General Discussion, Conclusions, and Future Perspectives

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SCOPE AND RELEVANCE OF THE THESIS

This thesis focuses on the importance of cerebral perfusion pressure. 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. Moreover, most anesthesiologists commonly do not monitor cerebral perfusion even in high-risk patients.

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

DEFINITION OF EFFECTIVE CEREBRAL PERFUSION PRESSURE

The classic concept defining cerebrovascular tone focuses on cerebral vascular resistance (CBF = CPP / CVR). It assumes that perfusion pressure and flow are linearly and proportionally related. When calculating the cerebral perfusion pressure, 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 CPPi = MAP - ICP).[1] Patients without cerebrovascular disease are expected to have a normal ICP between 7 - 15 mmHg in supine position.[2] When intracranial pressure is elevated by e.g. intracranial bleeding or hydrocephalus, CPPi will decrease unless reflex arterial hypertension occurs. If MAP increases less than ICP beyond this point, CBF will decrease.[3] However, the "classical model" has limitations. Using solely the intracranial pressure as effective downstream pressure of the cerebral circulation would neglect vascular tone properties of cerebral vessels.[3-5] Arteriolar wall tension arises from a combination of the stretched elastic components of the vessel wall and active contraction of vascular smooth muscle. Subsequently, a lot of studies of organ perfusion of the e.g. lung, myocardium, liver, muscle, skin, and the brain, have shown, that the EDP is rather determined by a critical closing pressure located at arteriolar level.[6-8]

The origin of the term critical closing pressure (CrCP) or later zero flow pressure (ZFP) is often attributed to *Alan Burton*.[9] He suggested the use of Laplace's law to explain the influence of active wall tension on collapsible vessels. 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 CrCP or ZFP.[9]

When dynamic measurement techniques are used, such as electromagnetic flowmetry or ultrasound Doppler, the limitations of the classical CPPi concept become evident.[3 10] Dynamically, flow may stop at pressure levels significantly higher than zero and even higher than venous pressure or ICP, respectively. The arterial blood pressure (ABP) level at which flow stops is defined as the CrCP[3 5 10-12] or zero-flow pressure (ZFP).[13 14] Graphically, this value is associated with the pressure-axis intercept of a linear regression plot of the blood flow (or velocity) as a function of ABP.[5] The ZFP represents vasomotor tone while its slope represents vascular bed resistance. Hence the diameter of the resistance vessel is the relationship between vasomotor tone and vessel diameter.[3 5 10 11 15 16] That means that flow is linearly, related to pressure (as long as vascular resistance is constant during the period of measurement) and that it can be regulated by changes in both, ZFP (the x intercept) and slope. The pressure-flow relation is mainly a function of the peripheral resistance.[17] Thus, the driving pressure for the flow through arterioles is, under many conditions, not the difference between arterial (inflow) pressure and venous (outflow) pressure, but rather the difference between arterial pressure and ZFP (alternative model CPPe = MAP - ZFP).

Another assumption, sometimes found in the literature, is that ZFP can be used as a substitute for ICP. This is possible only in situations where active wall tension remains constant, which seems to be unlikely unless in patients with impaired autoregulation. The difference between ZFP and ICP is explained by the tone of the small vessels, which is the wall tension.

In a former study, we suggested the 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 highest.[5 15]

To conclude, it can be said that defining the pressure-flow (velocity) relationship by a single parameter (CVR) can mislead interpretation and blunt key relationships. As an extreme case, it is possible to have repeated pressure-flow velocity measurements indicating a constant estimation of CVR = ABP/CBF or ABP/V_{MCA}, when in fact there had been changes in both, ZFP and RAP.[5 15]

Table 1 summarizes former investigations regarding the effects of $PaCO_2$, volatile anesthetics, vasoactive drugs, and patients' positing on CPPe, ZFP, RAP, MAP, and Vmca in cerebrovascular healthy patients.

Table 1: Effects of interventions on CPPe, ZFP, RAP, MAP, and Vmca in cerebrovascular healthy patients

Intervention	$PaCO_2$	CPPe	ZFP	RAP	MAP	V_{mca}	CBF	Source
CO_2 reactivity	Hypocapnia	↓↓	↑↑	-	→	↓↓	-	16
	Normocapnia	→	→	-	→	→	-	
	Hypercapnia	↑↑	↓↓	-	→	↑↑	-	
CO_2 reactivity # §	Hypocapnia	↓	↑↑	↑	→	↓↓	↓↓	18
	Hypercapnia	↑	↓↓	↓	→	↑↑	↑↑↑	
CO_2 reactivity # §	Hypocapnia	↓	↑↑	↑	→	↓↓	↓↓	19
	Normocapnia	→	→	→	→	→	→	
	Hypercapnia	↑	↓↓	↓	→	↑↑	↑↑↑	
Nitrous oxide 50%	Normocapnia	↑↑	↓↓	-	→	↑↑	-	20
Halothane # §	Hypocapnia	↓↓	→	↓↓	↓↓	→	→	21
	Hypercapnia	↓↓	→	↓↓	↓↓	→	→	
Isoflurane	Hypocapnia	↓↓↓	↑	-	↓↓	↓↓	-	22
	Normocapnia	↓↓	→	-	↓	↓	-	
Sevoflurane	Hypocapnia	↓	↓↓	-	↓↓	↓↓	-	23
	Normocapnia	→	↓	-	↓	↓	-	
Argon 70% # §	Normocapnia	→	→	→	→	→	-	24
Propofol	Hypocapnia	↓↓	↑↑	-	↓↓↓	↓↓↓	-	23
	Normocapnia	↓	↑↑	-	↓↓	↓↓	-	
Phenylephrine	Hypocapnia	↑↑	↑	↑↑	↑↑	→	-	25
	Normocapnia	↑↑	→	↑↑	↑↑	↑↑	-	
Noradrenaline	Normocapnia	→	↑↑	-	↑↑	→	-	26
Ephedrine	Normocapnia	→	↑↑	-	↑↑	→	-	27
Dobutamine	Normocapnia	→	↑↑	-	↑	→	-	27
Dopexamine	Normocapnia	→	→	-	→	→	-	27
NTG	Normocapnia	↑↑	↓↓	-	↓	↓	-	26
Exercise	Normocapnia	-	↑	→	↑	→	-	28 29
Trendelenburg position	Normocapnia	→	↑↑	-	↑	-	-	30

in addition to baseline anesthesia with fentanyl / midazolam
§ this thesis

CIRCLE OF WILLIS

With regard to the reactivity of cerebral vessels, basal cerebral arteries differ from more distal vessels. Compared to their downstream arterioles as main source of vasomotion, they appear to have constant diameters even after stimulation with vasoactive substances.[31] For the interpretation of TCD measurements, the macro and microanatomy of the cerebral vessels is of particular importance.

The blood-supply of the brain occurs bilaterally via the internal carotid arteries as well as the vertebral arteries. The paired vertebral arteries unite to the basilar artery, which, together with the internal carotic arteries, forms around the pituitary stalk a vascular ring, the "Circle of Willis". The internal carotid artery enters the interior of the skull through the carotid canal of the temporal bone, where it forms a loop at the end of the cavernous sinus - the carotid siphon. The short intracranial part of the internal carotid artery is located in the liquor-filled subarachnoid space, giving rise to relatively small ophthalmic artery and then it branches into the middle cerebral artery (MCA) and anterior cerebral artery (ACA). After entering the liquor-filled subarachnoid space, it continues laterally into the mean cerebral artery (MCA). The MCA runs sideways across the area olfactoria to the lateral cerebral sulcus. At the entrance to the lateral cerebral fossa, it divides into 2 to 4 strong branches, the arteries of the insula region. The MCA supplies the insula region, the frontal and temporal lobes, and the basal ganglia and represents up to 80% of hemispheric blood flow.[32]

The Circle of Willis provides a compensatory arterial supply between two cerebral hemispheres in case of occlusion.[32 33] In the perioperative setting of a patient with an endarteriectomy of the internal carotid artery, the anesthesiologist preserves a (supra-) normal arterial blood pressure during the arterial clamp phase in order to deliver enough cerebral blood flow via the anterior and posterior communicant arteries.[34]

The wall of an artery consists of a 1) tunica intima with the stratum subendotheliale and the membrana elastica interna, 2) the tunica media, which consists in young humans predominantly of muscle fibers, and 3) the tunica externa, in which particularly collagenous fibers and elastic fibers run. In intracranial arteries, a muscle-weaker and thinner wall is found.[35 36] Furthermore, cerebral arteries do have less fraction of elastin in the tunica media and adventitia which exhibit high resistance to axial deformation.[37 38] Thus, cerebral arteries are known to be stiff vessels and therefore their compliance plays a minor role in buffering the passage through the arterial compartment.[39]

CEREBRAL BLOOD FLOW (CBF) VERSUS VELOCITY OF THE MEAN CEREBRAL ARTERY (VMCA)

Transcranial Doppler sonography (TCD) allows non-invasive, continuous measurements of the flow velocity of cerebral vessels. 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.

With transcranial Doppler sonography is not possible to measure the diameter of the artery at the point of insonation because of the scatter of the ultrasound beam through the bone plate of the skull. Thus, a quantification of the absolute blood flow in the

isonated vessels is not possible. Based on the Hagen-Poiseuille law, the volumetric flow rate (*Q*) could be defined as function of flow velocity (*V*) and diameter or flow area. The (CSA = cross-sectional area, d = vessel diameter) of the insonated vascular segment.[40 41]

(1) $\dot{Q} = \bar{V} \cdot CSA$

(2) $\dot{Q} = \bar{V} \cdot \frac{\pi \cdot d^2}{4}$

According to the equation above, the CSA of the vessel in the 2nd power is dependent on the current vessel diameter. Thus, proportional changes in MCA velocity to global cerebral blood flow can only be expected if the diameter of the vessel lumen remains largely constant during the study period.[42-47] Hence, to equate TCD measurements over a given vessel with "cerebral blood flow velocity" is inappropriate, because doing so implies measurement of hemispheric cerebral blood flow. If velocity in the mean cerebral artery is described, the term MCA velocity (V_{MCA}) is more preferable.

Although Vmca is not a direct measure of global CBF, changes in flow velocity generally correlate well with changes in CBF[48], except for specific situations, which may affect MCA diameter such as vasospasm[49], migraine attacks[50], nitroglycerine[51], or other vasoactive agents.

In **Chapter 3 (Carbon dioxide)** we found that even a moderate variation of $PaCO_2$ (within a range of 30-50 mmHg) induced exponential changes in CBF and V_{MCA}. The relative cerebrovascular CO_2- reactivity of the blood flow velocity measured by TCD was lower when compared with measurements of cerebral blood flow by the Kety-Schmidt technique (figure 1).

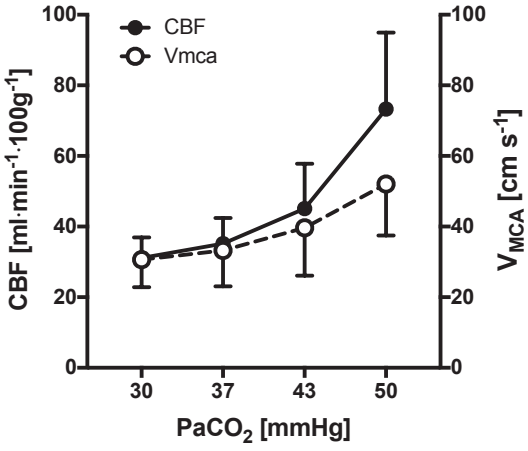

Figure 1: CBF versus Vmca at four different levels of $PaCO_2$ (Chapter 3)

As derived in formula (2) above, the mathematical relationship between flow (Q) and flow velocity (V) in a vessel allows the calculation of the cross-sectional area. Applying this relationship to the cerebral circulation, it has to be considered that the Kety Schmidt technique does not measure the blood flow of the mean cerebral artery but an average weight-related cerebral blood flow. Thus, the analogous calculation of the available data results in a cross-sectional index based on 100 g of brain tissue (CBF in ml /100g/ min, Vmca in cm/s, and CSAI in mm^2/100g).

(3) $$CSAI = \frac{\dot{Q}}{\bar{V}}$$

(4) $$CSAI\,(mm^2/100g) = \frac{CBF \cdot 100}{Vmca \cdot 60}$$

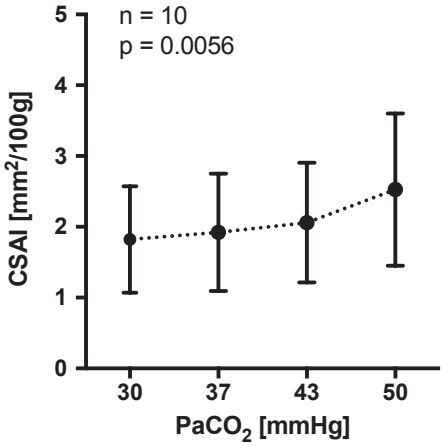

Figure 2: Cerebral cross-sectional area index (CSAI) at four different levels of $PaCO_2$ (Chapter 3)

When comparing measurements at $PaCO_2$ 37 mmHg with $PaCO_2$ 50 mmHg CBF was increased by 23 ml/100g/min. The relative rise of Vmca was smaller (figure 1). Consequently, the mean CSAI under hypercapnia showed a relative increase of 36% (figure 2). The most probable explanation is that changes of $PaCO_2$ do not only cause changes in vascular diameter at the arteriolar level but may also cause minor changes in MCA main trunk diameter resulting in a slight systematic difference between relative changes in flow and flow velocity[19] as described in **Chapter 3**.

Former investigations have shown that especially in diseases as impaired orthostasis, migraine attacks, and during CO_2-rebreathing or vasoactive medication could change the diameters of the mean cerebral artery by 5% to 12%.[45 50 52-54] However, there is still an ongoing debate where in the cerebrovascular tree cerebrovascular resistance occurs: at the level of the smaller precapillary arterioles, the major cerebral arteries or a combination of both.[55] Recently, *Warnert et al.* measured cerebral arterial compliance, a measure

that is inversely related to cerebrovascular resistance, by magnetic resonance imaging in eight normotensive men. Their results showed that during post exercise ischemia, cerebral arterial compliance was decreased in the major cerebral arteries at the level of and below the Circle of Willis, while no changes were measured in arteries above the Circle of Willis.[56] In an earlier publication, Bloor et al.[57] introduced CO_2-reactivity measurements to evaluate the functional capacity of the cerebrovascular autoregulatory system. In chapter 4a 4b[21], 7[19], and 8[18] CBF and Vmca were measured under different $PaCO_2$ levels. Capacitance effects of the middle cerebral artery may have changed during alterations of $PaCO_2$, which in turn may have weakened the accuracy of the extrapolation of ZFP and CPPe. However, the linearity of pressure-flow velocity relationships have not been influenced by $PaCO_2$ in an former study.[15] Thus, it could be assumed that possible effects on MCA compliance have minor methodological importance regarding the calculation of ZFP and CPPe.

OBJECTIVES AND RESEARCH QUESTIONS (THIS THESIS)

1. *What are important determinants of flow and blood pressure regulation in humans during surgery in the context of intraoperative hypotension?*

Chapter 1 gives an update on intraoperative hypotension and its cerebrovascular, coronary and renal pathophysiology and clinical implications.[58] Unfortunately, there is still no universally accepted definition of intraoperative hypotension. The mean arterial pressure is more suitable than the systolic arterial pressure due to the highly age-dependent pulse pressure. A lower threshold of 60 mmHg is usually considered, due to physiological considerations and on the basis of observational studies, to be sufficient for patients without specific risk factors. But, especially in patients with an elevated arterial baseline, a relative decrease in MAP >30% has been suggested as a limit.

The incidence of intraoperative hypotension is high, especially in patients aged above 65 years. 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.[59-61]

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 hypovolemia or an impairment of cardiac pump function, or both, in addition to a decreased SVR.

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

Chapter 2 discusses the results of a method comparison study regarding CPPe estimation. In 35 cardiovascular patients, invasive recordings of radial artery blood pressure

and cerebral blood flow velocity (transcranial Doppler ultrasound, middle cerebral artery) were obtained. In a secondary analysis CPPe, ZFP and RAP were estimated by four different methods. The 3-point intercept calculation (LR3, systolic/mean/diastolic), the methods according to Czosnyka (CZO, systolic/diastolic)[62], Belford (BEL, mean/diastolic)[63], and Schmidt (SCH, systolic/diastolic)[64] were validated against the reference method (LR, linear regression).[15 65] CPPe ZFP and RAP measurements based on LR3 and CZO calculation methods showed very small mean differences, good agreement, low percentage errors, and an excellent correlation when compared to the reference method. Agreement and correlation was moderate for the BEL method, and unsatisfying for the SCH method. In conclusion, CPPe, ZFP, and RAP measurements based on LR3 and CZO calculation methods are comparable to the LR reference method. These methods are much simpler to implement than regression analysis of digitized arterial pressure and Vmca curves and can thus easily be used for bedside assessments. Furthermore, a correction of the time delay between ABP and Vmca is not necessary.

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

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 CBF and V_{MCA} following an exponential function.[19] The hypocapnia-induced reduction in CBF and V_{MCA} under general anesthesia affected both components of the pressure-flow plot: an increase in ZFP and RAP. The increases of mean CVRe and RAP associated with hypocapnia were concordant. Nevertheless, correlation analysis showed only a weak linear relationship. *Panerai et al.* could demonstrate that the RAP is related to myogenic properties of the cerebrovascular system, while ZFP reflects metabolism and cerebrovascular reactivity to CO_2.[66] Our data, however, could not explain the regulatory mechanism between these two factors.

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) and cerebral oxygen delivery (cDO2).[18] **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, in patients with cardiovascular disease undergoing intravenous anesthesia increased net cerebral lactate efflux and markedly reduced CBF and partial pressure of oxygen of the jugular-venous bulb, consistent with partial impairment of cerebral metabolism at clinically relevant levels of hypocapnia.

5. Is hyperventilation during general anesthesia potentially hazardous?

Chapter 5 underlines that there is no evidence to support the therapeutic or prophylactic use of induced hypocapnia in any therapeutic context.[71] Overall, the benefits of preserving normocapnia for the maintenance of cardiac output and tissue oxygenation and perfusion, as well as for the maintenance of CPPe, CBF, CVRe, 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.[72 73] It is recommended to anesthesiologists to be familiar with the physiological effects of CO_2 and manage it according to their patient's situation.

6. Do volatile anesthetics affect cerebral CO_2 reactivity? Are there interactions regarding CPPe, ZFP, cerebrovascular resistance, and RAP?

Chapter 6a discusses the effects of 1 MAC Halothane (0.8 vol%) on cerebral blood flow and velocity of the mean cerebral artery. In the present study halothane showed only minimal changes in global CBF and V_{MCA} during hypocapnia as well as hypercapnia. The decrease in cerebrovascular resistance was mainly related to reduction in mean arterial pressure. The cerebrovascular CO_2-reactivity remained unchanged.

Studies about the effects on volatile anesthetics on CPPe and ZFP are rare. In **Chapter 6b** it could be demonstrated that 1 MAC Halothane (0.8 vol%) lead to a reduction in CPPe, RAP, and CVRe while ZFP, CBF and V_{MCA} were rather unchanged in cardiovascular patients. It seems that halothane as a "peripheral" vasodilatator rather affects the slope of the pressure flow plot than the vasomotor tone (ZFP). Interestingly, other volatile anesthetics appear to alter CPPe, ZFP, and RAP differently (Table 1). In an earlier study, *Marval et al*. could show that mean arterial pressure, Vmca and ZFP decreased significantly during sevoflurane anesthesia. The proportional reduction of ZFP was thus counterbalanced by a reduction in MAP, which lead to a preserved CPPe.[23] *Panerai et al.* showed that the RAP is linked to myogenic properties of the cerebrovascular system, while ZFP reflects metabolism and cerebrovascular reactivity to CO_2.[66] Our data could not fully explain the mechanism between differences of volatile anesthetics on CPPe regulation.

7. Does argon affect cerebral metabolism, CO_2 reactivity, effective cerebral perfusion, vasomotor tone and cerebrovascular resistance?

Chapter 7 discusses the cerebrovascular and cerebrometabolic effects of argon in humans, which may be essential for a possible future clinical application of argon as an organoprotective agent. In a secondary analysis of an earlier controlled cross-over trial we compared parameters of the cerebral circulation under 15 minutes exposure

to 70%Ar/30%O_2 versus 70%N_2/30%O_2 in 29 male patients under fentanyl-midazolam anesthesia before coronary surgery. Mechanical ventilation with 70% Ar showed no clinically relevant changes in jugular venous oxygen saturation, and/or arterio-jugular venous content difference of oxygen, glucose, and lactate. 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. The lack of cerebrovascular and cerebrometabolic effects suggests future studies on the use of argon which should confirm the safety of argon inhalation during longer periods and may investigate the organ protective effects of argon in humans.

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

Chapter 8 discusses the effects of antihypertensive therapy (methyldopa or methyldopa/nifedepine) in pre-eclamptic patients on CPPe, ZFP, and RAP. Pre-eclampsia complicates 3-5% of pregnancies and is a major cause of maternal and fetal morbidity and mortality.[67] The pathophysiology of cerebral impairment in preeclampsia is unclear, but studies conducted with TCD and MRI have shown an increased cerebral blood flow in women with preeclampsia.[68 69] Belfort et al. reported that women with severe preeclampsia have an increased effective cerebral perfusion pressure. (CPPe).[70] Increased CPPe has been suggested as a possible mechanism to induce a cerebral hyperperfusion syndrome and subsequent cerebrovascular complications in pre-eclamptic patients.

In the present study, all patients with pre-eclampsia were successfully treated following international and Dutch guidelines (target systolic blood pressure < 140 mmHg). Nevertheless, a significant correlation between blood pressure and CPPe in patients with pre-eclampsia was found, but not in controls. Pre-eclamptic women may have an increased cerebral perfusion due to a reduced ZFP and increased CPPe despite treatment with antihypertensive medication. More rigorous antihypertensive therapy, aimed at reducing CPPe, could result in a decrease in cerebral complications in pre-eclamptic patients. 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.

CONCLUSIONS

Based on results of the chapters 2 to 9 the following conclusions could be stated:

- It it possible and safe enough to estimate CPPe, ZFP and RAP with much simpler formula approaches like the CZO method or the LR3 method.
- Ensure perioperative homeostasis of patients at a level of preoperative baseline
  - Avoid hypotension below 65 mmHg, every minute counts.

  - o Ensure normotension (MAP >65 mmHg, or allow only a MAP reduction of 20% from baseline). Therapeutic interventions should be aimed primarily at the underlying causes, which may include hypovolemia or an impairment of cardiac pump function, or both, in addition to a decreased systemic vascular resistance.
- This thesis underlines the physiological model of effective perfusion pressure / zero flow pressure. Hypocapnia reduces cerebral blood volume and consequently decreases ICP. However, hypocapnia leads to a reduction of cerebral blood flow, Vmca, and increases net cerebral lactate efflux consistent with partial impairment of cerebral metabolism, as a consequence of an increase in ZFP and a reduced CPPe.
- Avoid any hyperventilation during the perioperative process unless clinically necessary for vital reasons. The threshold of markedly reduced CBF, decreased partial pressure of oxygen of the jugular-venous bulb, and increased net cerebral lactate efflux consistent with partial impairment of cerebral metabolism is about $PaCO_2$ 30 mmHg (4 kPa). Hyperventilation exaggerates any other vasoconstrictive drug effect.
- Halothane leads to only minimal changes in global CBF and V_{MCA} during hypocapnia as well as hypercapnia. The proportional decrease in cerebrovascular resistance and effective cerebral perfusion pressure was mainly related to reduction in mean arterial pressure. The cerebrovascular CO_2-reactivity remained unchanged, which is line with other volatile anesthetics.
- Argon has no effect on cerebral perfusion and metabolism. This result underlines the safety of Argon for a possible clinical application as a future organ-protective agent.
- In the past the goal of antihypertensive therapy in pre-eclampsia was mainly to reduce systolic blood pressure below 140 mmHg. The improved knowledge of the pathophysiology of pre-eclampsia may change the goals of therapeutic approaches towards an improved control of effective cerebral perfusion pressure.

FUTURE PERSPECTIVES

The WHO considers that in the ageing population, by 2030 chronic diseases will affect the lives of approximately 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.[74] A lot of our patients in the future will have disturbed cerebral autoregulation. There is thus a serious need for more research in the field in perioperative cerebrovascular pathophysiology, monitoring techniques and therapeutic strategies. In table 1 former investigations regarding the regulation of CPPe, ZFP, and RAP by carbon dioxide, volatile anesthetics, or vasoactive drugs are summarized.

The following questions will maintain the research process in this field:

- **Where and when in the cerebrovascular tree occurs the regulation of cerebrovascular tone and vessel diameter?**
  A combination of TCD / CPPe and magnetic resonance imaging might answer this question.
- **Does an optimized CPPe lead to improved cerebral oxygenation?**
  A combination of TCD / CPPe and mitochondrial oxygen tension measurements might answer this question.
- **Which vasoactive drug is most favorable in order to optimize CPPe and cerebral oxygenation?**
  Noradrenaline, phenylephrine and nitroglycerine could improve CPPe (Table 1). Which drug would be most favorable? A comparative trial might answer this question.

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