med Eng Phys* 2003;**25**:667–78

35. Zhao YL, Zhou JY, Zhu GH. Clinical experience with the noninvasive ICP monitoring system. *Acta Neurochir Suppl* 2005;**95**:351–5
36. Geeraerts T, Launey Y, Martin L, et al. Ultrasonography of the optic nerve sheath may be useful for detecting raised intracranial pressure after severe brain injury. *Intensive Care Med* 2007;**33**: 1704–11
37. Querfurth HW, Lieberman P, Arms S, Mundell S, Bennett M, van Horne C. Ophthalmodynamometry for ICP prediction and pilot test on Mt. Everest. *BMC Neurol* 2010;**10**:106
38. Bartusis L, Zakelis R, Daubaris G, et al. Ophthalmic Artery as a sensor for non-invasive intracranial pressure measurement electronic system. *ElAEE* 2012;**122**:45–8
39. Cardim D, Robba C, Donnelly J, et al. Prospective Study on Noninvasive Assessment of Intracranial Pressure in Traumatic Brain-Injured Patients: Comparison of Four Methods. *J Neurotrauma* 2016; **33**:792–802
40. Scheeren TWL, Schober P, Schwarte LA. Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications. *J Clin Monit Comput* Springer Netherlands; 2012;**26**:279–87
41. Shander A, Lobel GP, Mathews DM. Brain Monitoring and the depth of anesthesia: Another Goldilocks dilemma. *Anesth Analg* 2018;**126**:705–9
42. Moppett IK, Mahajan RP. Transcranial Doppler ultrasonography in anaesthesia and intensive care. *Br J Anaesth* 2004;**93**:710–24
43. Weyland A, Stephan H, Kazmaier S, et al. Flow velocity measurements as an index of cerebral blood flow. *Anesthesiology* 1994;**81**:1401–10
44. Müller HR, Lampl Y, Haefele M. [The transcranial Doppler ultrasound upright posture test for clinical evaluation of cerebral autoregulation]. *Ultraschall Med* 1991;**12**:218–21
45. Giller CA, Hatab MR, Giller AM. Estimation of vessel flow and diameter during cerebral vasospasm using transcranial Doppler indices. *Neurosurgery* 1998;**42**:1076–81; discussion1081–2
46. Valdueza JM, Draganski B, Hoffmann O, Dirnagl U, Einhäupl KM. Analysis of CO_2 vasomotor reactivity and vessel diameter changes by simultaneous venous and arterial Doppler recordings. *Stroke* 1999;**30**:81–6
47. Schreiber SJ, Gottschalk S, Weih M, Villringer A, Valdueza JM. Assessment of blood flow velocity and diameter of the middle cerebral artery during the acetazolamide provocation test by use of transcranial Doppler sonography and MR imaging. *Am J Neuroradiol* 2000;**21**:1207–11
48. Lunt MJ, Ragab S, Birch AA, Schley D, Jenkinson DF. Comparison of caffeine-induced changes in cerebral blood flow and middle cerebral artery blood velocity shows that caffeine reduces middle cerebral artery diameter. *Physiol Meas* 2004;**25**:467–74
49. Ashina M. Vascular changes have a primary role in migraine. *Cephalalgia* 2012;**32**:428–30
50. Aaslid R, Lundar T, Lindegaard KF, Nornes H. Estimation of cerebral perfusion pressure from arterial blood pressure and transcranial Doppler recordings. In: Miller JD, Teasdale GM, Rowan JO, Gailbraith SL, Mendelow AD, editors. *Intracranial Pressure VI* Berlin, Heidelberg: Springer, Berlin, Heidelberg; 1986. p. 226–9
51. Michel E, Zernikow B, wickel von J, Hillebrand S, Jorch G. Critical closing pressure in preterm neonates: Towards a comprehensive model of cerebral autoregulation. *Neurol Res* 1995;**17**:149–55
52. Belfort MA, Saade GR, Yared M, et al. Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia. *Am J Obstet Gynecol* 1999;**181**:402–7
53. Czosnyka M, Smielewski P, Piechnik S, et al. Critical closing pressure in cerebrovascular circulation. *J Neurol Neurosurg Psychiatr* 1999;**66**:606–11

54. Schmidt EA, Czosnyka M, Gooskens I, et al. Preliminary experience of the estimation of cerebral perfusion pressure using transcranial Doppler ultrasonography. *J Neurol Neurosurg Psychiatr* 2001;**70**:198–204
55. Ogoh S, Brothers RM, Jeschke M, Secher NH, Raven PB. Estimation of cerebral vascular tone during exercise; evaluation by critical closing pressure in humans. *Exp Physiol* 2010;**95**:678–85
56. Kashif FM, Verghese GC, Novak V, Czosnyka M, Heldt T. Model-Based Noninvasive Estimation of Intracranial Pressure from Cerebral Blood Flow Velocity and Arterial Pressure. *Sci Translational Med* 2012;**4**:129ra44–4
57. Marzban C, Illian PR, Morison D, et al. A method for estimating zero-flow pressure and intracranial pressure. *J Neurosurg Anesthesiol* 2013;**25**:25–32
58. Varsos GV, Kolias AG, Smielewski P, et al. A noninvasive estimation of cerebral perfusion pressure using critical closing pressure. *J Neurosurg* 2015;**123**:638–48
59. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KGM, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007;**107**:213–20
60. Bijker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology* 2009;**111**:1217–26
61. Soo JCL, Lacey S, Kluger R, Silbert BS. Defining intra-operative hypotension--a pilot comparison of blood pressure during sleep and general anaesthesia. *Anaesthesia* 2011;**66**:354–60
62. Belfort MA, Tooke-Miller C, Varner M, et al. Evaluation of a noninvasive transcranial Doppler and blood pressure-based method for the assessment of cerebral perfusion pressure in pregnant women. *Hypertens Pregnancy* 2000;**19**:331–40
63. Visser GH, Wieneke GH, van Huffelen AC, de Vries JW, Bakker PF. The development of spectral EEG changes during short periods of circulatory arrest. *Journal of Clinical Neurophysiology* 2001;**18**: 169–77
64. Buhre W, Heinzel FR, Grund S, Sonntag H, Weyland A. Extrapolation to zero-flow pressure in cerebral arteries to estimate intracranial pressure. *Br J Anaesth* 2003;**90**:291–5
65. Kontos HA. Validity of cerebral arterial blood flow calculations from velocity measurements. *Stroke* 1989;**20**:1–3
66. McCulloch TJ, Turner MJ. The effects of hypocapnia and the cerebral autoregulatory response on cerebrovascular resistance and apparent zero flow pressure during isoflurane anesthesia. *Anesth Analg* 2009;**108**:1284–90
67. Brian JE. Carbon dioxide and the cerebral circulation. *Anesthesiology* 1998;**88**:1365–86
68. Meyer JS, Sawada T, Kitamura A, Toyoda M. Cerebral oxygen, glucose, lactate, and pyruvate metabolism in stroke: Therapeutic considerations. *Circulation* 1968;**37**:1036–48
69. Robertson CS, Narayan RK, Gokaslan ZL, et al. Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *J Neurosurg* 1989;**70**:222–30
70. Thees C, Scholz M, Schaller M D C, et al. Relationship between intracranial pressure and critical closing pressure in patients with neurotrauma. *Anesthesiology* 2002;**96**:595–9
71. Coles JP, Minhas PS, Fryer TD, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: Clinical relevance and monitoring correlates. *Crit Care Med* 2002;**30**:1950–9
72. Møller K, Strauss GI, Thomsen G, et al. Cerebral blood flow, oxidative metabolism and cerebrovascular carbon dioxide reactivity in patients with acute bacterial meningitis. *Acta Anaesthesiol Scand* 2002;**46**:567–78
73. Wax DB, Lin H-M, Hossain S, Porter SB. Intraoperative carbon dioxide management and outcomes. *Eur J Anaesthesiol* 2010;**27**:819–23

74. Akça O. Optimizing the intraoperative management of carbon dioxide concentration. *Curr Opin Anaesthesiol* 2006;**19**:19–25
75. Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. Angiographic determination in man. *Invest Radiol* 1967;**2**:17–32
76. Kirkham FJ, Padayachee TS, Parsons S, Seargeant LS, House FR, Gosling RG. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. *Ultrasound Med Biol* 1986;**12**:15–21
77. Höllig A, Weinandy A, Liu J, Clusmann H, Rossaint R, Coburn M. Beneficial Properties of Argon After Experimental Subarachnoid Hemorrhage: Early Treatment Reduces Mortality and Influences Hippocampal Protein Expression. *Crit Care Med* 2016;**44**:e520–9
78. Deng J, Lei C, Chen Y, et al. Neuroprotective gases--fantasy or reality for clinical use? *Prog Neurobiol* 2014;**115**:210–45
79. Grüne F, Kazmaier S, Sonntag H, Stolker R-J, Weyland A. Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux. *Anesthesiology* 2014;**120**:335–42
80. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet* 2016;**387**:999–1011
81. Ohno Y, Kawai M, Wakahara Y, Kitagawa T, Kakihara M, Arii Y. Transcranial assessment of maternal cerebral blood flow velocity in patients with pre-eclampsia. *Acta Obstet Gynecol Scand* 1997;**76**:928–32
82. Zeeman GG, Hatab MR, Twickler DM. Increased cerebral blood flow in preeclampsia with magnetic resonance imaging. *Am J Obstet Gynecol* 2004;**191**:1425–9
83. Belfort MA, Varner MW, Dizon-Townson DS, Grunewald C, Nisell H. Cerebral perfusion pressure, and not cerebral blood flow, may be the critical determinant of intracranial injury in preeclampsia: a new hypothesis. *Am J Obstet Gynecol* 2002;**187**:626–34
84. Belfort MA, Anthony J, Saade GR, Allen JC, Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med* 2003;**348**:304–11