*If a job has to be done*
*the nature knows more than one way.*

Importance of the Effective Cerebral Perfusion Pressure

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ISBN: 978-94-6361-285-2

Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

**Importance Of The Effective Cerebral Perfusion Pressure**

Het belang van de effectieve cerebrale perfusiedruk

**Proefschrift**

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

vrijdag 05 juli 2019 om 13.30 uur

door

**Frank Grüne**
geboren te Bremen / Duitsland

**Erasmus University Rotterdam**

Erasmus

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**For my family.**

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# I

# 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.).[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

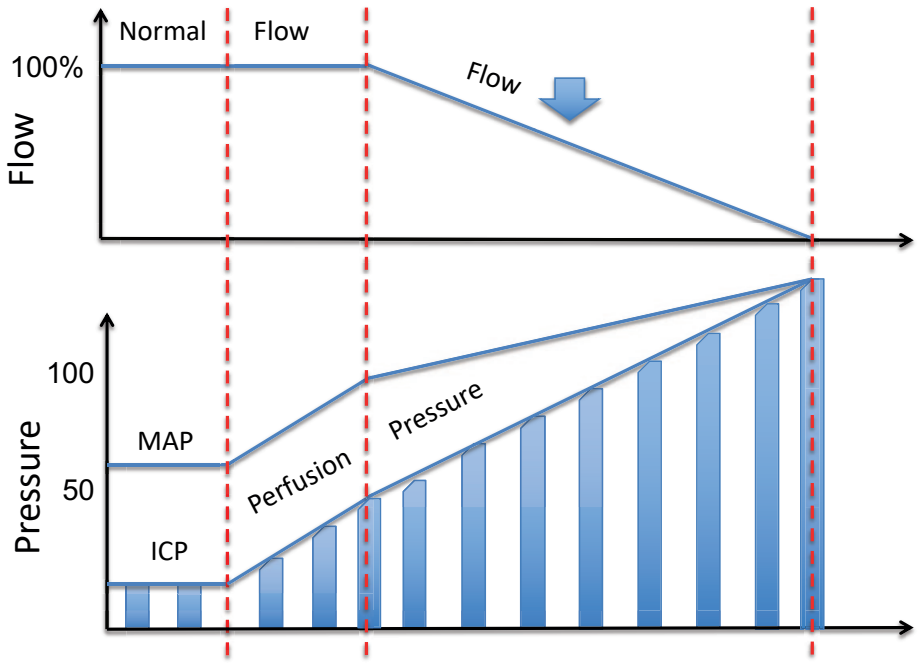


**Figure 1: Relationship between CBF, MAP and ICP (classical CPP model)**
The cerebral perfusion pressure (CPP) is commonly defined as difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP), 'classical model' CPP = MAP - ICP. Patients without cerebrovascular disease are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

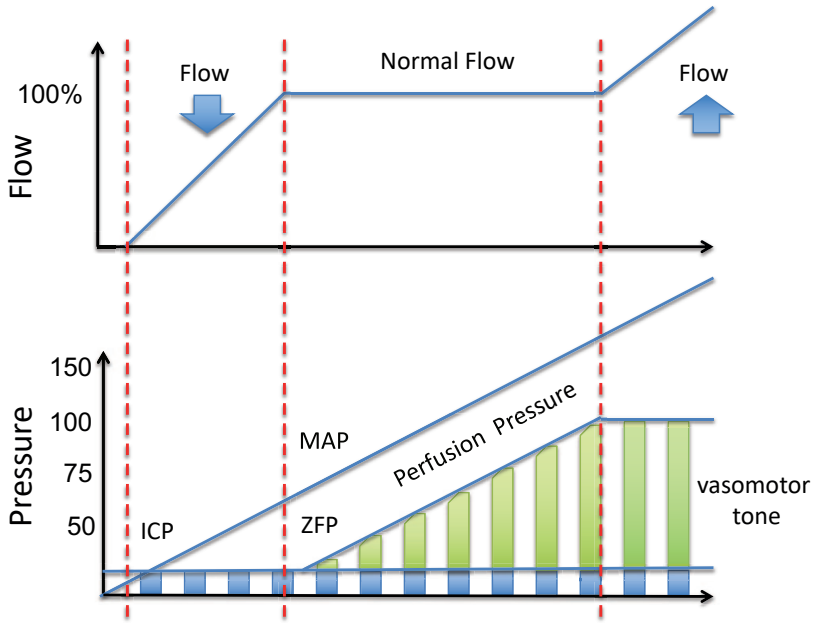


**Figure 2: Relationship between CBF, MAP and ZFP (CPPe model)**
Cerebral autoregulation maintains cerebral blood flow (CBF) relatively constant across a wide range of cerebral perfusion pressures (CPP). When pressure becomes excessively low, vascular bed resistance can no longer adjust to decreasing 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]

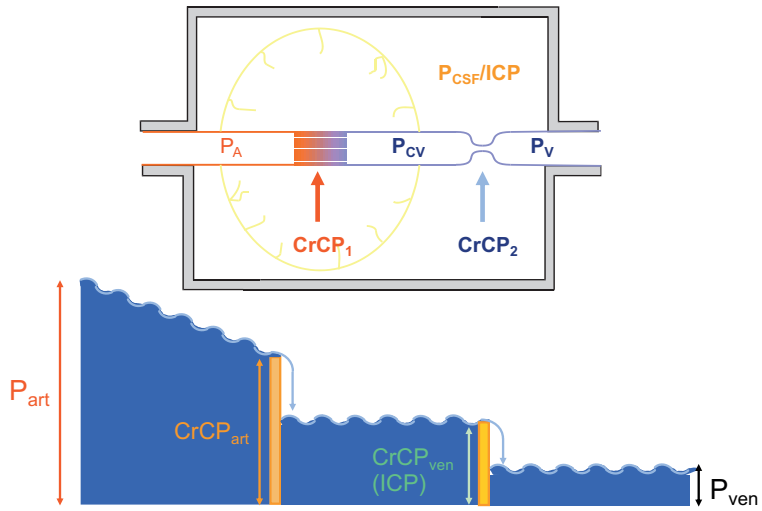


**Figure 3: Cerebral vascular waterfall of the circulation**
Hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels (CrCPart) and a second (distal) at the level of collapsible cerebral veins (CrCPven). The effective downstream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

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# Chapter 1

## Intraoperative hypotension – update on pathophysiology and clinical implications

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Anaesth Intensivmed 2013; 54:381-390
CME publication

Translated by Laura Perotto (MD) and Frank Grüne.

## SUMMARY

The incidence of intraoperative hypotension is high. An evidence-based definition of intraoperative hypotension, however, is still a matter of debate. Major risk factors include patient age, ASA physical status 3 or higher, blood loss, combination of regional and general anesthesia, duration of surgery, and emergency status. 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. Mean arterial pressure (MAP) seems more appropriate for intraoperative hemodynamic control than systolic arterial pressure (SAP), since pulse pressure and SAP are strongly dependent on stroke volume and arterial elastance. Because of physiological considerations and several observational studies a lower limit of 60 mm Hg is generally accepted in patients without risk factors. However, in patients with arterial hypertension the lower limit for hemodynamic intervention should be set at a relative decrease in MAP > 30 %. Similarly, impaired autoregulation, significant arterial stenosis and specific problems associated with intraoperative beach-chair position increase the lower limit of MAP which is necessary to ensure adequate organ blood flow. Several retrospective studies comprising large patient cohorts demonstrated that intraoperative hypotension is associated with increased 1-year mortality. A causal relationship, however, has not yet been verified. Treatment of intraoperative hypotension should not only rely on vasoactive agents to control decreased systemic vascular resistance, but should also focus on other reasons, which may include hypovolemia, redistribution of blood volume, and impaired myocardial performance.

**Keywords:** Hypotension, perfusion pressure, cerebral ischemia, myocardial ischemia

## INTRODUCTION

For decades, arterial blood pressure (ABP) has been an indispensable basic parameter in the perioperative monitoring of the cardiovascular system. This is because ABP is an easily quantifiable parameter of the circulatory system (according to Riva-Rocci, measured by oscillometrically or by using an electromechanical pressure transducer).

However, ABP is only an incomplete indicator of an adequate oxygen supply (oxygen-delivery,$DO_2$) as mean arterial pressure (MAP) depends not only on cardiac output (CO) - as the most important determinant of $DO_2$ - but also on systemic vascular resistance (SVR).

Recently increased attention has been brought to flow- and volume-related parameters of the systemic circulation, particularly in the case of perioperative optimization of high-risk patients and in critical care medicine, which allow a more direct assessment of cardiac function and $DO_2$. Nevertheless, ABP has a great physiological and clinical significance in various respects.

## PHYSIOLOGICAL ASPECTS

### Darcy's law

The relationship between perfusion pressure (PP), flow (Q) and resistance (R) is described by Darcy's law , representing an analogy to Ohm's law for liquids:

$$PP = R \cdot Q$$

For systemic perfusion pressure (MAP - CVP; CVP = central venous pressure), cardiac output (CO) and systemic vascular resistance (SVR) applies analogously

$$MAP - CVP = SVR \cdot CO / 80,$$

where the factor 80 results from the approximation of the dimensions (conversion of the pressure of mmHg in dyn $\cdot$ $cm^{-2}$, the conversion of CO of $L \cdot min^{-1}$ in $cm^3 \cdot sec^{-1}$. Disregarding the CVP then results in:

$$MAP \sim CO \cdot SVR$$
$$CO \sim MAP / SVR$$

The MAP is thus directly proportional to cardiac output (CO) and SVR. Conversely, cardiac output (at a given CVP) is then directly proportional to MAP and inversely proportional

to SVR. This relationship also applies analogously to the perfusion of individual organs and the respective regional vascular resistance.

*It has to be considered that flow, pressure and resistance are not independent variables but are linked through various physiological regulatory circuits.*

*Significance of arterial pressure for the organ perfusion*

*General*

MAP is the most important determinant of perfusion pressure and, in this respect, essential for organ perfusion. Organ specific reactive changes in vascular resistance can only provide limited compensation for fluctuations in MAP in order to keep blood flow constant:

"If each local tissue is to control its own blood flow by dilating and constricting its blood vessels, then it is essential that the arterial pressure be maintained at a pressure high enough to supply the blood demanded by the tissue" [1].

*Cerebral blood flow*

Due to the high oxidative metabolic activity, the resulting high $O_2$ demand and low ischemia tolerance, brain function is particularly dependent on adequate perfusion pressure (CPP; cerebral perfusion pressure). Under physiological conditions, the blood flow to the brain shows an effective autoregulation – cerebral blood flow is held constant within a MAP range of approximately 60 – 160 mmHg due to cerebral vasodilation and vasoconstriction.

A further reduction of the MAP may result in a shortfall below the critical cerebral $O_2$ supply with consecutive loss of function and structural neuronal damage. It should be noted that even though a sufficiently high cardiac output is an important requirement for the global $O_2$ supply, it does not guarantee an adequate organ perfusion due to limited regional autoregulation. Thus, a critical decrease in cerebral blood flow may occur due to a critical reduction of MAP even when the cardiac output is kept constant or even increased due to a greatly reduced peripheral resistance [2]. This is difficult to verify under clinical conditions, since a drop in a patient's MAP - due to changes in afterload amongst other things - is often coupled with changes in cardiac output. However, investigations during extracorporeal circulation clearly show that cerebral blood flow under cardiopulmonary bypass declines in parallel to MAP, even at a constant and sufficiently high cardiac output once a critical perfusion pressure has been undercut.

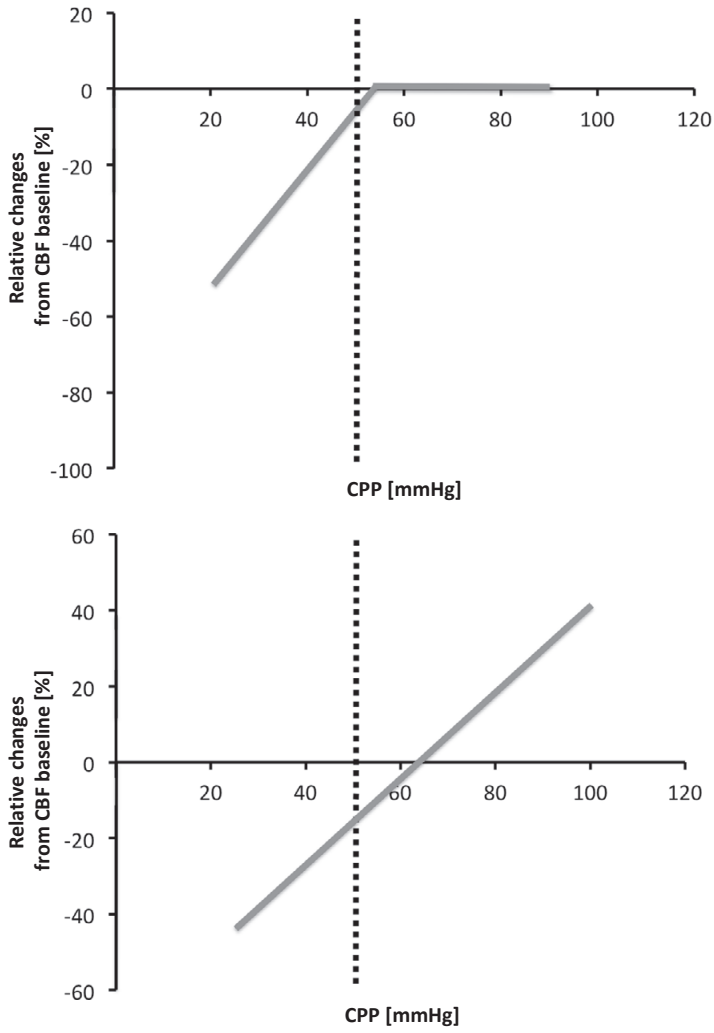


**Figure 1: Relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) with intact (above) and impaired autoregulation (below).**
The dotted vertical lines mark the lower border of the autoregulation. Modified from Lewis et al. 2001 [2].

*If MAP drops below 50 - 60 mmHg in healthy individuals, a steep drop in cerebral blood flow and a consecutive reduction in cerebral $O_2$ supply occurs, which can only be compensated within narrow limits by increased $O_2$ extraction.*

*Kidney perfusion*

An autoregulatory mechanism also exists for the perfusion of the kidney. In a healthy patient kidney perfusion and glomerular filtration is constant if the MAP ranges from about

60 – 150 mmHg. Renal blood flow is approximately 20% of cardiac output. The largest share thereof supplies the renal cortex, which is essentially required for ultrafiltration; only 10% of blood flow is necessary for metabolic needs. Due to the kidney's particular functional anatomy, hypoperfusion quickly leads to ischemic tubular damage.

*The kidney is the only organ with two capillary beds, the glomerular and peritubular capillaries, which are connected in series by intervening efferent arterioles. If there is a decrease in arterial pressure with depletion of autoregulation range, the Vasa efferentes contract significantly stronger than the Vasa afferentes, so that the peritubular vascular bed is particularly vulnerable to ischemia.*

*Coronary blood flow*

Sufficient perfusion is also required for sufficient coronary blood flow. Coronary perfusion pressure is, however, mainly determined by mean diastolic pressure (DAP; diastolic arterial pressure) in the aorta. When perfusion pressure drops, an autoregulatory decrease in coronary vascular resistance occurs, so that the myocardial perfusion remains constant under normal circumstances. However, there is a critical coronary perfusion pressure, below which there is an exhaustion of the coronary reserve and decrease in coronary blood flow.

*The critical perfusion pressure of the heart, unlike the autoregulation of cerebral and renal perfusion, will vary, depending on cardiac work and heart rate.*

### Importance of systolic arterial pressure

Systolic arterial pressure (SAP) is in contrast to MAP not only dependent on cardiac output and SVR, but largely on arterial elastance (EA) and stroke volume (SV). The arterial elastance in turn is determined through the interplay of impedance, compliance and resistance.

In older individuals, varying cardiac filling led to disproportionately greater changes in systolic arterial pressure as well as in changes of arterial pulse pressure (the difference between systolic and diastolic pressure) due to an increased vascular stiffening (EA) accompanied by increased ventricular stiffening (end systolic ventricular elastance, EES). These conditions should not divert attention from the importance of the MAP (or the mean DAP) for perfusion of the dependent organs [3].

*The progressive decrease in the compliance of the vascular system, in particular, occurring with age leads to a progressive widening in pulse pressure (the difference* between systolic and diastolic pressure).

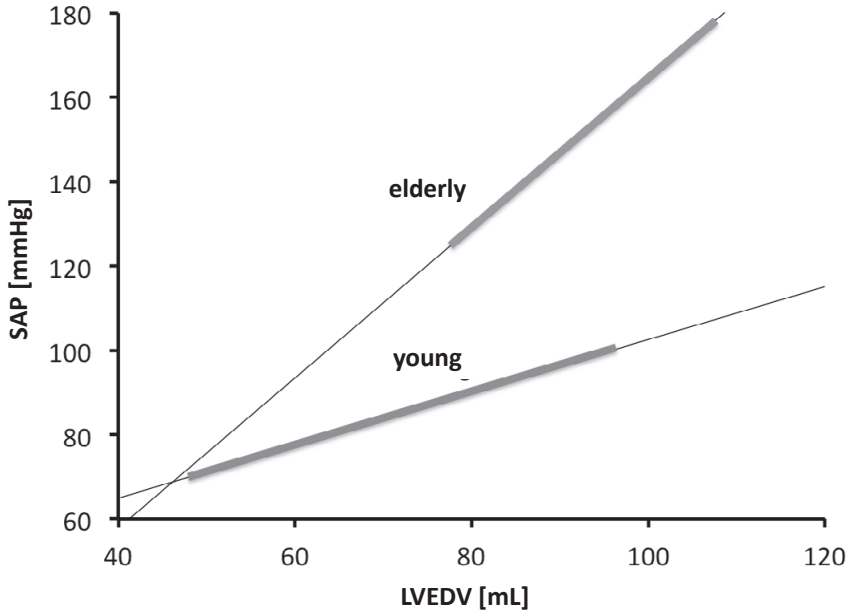


**Figure 2: Example of changes in systolic arterial pressure (SAP) to alterations in preload expressed as left ventricular diastolic volume (LVEDV) in a young and in an elderly patient.**
There is much greater sensitivity of systolic pressure to volume changes in the elderly patient, due to a reduced arterial compliance indicated by the steeper slope. Modified from Chen et al. 1998 [3].

## PATHOPHYSIOLOGICAL ASPECTS

### Impairment of autoregulatory mechanisms

The autoregulatory mechanism of the brain, in particular, can be affected by various acute and chronic disorders of homeostasis.

*In general, strong cerebral vasodilators significantly disturb the brain's ability to compensate for arterial pressure fluctuations and thus may lead to a pressure-passive decrease or increase in cerebral blood flow.*

Thus, a pronounced hypercapnia or hypoxia with consecutive cerebral vasodilation leads to a suppression of cerebral autoregulation [4]. In higher concentrations volatile anesthetics can also result in impaired autoregulation due to cerebral vasodilatation. Cerebral ischemia and severe traumatic brain injury are also accompanied by a disturbance of autoregulation, so that cerebral blood flow decreases passively with decreasing MAP relative to the perfusion pressure.

*Chronic hypertension shifts the autoregulation thresholds on the pressure-flow diagram to the right. This leads to the assumption that arterial blood pressure drops in patients with arterial hypertension cause a decrease in cerebral blood flow at blood pressure values that would be well compensated by a healthy individual.*

The kidney is also affected in patients with hypertension due to an analogous shift of the upper and lower limits of autoregulation.

**Importance of vascular and heart valve stenosis**

*Stenoses of the afferent vessels lead to a fall in perfusion pressure for the subsequent circulation of the organs depending on the degree of stenosis. As a consequence, despite normal systemic pressures the effective arterial pressure before the arterioles is already critically reduced and thus no longer reaches autoregulatory thresholds.*

As a result, even a small decrease of the MAP may lead to a critical reduction of organ perfusion and $O_2$ supply in affected patients. In the case of brain circulation, the extent of perfusion restriction depends greatly on the individual compensation by other brain supplying vessels due to the Circle of Willis.

*In an experimental coronary stenosis, as perfusion pressure decreases, the subendocardial blood flow decreases earlier than the subepicardial poststenotically. The subendocardial autoregulation range is therefore smaller than the subepicardial.*

Consequently, the subendocardial regions of the myocardium are mainly affected by a lack of $O_2$ supply at a low perfusion pressure. This is due to the fact that the intramyocardial pressures are higher there than in subepicardial areas and so the increased outflow pressure (see below) reduces the perfusion pressure additionally.

Patients with higher-grade aortic valve stenosis are particularly at risk in this context, as these patients are threatened in many ways by arterial hypotension.

*In the presence of an aortic valve stenosis, the SV is largely fixed by the impaired ejection of the left ventricle. Thus, a drop in the SVR cannot be compensated by an increase in cardiac output.*

The resulting decrease in arterial pressure leads to a critical reduction in coronary blood flow due to myocardial hypertrophy and the increased end-diastolic ventricular pressure - and by the consecutive impairment of ventricular function and further drop of the MAP to a vicious circle.

## Meaning of "downstream pressure"

The perfusion pressure in the systemic and regional blood circulation is calculated - as stated above - from the difference between the upstream prevailing arterial pressure (regularly the MAP) and the downstream prevailing (postcapillary) pressure, which is determined by the (central) venous pressure (classical physiological model). Since the CVP is much smaller in relation to the MAP, and also subject to less variation, the downstream prevailing pressure is often ignored in the estimating assessment of the perfusion pressure.

This however is not true for the brain circulation due to the specific anatomy of the cranial cavity and the compressibility of cerebral bridging veins. The CPP is therefore the difference between the MAP and the intracranial pressure (ICP), which exceeds the central venous outflow pressure already under normal circumstances. In cases of intracranial hypertension ICP becomes highly important. The effective downstream pressure (EDP) may even exceed the venous pressure in other organs under certain physiological and pathophysiological conditions, since a critical closing pressure (CCP) exists, determined by the vascular tone and the tissue pressure. Especially under pathological conditions (e.g. compartment syndrome, increased intra-abdominal pressure) it is to be considered that perfusion pressure is determined by the difference between the MAP and the EDP and therefore results in perfusion pressure being significantly lower in the case of hypotension than assumed in the simplified calculation using MAP and CVP.

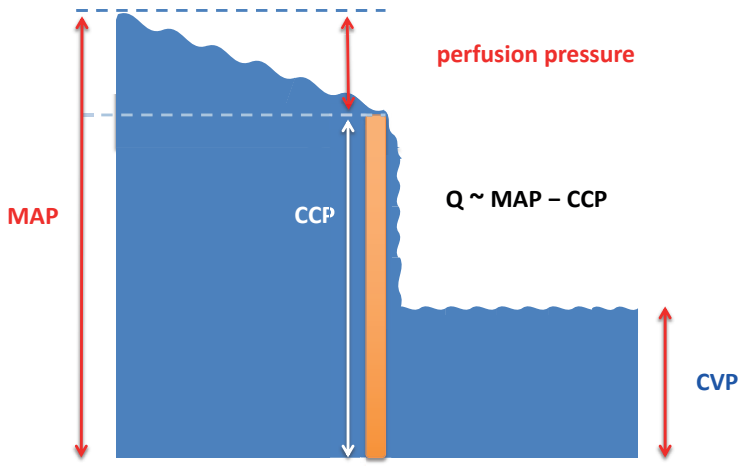


**Figure 3: Waterfall of the systemic circulation.**
MAP = mean arterial pressure; CCP = critical closing pressure; Q = blood flow; CVP = central venous pressure.

## CLINICAL ASPECTS

### Definition and incidence of intraoperative hypotension

*Intraoperative hypotension may occur due to various reasons. These include the type of anesthesia, the pathology of the disease and its indication for a surgical intervention, underlying comorbidities, pharmacological effects, intraoperative blood loss, and potential logistic and human errors in the perioperative patient care.*

The reported incidence in observational studies of intra- and perioperative hypotension varies greatly. This is not only due to different concepts of anesthesia and patient population, but also due to the very inconsistent and widely differing definitions of hypotension.

An analysis of 147,000 patients from the Swiss anesthesia database consisting of patients from 21 hospitals showed that despite predetermined definition (MAP reduction > 30% for > 10 min), a significant variability between the different hospitals in the incidence of hypotension exists, ranging between 0.6 and 5.2% [5]. Even greater was the influence of operational discipline, with a range from 0.3 to 12%, with the highest incidences in major thoracic-, vascular- and general surgery interventions.

A systematic literature search of Bijker et al. [6] analyzing 130 studies, showed the use of over 100 different, sometimes considerably varying definitions of hypotension. The most frequently used definitions entailed a systolic pressure <80 mm Hg, a relative decrease of the SAP by more than 20%, as well as a combination of SAP reduction <100mm Hg and a relative decline of the SAP by more than 30%. A study carried out following this literature review, applying these different definitions to the electronic anesthesia records of approximately 15,000 non-cardiac surgical patients, showed a variation in the incidence of 5 – 99% depending on the chosen definition. Very similar results were obtained in a systematic study of definitions of hypotension under spinal anesthesia. No definition of hypotension accepted by the majority could be identified in this study [7]. Even a survey conducted among members of the Society of Pediatric Anesthesia showed that no consensus on the definition of intraoperative hypotension in children could be reached [8].

The circadian fluctuations and the physiological decrease in arterial pressure during normal sleep complicate the definition of hypotension further [9]. Especially in elderly patients with atherosclerosis, a pronounced drop in habitual nightly MAP seems however to be associated with an increased cerebral ischemia risk [10].

## Risk factors and predictors of hypotension under general anesthesia

In a large observational study of more than 147,000 patients the following risk factors for intraoperative hypotension were identified [5]:

- Age (odds ratio / OR 6.6 at over 75 years compared to 18 - 25 years)
- ASA classification (OR 2.6 at ASA 4 compared to ASA 1)
- Combination of regional and general anesthesia (OR 1.7, compared to general anesthesia)
- Duration of the operation (OR 10.6 at > 6 h in comparison to short procedures of 15 min)

Although a significant correlation between emergency interventions and the occurrence of hypotension was detected, this relationship was surprisingly much less pronounced (OR 1.14) than with the above-mentioned factors [5]. A similar observational study in children [8] using multivariate logistic regression analyses showed that the risk of hypotension in pediatric patients under general anesthesia in the preoperative phase was increased significantly by the following factors:

- Pre-existing hypotension,
- ASA Risk group ≥ 3,
- Propofol induction and
- Age

*Antihypertensive premedication is also accompanied by an increase in the incidence of hypotension. However, on the morning of surgery the preoperative dose of diuretics and ACE (Angiotensin Converting Enzyme) inhibitors should be taken, if the medication is primarily for the treatment of heart insufficiency.*

## Overall impact on morbidity and mortality

Of crucial clinical importance for anesthetic care is the extent to which the incidence of hypotension is associated with an increase in perioperative complications and mortality. Monk et al. [11] demonstrated in a study of more than 1,000 non-cardiosurgical patients that cardiovascular comorbidity and especially the occurrence and duration of intraoperative hypotension are a significant (independent) predictors of one-year mortality after surgery under general anesthesia. Thus, a 10-minute hypotension (MAP <55 mm Hg, SAP <80 mm Hg) was already associated with an approximately 1.4-fold higher risk of mortality. Although this relationship between the duration of intraoperative hypotension and the one-year mortality could not be globally confirmed in a recent cohort study, a mortality increase in elderly patients in the event of prolonged hypotension was still observed [12]. The retrospective analysis of 147,000 patients from the Swiss anesthesia database was also able to demonstrate a strong correlation between the occurrence of intraoperative hypotension and perioperative mortality [5]. In particular, a combination

of intraoperative hypotension, low Bispectral Index (BIS) and a low volatile anesthesia concentration (presumably as an expression of a low anesthesia demand) seems to be associated with increased mortality [13].

*All abovementioned observational studies have in common that a causal relationship between the occurrence of hypotension and the observed mortality increase ultimately cannot be proven. Despite correction of the data for other risk factors, it cannot be excluded that intraoperative hypotension is not the direct cause but merely an indicator of an increased perioperative risk, caused by various other factors.*

Unsettling in this context, however, is that a large retrospective study of over 17,000 patients showed that early intervention with a vasopressor could reduce mortality risk almost entirely to the level of non-hypotensive patients. Thus suggesting, at least in the context of deep anesthesia and a low anesthetic concentration ("triple low"), a causal relationship [14].

In contrast, in a randomized prospective study on the effect of permissive hypotension during epidural anesthesia in 253 elderly patients no effect could be detected for either the postoperative complication rate, nor the mortality associated with the intraoperative hypotension (MAP 45 - 55 mmHg) [15]. To what extent the results of this study are specific to the performance of regional anesthesia, is - not least due to the limited number of patients - unclear. Especially, since some of the above-mentioned observational studies also included patients under regional anesthesia.

An indirect relationship between perioperative hypotension and the occurrence of cerebral ischemia can be postulated from the results of the POISE study [16] on the effect of high-dose perioperative beta-blockade. In the group of patients treated with metoprolol, increased mortality and increased incidence of stroke was associated with a significantly higher incidence of hypotensive episodes amongst other things. However, a direct causal relationship cannot be deduced because of the study design due to the complex pathophysiological processes in the context of perioperative myocardial and cerebral infarctions.

## Influence of intraoperative positioning

*Neurological risks*

*With regard to the incidence and consequences of intraoperative hypotension, elevated positioning of the upper body due to operative conditions becomes of particular importance in several respects.*

There were reports on cases of severe cerebral ischemia, vision loss and cases of dissociated brain death after surgery in the sitting (beach chair) position during shoulder surgery [17, 18]. This is all the more alarming as severe neurological damage also occurred in younger patients without increased cerebrovascular risk.

Possible causes include a critical reduction in cerebral blood flow due to inadequate perfusion pressure or compression of brain-supplying vessels by hyperextension and / or rotation of the cervical spine. Recent studies on changes in regional cerebral $O_2$ saturation ($rSO_2$) using near-infrared spectroscopy (NIRS) could show that a semi-sitting position under general anesthesia goes along with a significant reduction of $rSO_2$ as a sign of impaired equilibrium between cerebral $O_2$ supply and $O_2$ requirements [19, 20]. In a prospective study of orthopedic patients in 80% of the cases, a relative decrease of $rSO_2$ by more than 20% occurred [21]. Analogously Doppler-sonographic examinations in the beach chair position showed, a significant reduction of cerebral blood flow velocity as a sign of decreased cerebral blood flow [21]. All these changes were accompanied by simultaneous impairments of MAP and imply a failure to reach cerebral autoregulation threshold.

*Hemodynamic particularities*

Various reasons are responsible for the often pronounced hypotension occurring in a sitting position. A major cause is the redistribution of blood volume from central to peripheral compartments with subsequent decrease of cardiac preload. This was evident when repositioning the patient into an upright position under general anesthesia, causing a decrease of intrathoracic blood volume by 15%, which resulted in a decrease of the cardiac index from 2.4 to 1.8 L/min/$m^2$ body surface area [22]. Furthermore, due to the orthostatic effects the influence of antihypertensive medication under general anesthesia is heightened [23]. During shoulder arthroscopic surgery, permissive hypotension is often specifically requested due to the improved overview [24].

The MAP in an upright / seated position is of central importance, since the influence of the hydrostatic pressure gradient between the cerebral flow path and the heart in terms of its impact on the CPP is not fully understood and is scientifically highly controversial. Essentially there are two competing hypotheses regarding the hemodynamic effects of the hydrostatic pressure difference:

- The *"siphon hypothesis"* is based on a continuous closed tube system. This leads to the fact that the effects of the hydrostatic pressure in the afferent (arterial) side are irrelevant, as they are acting in the same way on the efferent (venous) side and thus cancelling themselves out with respect to the resulting perfusion pressure. This model is comparable to a running infusion. The infusion line is raised in a loop above the level of the infusion bag, which is known to have no effect on the flow rate, as long as the outlet of the infusion line is well below the liquid level. In terms of the

practical impact, this hypothesis implies that the measured values of arterial pressure at heart level when sitting are also valid for the CPP without having to correct the non-invasively measured pressure or having to reposition the pressure sensor in invasive measurements at skull base level [25].

- The *"waterfall hypothesis"*, on the other hand, assumes a functional discontinuity in the arteriovenous vascular system. For example, as a result of Starling's resistance and the related critical vascular closing pressure [26,27], through compression of the vessels from the outside or from serious stenoses [28]. The clinical consequences of this theory imply that the non-invasively measured arterial pressure must be corrected with respect to the hydrostatic effects or rather that the pressure transducer in invasive measurements of arterial pressure must be positioned at the height of the outer ear canal to determine a functionally relevant perfusion pressure. Although an assumed hydrostatic pressure difference of approximately 20 mmHg at normal MAP seems to be of little relevance, when measured at heart level a MAP of 55 mmHg can already be critically reduced to a CPP of 35 mmHg even when neglecting a relevant outflow pressure.

Regardless of the increasing evidence of the "waterfall" hypothesis [29], due to the existing case reports of severe neurological damage in cerebrovascular healthy patients and because of the hemodynamic consequences, the following procedure is to be recommended:

*In a sitting / half-sitting position the measured MAP is to be corrected by the hydrostatic pressure difference between the atrial level and the skull base. In addition, it should be ensured that this corrected value does not fall below the lower threshold of cerebral autoregulation.*

## PRACTICAL CONSEQUENCES AND RECOMMENDATIONS

Based on the present retrospective and prospective studies there still does not exist an evidence-based recommendation when to intervene in the case of intraoperative hypotension, despite the immense clinical importance. This fact is the cause of the greatly differing definitions of hypotension in clinical trials. The definitions most commonly used - presumably for historical reasons and aspects of practicality - refer to the SAP. Nonetheless, it is generally recommended for physiological reasons and because of the strong dependency of pulse pressure on age to use the MAP as a target parameter instead.

*For patients with no specific risk factors a MAP <60 mmHg is recommended instead of the commonly used SAP-limit <80 mm Hg as the lowest intervention limit. Especially for patients with hypertension, higher intervention limits apply, where a MAP drop > 30% applies as a relative threshold.*



Apart from the question of causality, recent analyses of large patient populations showed that the statistical association between the occurrence of intraoperative hypotension and postoperative mortality significantly depend on the duration and extent of hypotension [12] (Figure 4).

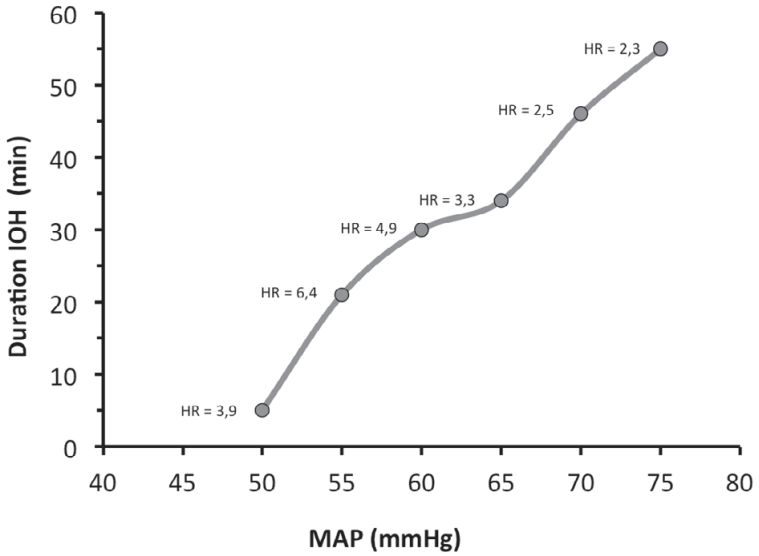


**Figure 4: Relationship between arterial blood pressure and duration of an intraoperative hypotension.**

Modified from Bijker et al. 2009 [12]. IOH = intraoperative Hypotension, HR = Hazard ratio, MAP = mean arterial blood pressure

*If prolonged hypotension occurs, greater intervention limits for the MAP must be adhered to than when there is a momentary drop in blood pressure.*

Since the perfusion pressure is calculated by the difference between MAP and the downstream pressure, the limits are only valid for a non-pathologically elevated ICP or for a normal venous outflow pressure. Further, in the case of hemodynamically significant stenoses, as well as in impaired cerebral or renal autoregulation, higher limits must also be applied.

*All therapeutic interventions, in terms of treatment of intraoperative hypotension, should counteract the cause of arterial pressure drop as directly as possible.*

Therefore one must primarily determine whether the hypotension is due to a predominant drop in SVR or due to a pathological decrease in cardiac output. In case of insufficient cardiac output it is important to distinguish to which extent the hemodynamic impairment is caused by hypovolemia (with subsequent decrease in pre-load) or by an impairment of contractility.

*Regardless of specific pre-existing medical conditions (e.g. severely impaired heart pumping function) or procedure-related disorders in hemodynamics (e.g. blood loss, obstruction of venous return), general anesthesia has an effect on all relevant hemodynamic variables and to varying degrees simultaneously - the SVR, the preload and the pumping function of the heart are all affected.*

In summary, it should be noted:

- The MAP is essentially determined by the product of cardiac output and SVR. The cardiac output in turn depends on heart rate, preload, afterload and inotropy. All of these variables can affect the MAP.
- The perfusion pressure of an organ is calculated from the difference between the upstream prevailing (arterial) and the downstream prevailing (mostly venous) pressure.
- There is a critical closing pressure of the circulation, which may determine the downstream pressure in place of CVP under certain conditions, depending on the ambient pressure (e.g. the ICP) and the vascular tone.
- Autoregulatory blood supply to the brain, kidneys and myocardium are dependent on perfusion pressure.
- Disturbances of autoregulation, pre-existing hypertension and relevant stenoses move the MAP threshold required for adequate organ perfusion upwards.
- There is no universally accepted definition of intraoperative hypotension. The MAP is more suitable than the SAP 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% is already determined as a limit.
- The incidence of intraoperative hypotension is high. The most important risk factors for intraoperative hypotension include the patient's age, the ASA status, the combination of general and regional anesthesia, the duration and the indication for an emergency surgery.

- Several retrospective studies on very large patient populations suggest a correlation between the occurrence of intraoperative hypotension and postoperative one-year mortality. However, direct causality cannot be established on the basis of the data.
- A sedentary or semi-sitting position (beach chair position) under general anesthesia requires special attention in many ways. Particularly due to recent case reports of severe and catastrophic neurological damage and due to prospective studies that point to a frequent impairment of cerebral blood flow. Due to the lack of conclusive evidence, and in light of the above described, it is currently recommended that the non-invasively measured MAP should be corrected by the hydrostatic pressure difference between the outer ear canal and atrial level or to position an arterial pressure transducer on skull base level. This allows the cerebral perfusion pressure to be set above the lower autoregulation limit with sufficient certainty.
- Treatment of intraoperative hypotension should not be done by means of indiscriminate use of vasoconstrictors. Interventions should be aimed primarily at the underlying causes, which may include hypervolemia and / or an impairment of cardiac pump function in addition to a decreased SVR.

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# Chapter 2

## Effective cerebral perfusion pressure: does the estimation method make a difference?

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J Neurosurg Anaesth 2019 (accepted)

## ABSTRACT

**Introduction:** The effective cerebral perfusion pressure (CPPe), zero-flow pressure (ZFP), and the resistance area product (RAP) are important determinants of cerebral blood flow. ZFP and RAP are estimated by linear regression analysis of pressure–velocity relationships of the middle cerebral artery. Aim of the study was to validate four other estimation methods against the linear regression method.

**Methods**: In a former study, recordings of EEG, blood pressure and mean cerebral artery velocity (transcranial Doppler) were obtained in patients, during internal cardioverter defibrillator implantation procedures in order to determine EEG frequency ranges that represent ischemic changes during periods of circulatory arrest. In this secondary analysis CPPe, ZFP and RAP estimated by four different methods, the 3-point intercept calculation (LR3, systolic/mean/diastolic), Czosnyka (CZO, systolic/diastolic), Belford (BEL, mean/diastolic), and Schmidt (SCH, systolic/diastolic) were validated against the reference method (LR, linear regression). CPPe is calculated as the difference between mean arterial pressure and ZFP. Primary endpoint was difference, correlation, and agreement of these CPPe measurements.

**Results**: In total, 174 measurements in 35 patients under steady state conditions during general anesthesia before the first cardiac arrest phase were collected. CPPe ZFP and RAP measurements based on LR3 and CZO calculation methods showed small mean differences, good agreement, low percentage errors, and an excellent correlation when compared to references method. Agreement and correlation were moderate for the BEL method, and unsatisfying for the SCH method.

**Conclusions:** CPPe, ZFP, and RAP measurements based on LR3 and CZO calculation methods are comparable to the LR reference method.


**Keywords:** Transcranial Doppler sonography, Cerebral circulation, Zero-flow pressure, Critical closing pressure, Cerebral perfusion pressure, Resistance area product, Agreement

## INTRODUCTION

Knowledge of the cerebral perfusion pressure (CPP) and its components are important in understanding and treating patients with intracranial pathologies in the perioperative period. When calculating the CPP, the mean arterial pressure (MAP) has been used as effective upstream pressure and the intracranial pressure (ICP) as effective downstream pressure of the cerebral circulation, because of a Starling resistor phenomenon located at the level of cerebral veins ('classical model' CPPi=MAP-ICP).[1] However, the "classical model" has limitations, because it assumes that cerebral blood flow or blood flow velocity only reach zero when the arterial blood pressure is zero, which is unlikely. Using solely intracranial pressure as a measure of the effective downstream pressure of the brain, would neglect vascular tone properties of the vessels.[2 3]



In vivo pressure-flow relationships per cardiac cycles 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 vasomotor tone.[2 4-6] The inverse slope of the pressure-flow plot represents vascular bed resistance.[6] 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).[3 7] Assessment of ZFP may help to evaluate cerebral vascular reserve, indicating the degree of vasomotor tone. If tone is low this would suggest maximal vasodilation and indicate that the patient may not tolerate anemia or hypotension.

Since the introduction of transcranial Doppler sonography, a number of methods have been developed to assess cerebral ZFP, CPPe, and vascular resistance by pressure-velocity relationships (figure 1).[7-11] The "resistance area product (RAP)", a Doppler ultrasound index, characterizes vascular resistance according to the inverse slope of the linear pressure-velocity relationship.[12] Deciding which method is the most appropriate for ZFP, RAP and CPPe measurements is still challenging.

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 this study electroencephalogram (EEG), transcranial Doppler sonography (Vmca) and invasive arterial blood pressure was continuously measured under general anesthesia.[13] In a secondary analysis we estimated CPPe, ZFP, and RAP by four different methods[10 11 14 15] and validated them against the reference method (LR, linear regression).[7 16] We hypothesized that estimation based on three points (systolic, mean, and diastolic) is superior to a two-point estimation method (systolic/diastolic or mean/diastolic) when compared to regression analysis of the whole wave tracings (reference method).

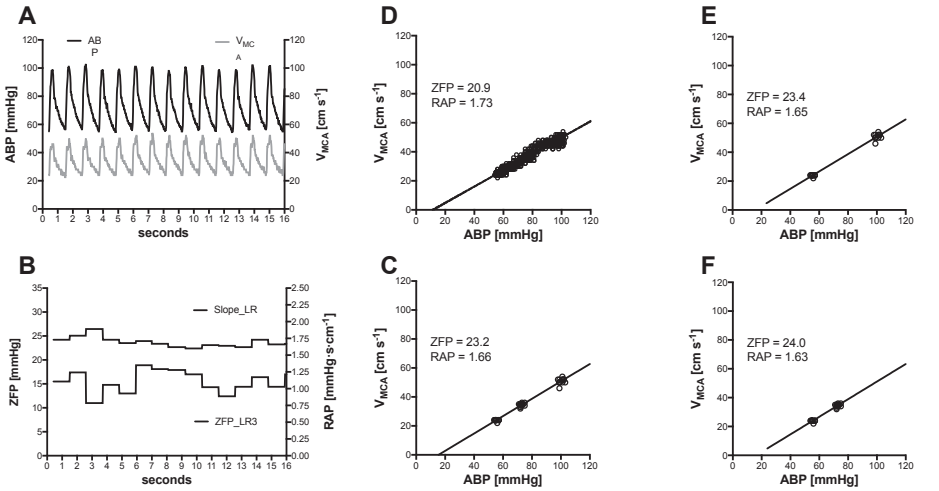



**Figure 1. Estimation of cerebral zero flow pressure (ZFP) and resistance area product (RAP).**
Arterial blood pressure (ABP) and velocity of the mean cerebral artery (Vmca) are usually graphically plotted against time (A). The time delay between the two waveforms has been synchronized before ZFP estimation. The zero-flow pressure (ZFP), the pressure when flow ceases, can be extrapolated by linear regression of the instantaneous pairs of the pressure-flow (velocity) relationship, which represents vasomotor tone while its inverse slope (RAP) represents the value of vascular bed resistance (C). The beat-to-beat values of ZFP and RAP provide an indication of the short-term variability of these estimates. Therefore, many research groups use multiple cardiac cycles (i.e. 10-12 heartbeats within two breaths) to determine the ZFP and RAP. The $ZFP_{LR3}$ was estimated by x-axis intercept determination from the linear regression line based on corresponding data pairs of systolic, mean and diastolic values of ABP (abscissa) and Vmca (ordinate, panel D). Other methods use a formula to calculate ZFP, which is based on the slope-intercept form. With corresponding pairs of systolic/diastolic ($ZFP_{CZO}$, $ZFP_{SCH}$, panel E) or mean/diastolic ($ZFP_{BEL}$ panel F) values of blood pressures and MCA velocity of the same time period it is also possible to calculate the intercept pressure at zero flow.

## METHODS

### Design

In a former study, recordings of EEG, arterial blood pressure and mean cerebral artery velocity (transcranial Doppler) were obtained in patients, during the whole internal cardioverter defibrillator implantation procedure in order to determine EEG frequency ranges that represent ischemic changes during short periods of circulatory arrest. Patients were eligible for inclusion if scheduled for ICD implantation or replacement. Exclusion criteria were patient refusal, active neurological disease, and a history of cerebrovascular disease, brain injury, or intracranial surgery. All patients were informed of the purpose of the study and provided written informed consent before being enrolled. The Medical Ethical Committee of the University of Utrecht provided ethical approval for the original study (Nr.:92/59). The study project followed the recommendations of the

Declarations of Helsinki and the European Union Commission and European Medicines Agency.[13] The trial was planned and done before CONSORT 2010. Dutch laws did not require international registration of this type of clinical trial at that time.

This report is a secondary analysis of the former recordings of arterial blood pressure and mean cerebral artery velocity in the phase before the induction of cardiac arrest by ventricular fibrillation. We estimated CPPe, ZFP, and RAP by four different methods and validated them against the reference method.



### Endpoints

The main endpoint of this investigation was the CPPe based on five different ZFP estimations methods (CPPe=MAP–ZFP). The ZFP and RAP were estimated by five different methods: (1) the 3-point intercept estimation (LR3), (2) Czosnyka (CZO, 2 point systolic/diastolic)[10], (3) Belford (BEL, 2 point mean/diastolic)[14], and (4) Schmidt (SCH, 2 point systolic/diastolic)[11 15], which were validated against the (5) reference method (LR, linear regression).[7 16]

### Anesthesia Procedure

Anesthesia was standardized to reduce the variance in measurements. Patients were premedicated orally with 2.5 mg lorazepam 2 hours before arrival in the operating theatre. Anesthesia was induced by intravenous administration of 4 µg/kg fentanyl, 0.1 mg/kg midazolam 0.1-0.2 mg/kg etomidate, and 0.07 mg/kg pancuronium. Anesthesia was maintained with 7-10 µg/kg/h of fentanyl and 150 µg/kg/h of midazolam. All patients received an endotracheal tube, a nasogastric tube, a urine catheter, a peripheral intravenous line, an arterial catheter, a Swan-Ganz catheter, and a central venous catheter. For jugular venous bulb oximetry measurements, a fiberoptic catheter was inserted retrogradely into the right internal jugular vein. Positioning of the tip of the catheter into the jugular bulb was confirmed by fluoroscopy. Ventilation was performed with a mixture of oxygen in air ($FIO_2$ 0.35). Steady state end-tidal partial pressure of carbon dioxide was kept normal between 30 and 43 mmHg (4.0 and 5.6 kPa). Nasopharyngeal temperature was maintained between 35.5°C and 37.0°C.

### Study protocol & measurements

All measurements were performed during hemodynamic and respiratory steady-state conditions by the same neurophysiological research team.

Arterial blood pressure (ABP) was monitored via a cannula placed in the radial artery with the transducer positioned at the level of the base of the skull/ear. Cerebral blood flow velocity in both middle cerebral arteries (Vmca) was monitored with transcranial Doppler sonography device (DWL multidop-X device with two 2-MHz pulsed Doppler probes, DWL TCD 7 software, DWL Elektronische Systeme GmbH, Sipplingen, Germany).

All patients were positioned supine on an operation table. The patient's heads were positioned and fixed *in-line* in midline position on a pillow. The ultrasound transducer was placed over the temporal area just above the zygomatic arch and in front of the tragus of the ear. After identification of the middle cerebral artery, the depth of insonation was adjusted in 1-2 mm increments to obtain signals from the proximal segment (M1) of the MCA. Accurate care was taken to ensure a stable position of the ultrasound probe during the study period. The ultrasound probe was therefore fixed using a monitoring probe holder attached to the patient's head (DWL, Sipplingen, Germany). Doppler ultrasound variables such as depth, gain, sample volume, and power of the ultrasound beam were unchanged during the measurement procedure. At each measurement, simultaneous data recordings of Vmca, arterial blood pressure (ABP, mmHg), expiratory concentration carbon dioxide concentration ($PeCO_2$, mmHg), and jugular venous bulb oxygen saturation ($SjO_2$, %) were acquired and stored on a microcomputer via analogue/digital converters.

**Estimation of the ZFP by pressure-flow velocity plot analysis.**

The analyses of the ZFP, CPPe and RAP have been performed after the study period. For the secondary analyses, we looked at the period after induction of anesthesia and before ICD-testing. We extracted five consecutive data sets of 10-12 seconds (two breaths) each within 3 min from the raw data files of the primary investigation.

For the CPPe/ZFP analysis we used dedicated custom-developed software (LabView®, USA, written by Dr. E.G. Mik, Erasmus MC). After visual inspection of the pressure curves and the velocity waveforms, we used corresponding pairs of ABP (abscissa) and Vmca (ordinate, figure 1 C) curves from 2 breathing cycles, (10-12 cardiac cycles) to determine ZFP and RAP. Hysteresis in the pressure-flow velocity plots because of a time delay between pressure and flow velocity recordings was minimized for each heartbeat by synchronizing the point of maximal positive slope of both waveforms. ZFP and RAP were calculated for every heart cycle by regression analysis of the pressure-flow velocity plot. Extrapolated ZFP and RAP data of all heart beats within these respiratory cycles were averaged for further analysis.[7 16] For a detailed description we refer to appendix 1 in the supplemental information content section.

The $ZFP_{LR3}$ was estimated by x-axis intercept determination from the linear regression line based on corresponding data pairs of systolic, mean and diastolic values of ABP (abscissa) and Vmca (ordinate, figure 1 D). The other methods primarily use formulas to calculate ZFP. With diastolic, mean or systolic values of blood pressures and flow-velocity from the same time period it is possible to calculate the intercept pressure at zero flow. All formulas used in this investigation had been suggested by Belfort and colleagues[14], Czosnyka and colleagues[10] and Schmidt and colleagues[11 15] (see table 1). For a detailed description of the mathematical basis of the calculation methods we refer to appendix 1 and 2 in the Supplemental Digital Content (SDC) section.

**Table 1. ZFP estimation by formulas**

| | |
|---|---|
| Belfort[19] | $ZFP_{BEL} = MAP - Vm \cdot \frac{(MAP - DAP)}{(Vm - Vd)}$ |
| Czosnyka[15] | $ZFP_{CZO} = SAP - Vs \cdot \frac{(SAP - DAP)}{(Vs - Vd)}$ |
| Schmidt[16 20] | $ZFP_{SCH} = MAP - (MAP \cdot \frac{Vd}{Vm} + 14)$ |

The effective zero flow pressure (ZFP) estimated by different methods: Belford (BEL, 2-point: mean/diastolic), Czosnyka (CZO, 2-point: systolic/diastolic), and Schmidt (SCH, 2-point: systolic/diastolic). DAP, MAP, SAP = diastolic, mean, and systolic arterial pressure, Vd, Vm, Vs = diastolic, mean, and systolic blood flow velocity. One CPPe measurement corresponds to the cumulative analysis of 10-12 cardiac cycles within two breaths. 174 measurements were performed on 35 cardiovascular patients (5 each per patient) under general anesthesia and normocapnia



When using transcranial Doppler sonography, an estimate of vascular resistance has been defined as the inverse slope of a linear regression line of the driving blood pressure and flow velocity, the resistance area product (RAP).[6 12] Subsequently, we calculated the RAP as: RAP=(MAP–ZFP)/mean Vmca. The CPPe of all methods was calculated from the difference between MAP and the respective ZFP. For a detailed description of the CPPe model we refer to appendix 1 in the Supplemental Digital Content (SDC) section.

## Statistical analysis

This analysis was based on the recommendation of current guidelines for reporting agreement studies.[17 18] In this secondary analysis study setting a prior sample size calculation could not be applied.[13] Each patient served as his own control.

Normal distribution of data was assessed both visually by inspection of histograms and with the D'Agostino-Pearson omnibus K2 method.[19] Results are presented as mean values (standard deviation, SD) unless otherwise stated. Four methods of CPPe, ZFP and RAP estimation (LR3, BEL, CZO SCH) were compared to the reference method (LR) by ANOVA with correction for multiple comparison (Dunnett). The relationship between the four methods of CPPe, ZFP and RAP estimation (LR3, BEL, CZO SCH) and the reference method (LR) was examined by regression analysis and by using Pearson's or Spearman correlation tests, depending on data distribution.

To evaluate the *accuracy* (*i.e.* the closeness of ZFP, RAP or CPPe measurements to its reference value) of the $ZFP_{LR}$ versus $ZFP_{LR3}$, $ZFP_{BEL}$, $ZFP_{CZO}$, and $ZF_{SCH}$ we described the *agreement* between these paired data using the Bland-Altman analysis with correction for multiple measurements per subject.[20] The *bias* (mean difference between the reference and test-method) represents the systematic error between the two methods. As a measure of *precision* (*i.e.* the distribution of repeated measurements), the limits of agreement (LoA) were commonly calculated as bias +/-1.96 SD, defining the range in which 95% of the differences between the methods are expected to lie.[21] In this analysis

we used the LoA calculation approach with correction for multiple measurements per subject.[20]

Subsequently, the percentage error (PE) was calculated as 1.96*SD of the bias of the tested method divided by the mean value of the tested and the reference method.[21] To the best of our knowledge, an acceptable PE and acceptable agreement for ZFP, RAP and CPPe measurements have not yet been described. A precision (LoA) of less than 10mmHg for a CPPe of around 60mmHg could be clinically acceptable.

All statistical analyses were performed two-sided, and a P value of less than 0.05 was considered to be significant. Database sheets were created with MS Excel for Mac2011 (Microsoft Corp, USA). Statistical analysis and graphs were executed using Prism7.0 (GraphPad Software, USA).

## RESULTS

### Eligibility

Over a period of 17 months (02-08-1994 until 9-12-1995), 56 consecutive cardiovascular patients were scheduled for implantation (n=32) or replacement (n=24) of an ICD.[13] Out of these 56 patients we excluded 19 patients for secondary analysis. One patient had an insufficient arterial pressure curve. 17 patients had a no or a very small acoustic window for transcranial Doppler sonography examinations, insufficient to use for pressure-flow velocity relationship analysis.

37 patients were eligible for secondary analysis. One patient had a labile arterial blood pressure, another patient showed atrial fibrillation. Both datasets were insufficient to use for pressure-flow velocity relationship analysis (two outliers). During the period of measurements, we obtained five data sets for each patient. In one patient, we could obtain only four measurements; one measurement has been excluded due to supraventricular extra-systolic beats. Secondary analysis was thus performed in 35 patients with 174 measurements (Figure 2: STROBE flow chart of participants).

### Patients

The group consisted of 6 women and 29 men with a median age of 50 years (range, 15-73 years). The underlying cardiac diseases were: ischemic heart disease in 14 patients, primary electrical heart disease in 13 patients, and cardiomyopathy in 7 patients; 1 patient received an ICD for other reasons. Left ventricular pump function was normal in 14 patients, moderately reduced in 13 patients, and severely reduced in 7 patients. Arterial hypertension was treated in 8 patients. In 25 patients, the ICD was placed for the first time; in 10 patients, the ICD was replaced.

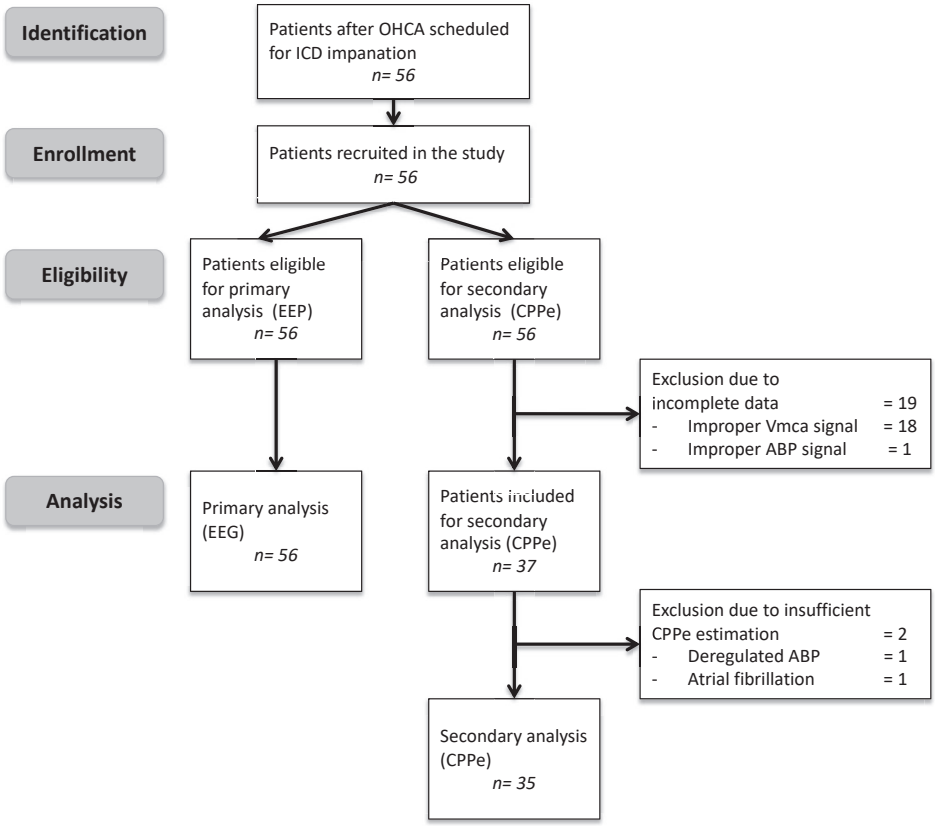


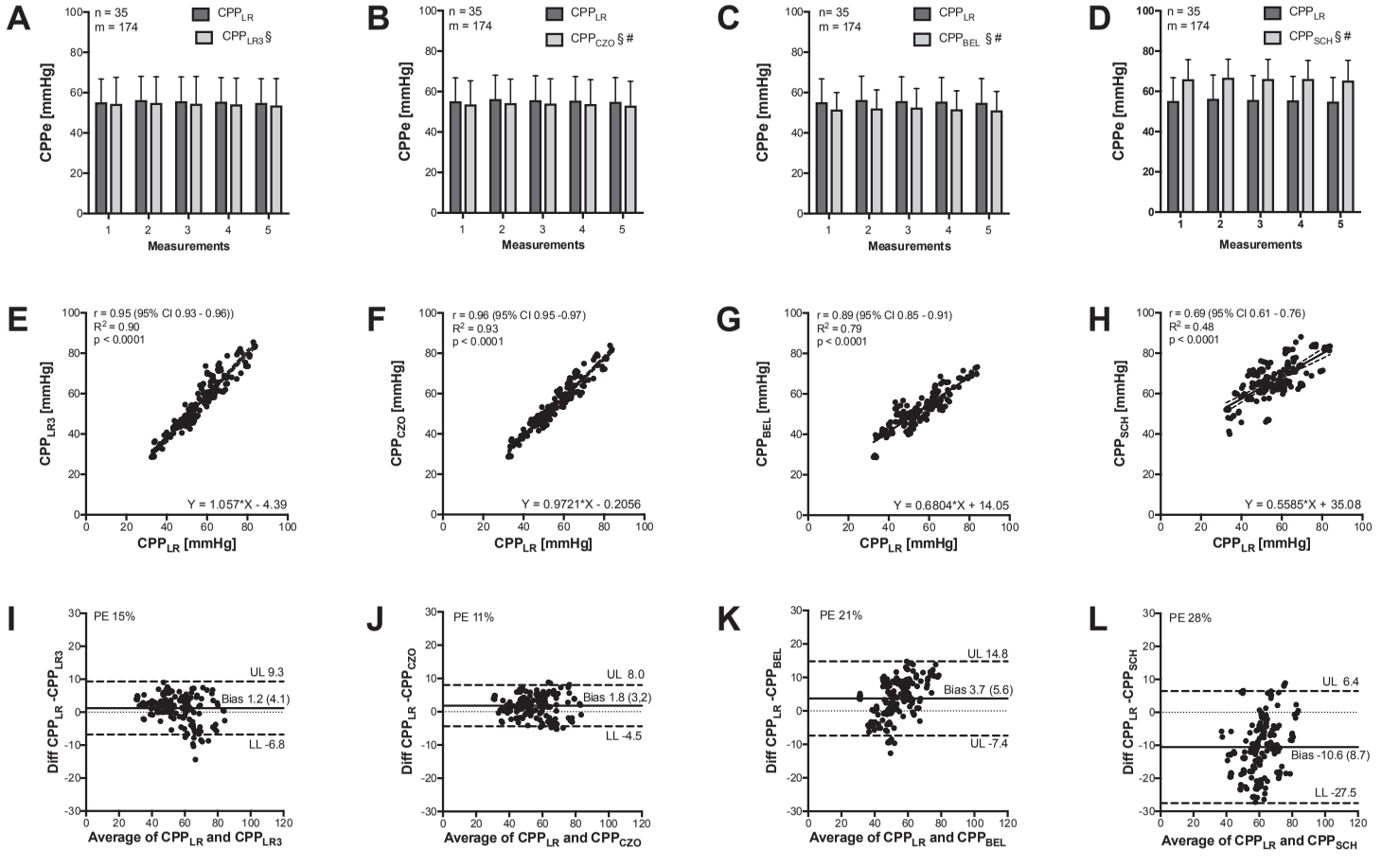

**Figure 2. STROBE flow chart of participants**

Over a period of 17 months, 56 consecutive cardiovascular patients were scheduled for implantation (n=32) or replacement (n=24) of an internal cardioverter defibrillator device (ICD), which could be included in the primary analysis. 37 patients were eligible for secondary analysis (19 exclusions due to incomplete measurements). Two datasets were insufficient to use for pressure-flow velocity relationship analysis (two outliers). During the period of measurements, we obtained five data sets for each patient. In one patient, we could obtain only four measurements; one measurement has been excluded due to supraventricular extra-systolic beats. Secondary analysis was thus performed in 35 patients with 174 measurements.

## Observations and their subject means

In 35 patients (5 measurements per patient, in total 174 observations) mean heart rate was 65 bpm with and a standard variation (SD) of 9 bpm (range from 44 to 79 bpm). Jugular venous oxygen saturation was 66 (9)% (range from 51 to 78 %). End tidal partial pressure of carbon dioxide was 33 (2) mmHg (range from 29 to 38 mmHg).

The values of effective cerebral perfusion pressure according to the reference method ($CPP_{LR}$) ranged from 32 to 84 mmHg (CV 21%), with a mean(SD) of 56 (13) mmHg. Descriptive analysis per subject of the five $CPP_{LR}$ measurements showed again a small variability (subject means: 35 mmHg, averaged $CPP_{LR}$ 56 mmHg, range 53–58 mmHg, average SD


A
n = 35
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CPP_LR
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B
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E
r = 0.95 (95% CI 0.93 - 0.96))
R2 = 0.90
p < 0.0001
Y = 1.057*X - 4.39
CPP_LR3 [mmHg]
CPP_LR [mmHg]
F
r = 0.96 (95% CI 0.95 -0.97)
R2 = 0.93
p < 0.0001
Y = 0.9721*X - 0.2056
CPP_CZO [mmHg]
CPP_LR [mmHg]
G
r = 0.89 (95% CI 0.85 - 0.91)
R2 = 0.79
p < 0.0001
Y = 0.6804*X + 14.05
CPP_BEL [mmHg]
CPP_LR [mmHg]
H
r = 0.69 (95% CI 0.61 - 0.76)
R2 = 0.48
p < 0.0001
Y = 0.5585*X + 35.08
CPP_SCH [mmHg]
CPP_LR [mmHg]
I
PE 15%
UL 9.3
Bias 1.2 (4.1)
LL -6.8
Diff CPP_LR -CPP_LR3
Average of CPP_LR and CPP_LR3
J
PE 11%
UL 8.0
Bias 1.8 (3.2)
LL -4.5
Diff CPP_LR -CPP_CZO
Average of CPP_LR and CPP_CZO
K
PE 21%
UL 14.8
Bias 3.7 (5.6)
UL -7.4
Diff CPP_LR -CPP_BEL
Average of CPP_LR and CPP_BEL
L
PE 28%
UL 6.4
Bias -10.6 (8.7)
LL -27.5
Diff CPP_LR -CPP_SCH
Average of CPP_LR and CPP_SCH

2, CV 4%). The characteristics of variation and dispersion within the other CPPe, ZFP and RAP were small too. Hemodynamic data are summarized for all observations and averaged subject means in Table 2.

Bland-Altman analysis of CPPe, corrected for repeated measurements, revealed a small positive mean bias (SD) and good precision when comparing $CPP_{LR}$ measurements with $CPP_{LR3}$ (mean bias 1.2 (4.1) mmHg, LoA -6.8 to 9.3 mmHg, PE 15%) and with $CPP_{CZO}$ measurements (mean bias 1.8 (3.2) mmHg, LoA - 4.5 to 8.0 mmHg, PE 11%). Comparing $CPP_{LR}$ measurements with $CPP_{BEL}$ mean bias was moderately higher with more widespread LoA (mean bias 3.7 (5.6) mmHg, LoA -7.4 to 14.8 mmHg, PE 21%). Analysis of $CPP_{SCH}$ and the reference method showed less agreement with a negative mean bias of -10.6 (8.7) mmHg and wide-ranging LoA of -27.5 to 6.4 mmHg, PE 28%.



As expected, Bland Altman analysis of the five ZFP estimation methods showed similar results, because CPPe is defined as difference between MAP and ZFP while MAP values were unchanged ((1) $ZFP_{LR}$ versus $ZFP_{LR3}$: mean bias -0.95 (4.88) mmHg, LoA -10.51 to 8.61 mmHg, PE 40%); (2) $ZFP_{LR}$ versus $ZFP_{CZO}$: mean bias -1.90 (3.42) mmHg, LoA -8.60 to 4.81 mmHg, PE 27%; (3) $ZFP_{LR}$ versus $ZFP_{BEL}$: mean bias -3.44 (5.81) mmHg, LoA -14.83 to 7.96 mmHg, PE 45%, (4) $ZFP_{LR}$ versus $ZFP_{SCH}$: mean bias -11.14 (8.10) mmHg, LoA -4.73 to 27.01 mmHg, PE 88%).

Biases and LoA between $RAP_{LR}$ values (reference method) and $RAP_{LR3}$, $RAP_{CZO}$ as well as the $RAP_{BEL}$ calculation methods have been small. However, the accuracy and precision for $RAP_{SCH}$ method was more wide-ranging ((1) $RAP_{LR}$ versus $RAP_{LR3}$: mean bias 0.022 (0.115) mmHg, LoA -0.204 to 0.248 mmHg, PE 16%); (2) $RAP_{LR}$ versus $RAP_{CZO}$: mean bias 0.051 (0.080) mmHg, LoA -0.108 to 0.206 mmHg, PE 12%; (3) $RAP_{LR}$ versus $RAP_{BEL}$: mean

**Figure 3. Comparison $CPP_{LR}$ versus $CPP_{LR3}$, $CPP_{CZO}$, $CPP_{BEL}$, and $CPP_{SCH}$**

The effective cerebral perfusion pressure (CPPe) estimated by four different methods, the 3-point intercept estimation (LR3, systolic/mean/diastolic), Czosnyka (CZO, 2 point systolic/diastolic), Belford (BEL, 2 point mean/diastolic), and Schmidt (SCH, 2 point systolic/diastolic) were validated against the reference method (LR, linear regression). One CPPe measurement corresponds to the cumulative analysis of 10-12 cardiac cycles within two breaths. 174 measurements were performed on 35 cardiovascular patients (5 each per patient) under general anesthesia and normocapnia. The figures explain differences (top rows: A-D), correlations (middle rows E-H) and agreement (bottom rows I-L) of the CPPe measurements. All statistical analyses were performed two-sided, and a P value of less than 0.05 was considered to be significant. All results are presented as mean (standard deviation).

Differences between the four tests methods of CPPe estimation (LR3, BEL, CZO SCH) and reference method (LR) were tested by ANOVA with correction for multiple comparison (Dunnett); § significant for all measurements; # significant for subject means.

Pearson r correlation coefficients between four CPPe values and the reference method (LR) of all observation were computed to assess their relationship. Agreement was analyzed by Bland-Altman plot analysis with correction for multiple measurements per subject (LL = lower limits of agreement, UL = upper limits of agreement, PE = percentage error).

**Table 2. Hemodynamic and transcranial Doppler sonography measurements**

| Parameter | Dimension | Analysis | Mean | SD | Min | Max | CV | MD (SD) | adj. P |
|---|---|---|---|---|---|---|---|---|---|
| $Vmca_{mean}$ | $cm \cdot s^{-1}$ | OB | 43 | 10 | 26 | 68 | 24 | - | - |
| | | SM | 43 | 1 | 42 | 44 | 3 | - | - |
| MAP | mmHg | OB | 79 | 11 | 58 | 101 | 13 | - | - |
| | | SM | 79 | 2 | 77 | 81 | 2 | - | - |
| $CPP_{LR}$ | mmHg | OB | 56 | 12 | 32 | 84 | 21 | **Ref 1** | - |
| | | SM | 56 | 2 | 53 | 58 | 4 | **Ref 2** | - |
| $CPP_{LR3}$ | mmHg | OB | 54 | 13 | 29 | 86 | 24 | 1.2 (4.1) | 0.0005 |
| | | SM | 54 | 3 | 51 | 58 | 5 | 1.2 (3.7) | 0.1747 |
| $CPP_{CZO}$ | mmHg | OB | 54 | 12 | 29 | 84 | 22 | 1.8 (3.1) | 0.0001 |
| | | SM | 54 | 2 | 51 | 57 | 4 | 1.8 (2.9) | 0.0029 |
| $CPP_{BEL}$ | mmHg | OB | 52 | 9 | 29 | 73 | 17 | 3.7 (5.6) | 0,0001 |
| | | SM | 52 | 2 | 49 | 55 | 4 | 3.7 (5.3) | 0.0008 |
| $CPP_{SCH}$ | mmHg | OB | 66 | 9 | 40 | 88 | 14 | -10.6 (8.6) | 0.0001 |
| | | SM | 66 | 1 | 64 | 68 | 2 | -10.5 (8.7) | 0.0001 |
| $ZFP_{LR}$ | mmHg | OB | 24 | 8 | 6 | 39 | 32 | **Ref 3** | |
| | | SM | 24 | 1 | 22 | 25 | 5 | **Ref 4** | |
| $ZFP_{LR3}$ | mmHg | OB | 25 | 9 | 1 | 40 | 38 | -1.0 (4.7) | 0.0284 |
| | | SM | 25 | 2 | 22 | 27 | 11 | -1.0 (4.5) | 0.5060 |
| $ZFP_{CZO}$ | mmHg | OB | 26 | 8 | 7 | 41 | 32 | -1,9 (3.4) | 0.0001 |
| | | SM | 26 | 2 | 23 | 28 | 8 | -1.9 (3.1) | 0.0033 |
| $ZFP_{BEL}$ | mmHg | OB | 27 | 7 | 6 | 44 | 25 | -3.4 (5.8) | 0.0001 |
| | | SM | 27 | 2 | 24 | 29 | 8 | -3.5 (5.5) | 0.0025 |
| $ZFP_{SCH}$ | mmHg | OB | 12 | 6 | 4 | 35 | 48 | 11.1 (8.0) | 0.0001 |
| | | SM | 13 | 1 | 11 | 14 | 9 | 11.0 (8.1) | 0.0001 |
| $RAP_{LR}$ | $mmHg \cdot s \cdot cm^{-1}$ | OB | 1.39 | 0.46 | 0.54 | 2.76 | 33 | **Ref 5** | |
| | | SM | 1.40 | 0.04 | 1.35 | 1.46 | 3 | **Ref 6** | |
| $RAP_{LR3}$ | $mmHg \cdot s \cdot cm^{-1}$ | OB | 1.37 | 0.47 | 0.46 | 2.66 | 34 | 0.02 (0.12) | 0.0587 |
| | | SM | 1.38 | 0.06 | 1.31 | 1.45 | 4 | 0.02 (0.11) | 0.5759 |
| $RAP_{CZO}$ | $mmHg \cdot s \cdot cm^{-1}$ | OB | 1.34 | 0.44 | 0.54 | 2.51 | 32 | 0.05 (0.08) | 0.0001 |
| | | SM | 1.35 | 0.05 | 1.29 | 1.41 | 4 | 0.05 (0.07) | 0.0011 |
| $RAP_{BEL}$ | $mmHg \cdot s \cdot cm^{-1}$ | OB | 1.29 | 0.38 | 0.61 | 2.43 | 30 | 0.10 (0.15) | 0.0001 |
| | | SM | 1.30 | 0.06 | 1.22 | 1.37 | 5 | 0.10 (0.07) | 0.0008 |
| $RAP_{SCH}$ | $mmHg \cdot s \cdot cm^{-1}$ | OB | 1.65 | 0.47 | 0.74 | 2.68 | 28 | -0.26 (0.24) | 0.0001 |
| | | SM | 1.65 | 0.04 | 1.60 | 1.71 | 3 | -0.25 (0.24) | 0.0001 |

The effective cerebral perfusion pressure (CPPe), the zero flow pressure (ZFP) and the resistance area product (RAP) estimated by four different methods, the 3-point intercept estimation (LR3, systolic/mean/diastolic), Czosnyka (CZO, 2-point: systolic/diastolic), Belford (BEL, 2-point: mean/diastolic), and Schmidt (SCH, 2-point: systolic/diastolic) were validated against the reference method (LR, linear regression). One CPPe measurement corresponds to the cumulative analysis of 10-12 cardiac cycles within two breaths. 174 measurements were performed on 35 cardiovascular patients (5 each per patient) under general anesthesia

and normocapnia. All statistical analyses were performed two-sided, and a P value of less than 0.05 was considered to be significant. All results are presented as mean (standard deviation). Differences between the four tests methods of estimation (LR3, BEL, CZO SCH) and reference method (LR) were tested by ANOVA with correction for multiple comparison (Dunnett). CV = coefficient of variation (%), MAP = mean arterial pressure, MD = mean differences, Min = minimum, Max = maximum, OB = observations (results within all 174 measurements), SM = subject means (results within the 5 measurements per subject), SD = standard deviation, Vmca = blood flow velocity of the mean cerebral artery.

bias 0.097 (0.154) mmHg, LoA -0.204 to 0.398 mmHg, PE 22%; (4) $RAP_{LR}$ versus $RAP_{SCH}$: mean bias -2.58 (0.244) mmHg, LoA -0.735 to 0.220 mmHg, PE 31%).

Pearson r correlation coefficients between four CPPe values and the reference method (LR) of all observation were computed to assess their relationship (n=174, 2-tailed). $CPP_{LR3}$, $CPP_{CZO}$ and $CPP_{BEL}$ values showed a very strong positive correlation when compared to the reference method ((1) $CPP_{LR3}$ r=0.95 ranging from 0.93-0.96, p<0.001, $R^2$ 0.90; (2) $CPP_{CZO}$ r=0.96 ranging from 0.95-0.97, p<0.001, $R^2$ 0.93; (3) $CPP_{BEL}$ r=0.89 ranging from 0.85-0.91, p<0.001, $R^2$ 0.79). The correlation analysis between $CPP_{LR}$ and $CPP_{SCH}$ revealed a moderate positive relationship (r=0.69 ranging from 0.61-0.76, p<0.001 $R^2$ 0.48).

Correlation analysis of ZFP values showed almost similar results. Correlation analysis of $ZFP_{LR3}$ and $ZFP_{CZO}$ showed a strong relationship versus the reference method $ZFP_{LR}$. The correlation of $ZFP_{BEL}$ was moderate, and of $ZFP_{SCH}$ was weak ((1) $ZFP_{LR}$ versus $ZFP_{LR3}$ r=0.87 ranging from 0.83-0.90, $R^2$ 0.76; (2) $ZFP_{LR}$ versus $ZFP_{CZO}$ r=0.91 ranging from 0.88-0.93, $R^2$ 0.83; (3) $ZFP_{LR}$ versus $ZFP_{BEL}$ r=0.69 ranging from 0.60-0.76, $R^2$ 0.47; (4) $ZFP_{LR}$ versus $ZFP_{SCH}$ r=0.32 ranging from 0.18-0.45, $R^2$ 0.10).

RAP computations showed fewer differences. They all showed very strong or strong positive correlations, when compared to the reference method ((1) $RAP_{LR}$ versus $RAP_{LR3}$ r=0.97 ranging from 0.96-0.98, $R^2$ 0.94; (2) $RAP_{LR}$ versus $RAP_{CZO}$ r=0.99 ranging from 0.98-0.99, $R^2$ 0.97; (3) $RAP_{LR}$ versus $RAP_{BEL}$ r=0.95 ranging from 0.94-0.96, $R^2$ 0.91; (4) $RAP_{LR}$ versus $RAP_{SCH}$ r=0.87 ranging from 0.82-0.90, $R^2$ 0.75).

The CPPe analysis of differences, correlation and agreement are graphically summarized in figure 3. For further figures regarding analyzes of ZFP and RAP, we refer to appendix 4 of the SDC.

## DISCUSSION

In a secondary analysis, we validated four different estimation methods of effective cerebral perfusion pressure, zero-flow pressure, and resistance area product against a reference method in 35 cardiovascular patients under steady state conditions during fentanyl-midazolam anesthesia and normocapnia. The study was performed to identify differences, correlation and agreement of these methods.

The most prominent results of the study are:

i. CPPe, ZFP and RAP measurements based on LR3 and CZO calculation methods showed small mean differences, good agreement, low percentage errors, and an excellent correlation when compared to LR reference method.
ii. Agreement and correlation of CPPe ZFP and RAP was moderate for the BEL method, and weak for the SCH method.
iii. It is possible and safe enough to estimate CPPe, ZFP and RAP with simpler approaches like the CZO method or the LR3 method when compared to the LR method.
iv. ZFP estimation by intercept calculation based on a 3 point-extrapolation (systolic/mean/diastolic LR3) does not seem to be more advantageous than by a 2 point-extrapolation (systolic/diastolic CZO).
v. The RAP seems to be rather unaffected by the method of estimation

Mainly, there are two methods for determining the zero-flow pressure using transcranial Doppler sonography. The most fundamental method estimates the ZFP by regression analysis of the pressure-flow velocity plot derived from complete pressure and flow velocity tracings.[7 16] The second group of ZFP estimation methods were based on the slope-intercept-form (figure 1). 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 arterial blood pressure and velocity of the mean cerebral artery is not necessary. For further mathematical explanation we refer to the appendix 1 of this report in the SDC section.

Linear pressure-flow velocity relationships in an elastic vessel based on systolic/diastolic (CZO), mean/diastolic values (BEL) or all 3 values (LR3) are based on the assumption that the vessel's resistance behavior remains constant within the whole cardiac circle and throughout its diameter. Here, our study data demonstrated that ZFP estimation by intercept calculation based on a 3 point-extrapolation (systolic/mean/diastolic LR3) seems to be a little more advantageous when compared by a 2 point-extrapolation based on systolic/diastolic data (CZO). Using only mean and diastolic values and thus skipping the systolic values of the ABP and Vmca, on the other part, will shorten the distance of the velocity plot, which might weaken the estimation of ZFP and RAP. This could be a reason for the wider limits of agreement and thus moderate agreement of the BEL method. Thus, the systolic part of the pressure and velocity curves seems to be important for the accuracy of the ZFP calculation.

To the best of our knowledge, there are only a few (method comparison) on ZFP, CPPe or RAP studies using pressure-flow velocity analysis in patients without intracranial pathologies. They are difficult to compare with our results because they unfortunately differ in study design, study population, statistical analysis and used CPPe, ZFP and RAP estimation methods. Recently *Baker et al*.[22] compared ZFP obtained by optical diffuse correlation spectroscopy (DCS) measurements with ZFP measurements based on Dop-

pler sonographic pressure-velocity plots in 18 awake healthy adults laying supine at rest, which showed good agreement.

*Panerai and colleagues*[23] compared seven different ZFP/RAP estimation methods to assess their robustness and reproducibility in ten healthy subjects. Their data showed a high incidence of negative ZFP, which could be related on the calculation method. The authors suggested that the classical use of LR of the instantaneous pressure-flow velocity relationship of the entire cardiac cycle should *not* be used for static applications due to poor reproducibility and high occurrence of negative values of ZFP. They recommended further that first harmonic fitting (H1) and 2-point mean/diastolic values (2Pm) perform better than LR analysis and should be used for the estimation of ZFP and RAP for both static and dynamic applications. In our study, we did not find any negative ZFP values in our study. Negative ZFP values have been described during hyperemia, vasospasm, or with artificially elevated diastolic Vmca.[24-26] However, at present, there is no physiologically relevant interpretation for these findings and they are commonly viewed as methodological limitations. Interestingly, the ZFP(LR) values from *Baker et al.*[22] and *Panerai et al.*[23] were about 10 mmHg lower compared to our data, which perhaps could be related to differences in study population, non-invasive arterial pressure measurements (Finapress®), general anesthesia and artificial ventilation.

Some methodological aspects of our study have to be considered. A major problem in defining pressure-flow relationships in living vascular beds is that autoregulation can alter bed characteristics during the period of observation. In situations of CPP below 40 mmHg, which corresponds to a maximal vasodilation of small pial arteries, autoregulation is progressively exhausted. Here the shape of the pressure-flow plot could be non-linear. Most methods proposed for estimation of ZFP can only represent the linear range of the pressure-flow (or velocity) relationship. Thus, "in vivo"-estimation of ZFP by linear pressure-flow(velocity) plot analysis can give only "presumptive" or "apparent" values rather than "true" values.[3] To define the $ZFP_{LR}$ as reference method is thus still debatable.

Analysis of the long diastolic fall in pressure and flow after cessation of cardiac function was the "classic" method the zero-flow pressure estimation of the coronary circulation in dogs[27] and later in humans. *Aaslid et al.* transferred this approach for the cerebral perfusion with transcranial Doppler sonography.[28] The ZFP based on long diastoles with an duration of was about 6 mmHg lower when compared to the $ZFP_{LR}$ method. In order to verify the $ZFP_{LR}$ method as suitable reference method in our patients we additionally measured ZFP based on the first long diastole during ICD testing-induced cardiac arrest ($ZFP_{LD}$ and $RAP_{LD}$). We performed pressure-velocity plots analyses at different durations of the long diastole (1s-10s, and the whole long diastole). Our additional analysis of ZFP based on long diastoles demonstrated that pressure velocity relationships with a duration of 4s or longer showed a less linear relationship. Subsequently, the extrapolated $ZFP_{LD}$ (4s or longer) showed lower values when compared to $ZFP_{LR}$. The use $ZFP_{LR}$ as

reference method seems to safe and a good alternative to $ZFP_{LD}$ measurements. Based on our results we recommend a standard diastolic time of 3s when ZFP is assessed by long diastoles. For further information we refer to Appendix 3 of the SDC section.

## CONCLUSIONS

We validated four different estimation methods of CPPe pressure, ZFP, and RAP against a reference method in 35 cardiovascular patients under steady state conditions during fentanyl-midazolam anesthesia and normocapnia. CPPe ZFP and RAP measurements based on LR3 and CZO calculation methods showed small mean differences, good agreement, low percentage errors, and an excellent correlation when compared to references method. Agreement and correlation were moderate for the BEL method, and unsatisfying for the SCH method. The RAP seems to be rather unaffected by the method of estimation. Our study results demonstrate that is it possible and safe enough to estimate CPPe, ZFP and RAP with simpler approaches like the CZO method or the LR3 method.

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## APPENDIX 1 - ZERO FLOW PRESSURE (ZFP) ESTIMATION

### Background

*Models defining cerebrovascular tone*

The classic concept defining cerebrovascular tone is cerebral vascular resistance (CBF = CPP / CVR). It assumes that perfusion pressure and flow are linearly and proportionally related. When calculating the CPP, the 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 ICP is elevated by i.e. 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 ICP as effective downstream pressure (EDP) of the cerebral circulation, would neglect vascular tone properties of the 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 i.e. lung, myocardium, liver, muscle, skin, and the brain, have shown, that the EDP is more 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 perfusion 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. 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 the value of 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 (but not proportionally) related to pressure 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 periph-

eral 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).

In a former investigation, 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 the highest (figure S1).[5 15] In the light of this concept, some researchers have created the term "effective cerebral perfusion pressure" to refer to the difference between MAP and ZFP, by considering the tone of the vessels.

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, i.e. wall tension.

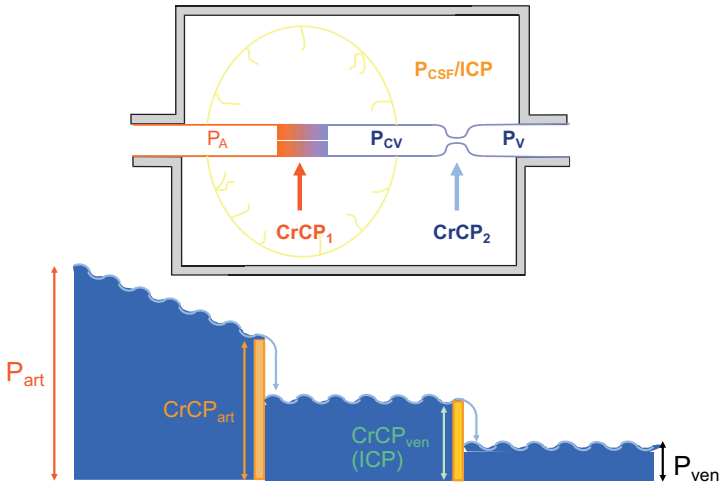



**Figure S1: Cerebral vascular waterfall of the circulation**
Hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels (CrCPart) and a second (distal) at the level of collapsible cerebral veins (CrCPven). The effective downstream 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.[5 15]

*Resistance area product (RAP)*

The slope of the pressure-**flow** velocity plot is inversely related to arterial resistance.[12] Many research groups used the inverse of the slope of the pressure-**velocity** plot to de-

termine cerebral vascular resistance by transcranial Doppler sonography measurements. In 1988, *David Evans et al.* introduced the Doppler sonographic index, the resistance area product (RAP). Derived from Hagen-Poiseuille law, the slope of a pressure-**velocity** relationship could also be equated to the product of velocity and the cross-sectional area of the vessel at the site of insonation. This definition is a misnomer, because it is not possible to measure the diameter of the artery by transcranial Doppler sonography at the point of insonation. Nevertheless, the resistance area product (RAP) is an important estimate of vascular resistance, because it takes the cerebral zero flow pressure into account. The driving pressure of the brain is the effective perfusion pressure rather mean arterial pressure, as mentioned above.

Simplified, the RAP can also be calculated as a quotient of effective cerebral perfusion pressure and mean MCA velocity (RAP = CPPe / mean Vmca). This definition or calculation of the RAP however, is not consistently used.[18-20]

*Methods for non-invasive assessment of the EDP of the cerebral perfusion*

Several methods for non-invasive assessment of the effective downstream pressure of the cerebral perfusion have been described by using: sensing tympanic membrane displacement[21], skull vibrations[22], otoacoustic emissions[23], magnetic resonance imaging to estimate intracranial compliance[24], brain tissue resonance[25], transcranial time of flight[26], recordings of visual evoked potentials[27], optic nerve sheath diameter assessment[28], venous ophthalmodynamometry[29], and ultrasound-guided eyeball compression[30], and the optical diffuse correlation spectroscopy (DCS)[31]. 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.[32]

Transcranial Doppler sonography (TCD) allows non-invasive, continuous measurements of the flow velocity of the middle cerebral artery (Vmca), which represents with 80% the major portion of global cerebral blood flow. In a number of previous studies, relative changes in CBF were reflected by changes in Vmca in a proportional manner, suggesting that MCA diameter remains constant.[33] A good correlation between changes in Vmca and changes in CBF has been found during carotid endarterectomy.[34]

Since the introduction of TCD, a number of methods have been developed to assess cerebral ZFP by pressure-(flow)velocity relationship analysis.[15 16 35-43]

Other research groups tried to develop alternative mathematical models for EDP / CrCP / ZFP calculations including values of ICP, ABP, autoregulation and intracranial compliance.[41 44-46] However, these models are rather complex and therefore less suitable for the clinical setting.

*Linear relationship between blood flow (velocity) and blood pressure*

It has been proven that in vivo dynamic pressure-flow relationships are straight lines for many vascular beds even for the cerebral vessels.[3 10-12 47-50] The most common approach to estimate the cerebral CrCP or ZFP is thus to perform a linear regression on continuous measurements of ABP and Vmca taken from a single cardiac cycle. These waveforms oscillate between the diastolic and systolic values. Therefore, the linear regression line uses only the values represented by circles, corresponding to i.e. 80 > Pa < 120 mmHg.

A lot of animal studies support the linear relationship between flow and pressure even for situations of very low arterial blood pressures (ABP). *Walter Ehrlich* evaluated instantaneous femoral artery pressure-flow relations during cardiac arrest in anesthetized dogs. He could demonstrate, that in all pressure-flow plots obtained under conditions of normal or elevated venous pressure, either with or without alpha- blockade, the pressure-flow relations were linear, and the zero-flow intercept on the pressure axis was reached in less than 3 seconds after the onset of cardiac arrest, which was markedly higher than the simultaneous venous pressure.[49] *Richard C. Dewey* evaluated cerebral pressure-flow relationships in anesthetized monkeys. Changes from arterial hypertension to hypotension did not affect the linearity of the measured pressure-flow plots of carotid artery.[10]

The linear pressure-flow(velocity) plot model may has limitations. Cardiac arrhythmia or function tests with implantable cardioverter defibrillators devices are situations with very long diastolic phases and low diastolic pressures.

This approach has been used to estimate and to confirm a "true" ZFP in the coronary circulation, systemic and even cerebral circulation in humans.[5 17 51] Analysis of prolonged diastolic pressure and flow curves however showed non-linear parts of the pressure-flow curve. Some "non-linear" factors (i.e. cerebral venous circulation, vascular capacitance, elasticity of the insonated part of the vessel, rheological properties of the blood, pulse rate, radius-dependent active wall tension etc.) of the cerebrovascular tree regulation are less represented in this model.[52-54] Comparable factors may also disturb the arterial pressure waveform like changes in cardiac output or stroke volume. When using normal ranges of systolic and diastolic of arterial blood pressures and Vmca, any extrapolation to calculate ZFP is likely to vary significantly given the wide ranges of the normal values within these variables. This may explain the wide ranges of ZFP reported in our study as well in previous studies (figure S2).[55]

However, the linearity of pressure-flow plots seems to be stable within normal physiologic values. There are some experimental data about vascular compliance available, predominantly for the coronary perfusion.[8 56-60] It has been shown that the compliance of the cerebral vessels, however, seems to be lower than other vascular beds.[61] Thus, the influence of capacitance effects under "in vivo" conditions appears to be small. Variations of the partial pressure of carbon dioxide, a strong vasodilator, could affect vascular ca-

pacitance of the middle cerebral artery, which in turn may impair the accuracy of linear extrapolation of ZFP. In a prior investigation we could demonstrate that the linearity of pressure-flow velocity relationships have not been influenced by $PaCO_2$ and its potential effects on compliance are thus assumed to be of minor methodological importance.[62]

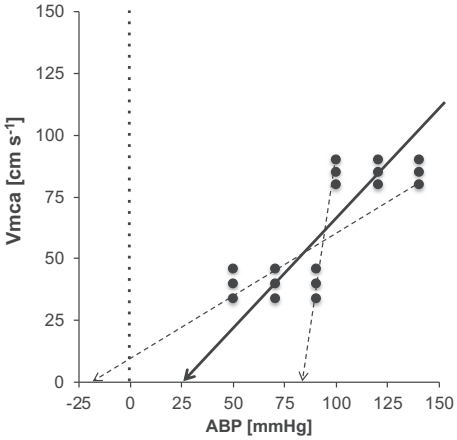



**Figure S2: Possible bias in ZFP and RAP estimation by linear regression**
This figure explains the possible wide ranges of estimated cerebral zero flow pressures (ZFP) in a normal population. The dot boxes show all possible combinations of the systolic (upper box) and the diastolic (lower box) values of blood pressure (ABP) and middle cerebral artery flow velocity (Vmca) in a normal population (ranges of ABP, systolic =145-100mmHg, diastolic = 90-50 mmHg; ranges of the Vmca, systolic = 90-80 cm/s, diastolic 46-33 cm/s).[63] The solid line arrows point to the extrapolated ZFP, if the values of blood pressure and flow velocity are close to the average. The dotted line arrows point to the possible range of extrapolated ZFP if the values of blood pressure or flow velocity (and the pulsatility of their waveforms) approach the limits of their normal range (modified from Athanassiou et al. 2005.[55]

*"Apparent" versus "true" ZFP*

Most methods proposed for estimation of ZFP can only represent the linear range of the pressure-flow (or velocity) relationship. As a consequence, only estimates of a "presumptive" or "apparent" ZFP can be obtained, and these tend to be significantly higher than the "true" ZFP.[5]

In the past, many research groups have tried to identify a "true" ZFP. In animal studies, it is possible to isolate brain circulation from other systems (e.g., by ligating the carotid artery) and thus to perform repeated measurements of blood pressure, blood flow, and flow velocity under different conditions. Later, analyzes of the long diastolic fall in pressure and flow after cessation of cardiac function (i.e. induced by ventricular fibrillation) was used for zero-flow pressure estimation of the coronary circulation in dogs and later in humans.[56 64]

*Eva Kottenberg-Assenmacher and her group* estimated the ZFP/CrCP of the systemic circulation with different mathematical models during internal cardiac defibrillator

testing in 10 patients under general anesthesia.[51] Interestingly, they could demonstrate that arterial ZFP based on heart beating data, was substantially higher than ZFP values found during cardiac arrest. They explained the discrepancy between heart beating and cardiac arrest values by a leak in the waterfall. In an intact circulation the height of the waterfall will be intact as long as the volume supply exceeds the volume loss. However, when supply becomes less than the volume loss, as is the case during a cardiac arrest, the drain of arterial blood through those vascular waterfalls with lower local ZFP values will result in a reduction of measured ZFP. They could demonstrate that the ZFP measured or calculated by curve fitting after prolonged periods of circulatory arrest was lower than that with a circulatory arrest of shorter duration.



*Rune Aaslid et al.* transferred this approach for the cerebral perfusion with transcranial Doppler sonography.[17] Their study aim was to validate estimates of ZFP based on regular heartbeat data (linear regression method) against ZFP estimates based on long diastole determinations (about 3 seconds) after induced ventricular fibrillation (VF) during internal cardiac defibrillator testing in 13 patients under general anesthesia. The ZFP based on long diastoles was about 6 mmHg lower when compared to the $ZFP_{LR}$ method.

Obtaining ZFP from long diastoles induced by ventricular fibrillation has also some disadvantages:

- Any circulatory arrest is an abnormal state likely to change vascular properties even in the brain. There are no oxygen stores in the brain in contrast to myoglobin, which stores oxygen in the muscle. For example, ischemia during circulatory arrest might induce peripheral arteriolar vasodilation within seconds, which subsequently will result in a too-low ZFP.
- Although the venous compliance is certainly greater than the compliance of the arterial vascular tree, the further fall in arterial pressure after circulatory arrest may be related to a reduction in vascular tone rather than drainage of the remaining arterial flow.
- Conversely, the induction of ventricular fibrillation with a quick reduction in arterial pressure could also induce intense efferent neural sympathetic outflow and consequently arteriolar vasoconstriction, giving rise to a too-high ZFP.
- Furthermore, aortic valve flutter has been described using transesophageal echocardiography during ventricular fibrillation.[65] In this case, aortic valve regurgitation in addition to peripheral arterial flow runoff could speed aortic pressure decay and shorten the decay time constant, and consequently underestimate calculated ZFP.

However, measurements of a "true" ZFP might be an elusive concept. A major problem in defining pressure-flow relationships in living vascular beds is that autoregulation can alter bed characteristics during the period of observation. Any circulatory arrest is an abnormal state likely to change vascular properties even in the brain. In situations of CPPs below 40 mmHg, which corresponds to a maximal vasodilation of small pial arter-

ies, autoregulation is progressively exhausted. Here the shape of the pressure-flow plot could be non-linear.

It is thus debatable whether fibrillation- induced circulatory arrest allowed measurements of the ZFP that prevails physiologically.[51]

## Mathematical principle of the ZFP calculation

Two respiratory cycles of each measurement period are randomly selected and extrapolated ZFP data of all heartbeats within these respiratory cycles are averaged for further analysis of ZFP, RAP and CPPe. In algebraic geometry, a straight line in an axis system is described by the linear function. In two dimensions, the equation for non-vertical lines is often given in the slope-intercept form (see figure S8):

$$y = a \cdot x + b \tag{1}$$

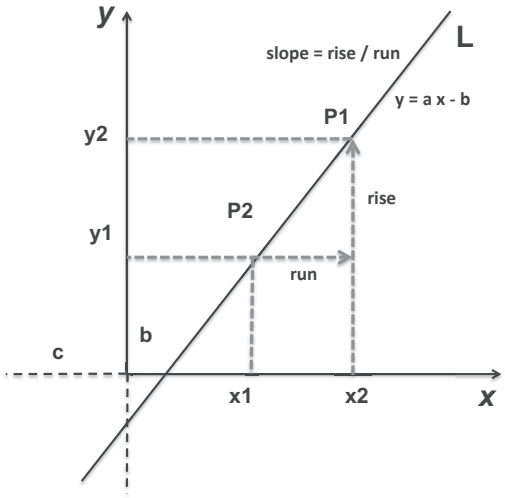



**Figure S3: Slope intercept form**

In figure S3 *a* is the slope and *b* is the y-intercept of the line. If P1 = (x1, y1) and P2 = (x2, y2) are points on the non-vertical line L then the equation of the line can be found using the point-slope-formula or the two-point form.

$$y - y1 = a \cdot (x - x1) \tag{2a}$$

$$y - y1 = \frac{(x2 - x1)}{(x2 - x1)}(x - x1) \tag{2b}$$

To calculate the line L intercept, compare equation (1) to:

$$b = y - a \cdot x \tag{3}$$

The intersection of line L with the x axis [(X, 0), c in figure S6] can be found by equating (1) equal to 0 and solving:

$$0 = a \cdot x + b \tag{4a}$$

$$-b = a \cdot x \tag{4b}$$

$$a = \frac{b}{x} \tag{4c}$$

With this background, it is possible to redirect a graph as in figure S4 to a formula, as done by Belfort et al, to calculate the ZFP.[66]

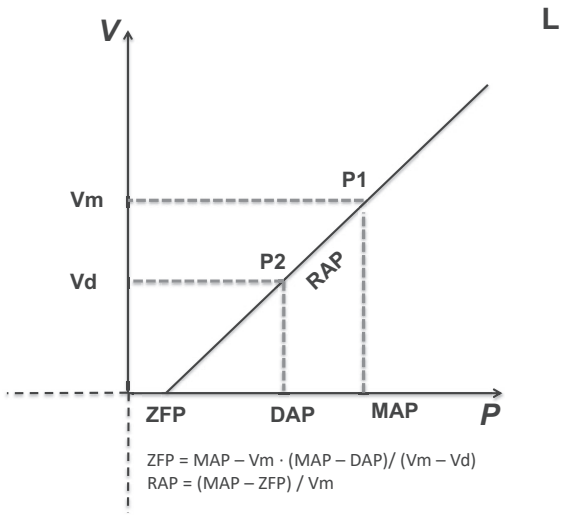



**Figure S4: Mathematically explanation of the x-intercept calculation of a pressure-flow velocity plot by Belfort.**

For a pressure-flow plot analysis the diastolic and mean flow velocity (Vd, Vm) have to be put on the y -axis as the independent variable. The diastolic and mean arterial blood pressure (DAP, MAP) are put on the x-axis as dependent variable. Thus, the linear graph of a pressure-flow(velocity)-plot could be defined regarding to equation (1) as:

$$Vm = a \cdot MAP + b \tag{5a}$$

Then the y-intercept would be:

$$b = Vm - a \cdot MAP \tag{5b}$$

The slope could be defined as:

$$a = \frac{(Vm - Vd)}{(MAP - DAP)} \tag{5c}$$

To calculate the intercept a zero velocity (P0 = ZFP) we have to rearrange the forms 5a-c with the following steps:

$$0 = a \cdot P0 + b \tag{6a}$$

$$-b = a \cdot P0 \tag{6b}$$

$$P0 = -b \,/\, a \tag{6c}$$

$$ZFP = -b \cdot \frac{(MAP - DAP)}{(Vm - Vd)} \tag{6d}$$

$$ZFP = -(Vm - a \cdot MAP) \cdot \frac{(MAP - DAP)}{(Vm - Vd)} \tag{6e}$$

$$ZFP = -Vm \cdot \frac{(MAP - DAP)}{(Vm - Vd)} + a \cdot MAP \cdot \frac{(MAP - DAP)}{(Vm - Vd)} \tag{6f}$$

$$ZFP = -Vm \cdot \frac{(MAP - DAP)}{(Vm - Vd)} + MAP \cdot \frac{(Vm - Vd)}{(MAP - DAP)} \cdot \frac{(MAP - DAP)}{(Vm - Vd)} \tag{6g}$$

$$ZFP = -Vm \cdot \frac{(MAP - DAP)}{(Vm - Vd)} + MAP \cdot 1 \tag{6h}$$

$$ZFP = MAP - Vm \cdot \frac{(MAP - DAP)}{(Vm - Vd)} \tag{6f}$$

Then CPPe can be calculated by:

$$CPPe = MAP - ZFP \tag{7a}$$

Or by:

$$CPPe = Vm \cdot \frac{(MAP - DAP)}{(Vm - Vd)} \tag{7b}$$

## APPENDIX 2 STUDY PROTOCOL CPPE, ZFP, AND RAP ANALYSIS

### "In vivo" estimation of ZFP by linear pressure-flow(velocity) plot analysis

*Arterial blood pressure measurements*
Arterial blood pressure (ABP) was monitored via a cannula placed in the radial artery with the transducer positioned at the level of the base of the skull/ear.

*Blood flow velocity measurements of the middle cerebral artery*
Blood flow velocity of the middle cerebral artery (Vmca) was measured via the temporal window with a commercially available 2 MHz transcranial Doppler device (DWL multidop-X device with two 2-MHz pulsed Doppler probes, DWL TCD 7 software, DWL Elektronische Systeme GmbH, Sipplingen, Germany).



**Figure S5: TCD measurements of the mean cerebral artery**
(with permission from Mr. Arnoud Steutel)

The ultrasound transducer was placed over the temporal area just above the zygomatic arch and in front of the tragus of the ear. After identification of the middle cerebral artery, the depth of insonation was adjusted in 1-2 mm increments to obtain signals from the proximal segment (M1) of the MCA. Accurate care was taken to ensure a stable position of the ultrasound probe during the study period. The ultrasound probe was therefore fixed using a monitoring probe holder attached to the patient's head (see figure S5). Doppler ultrasound variables such as depth, gain, sample volume, and power of the

ultrasound beam were unchanged during the measurement procedure. Determinations of flow velocity were based on envelope curves of maximum intravascular velocity.

*Data recordings and storage*

Simultaneous data recordings of ABP and Vmca envelope curves were acquired over periods of 2-5 minutes. At each measurement, simultaneous data recordings of Vmca, arterial blood pressure (ABP, mmHg), expiratory concentration carbon dioxide concentration ($PeCO_2$, mmHg), and jugular venous bulb oxygen saturation ($SjO_2$, %) were acquired and stored on a microcomputer via analogue/digital converters. These files are still available (DWL software format).

The analyses of the ZFP, CPPe and RAP have been performed after the study period. For the secondary analyses, we looked at the period after induction of anesthesia and before ICD-testing. We extracted five consecutive data sets of 10-12 seconds (two breaths) each within 3 min from the raw data files of the primary investigation. These data sets were exported (ASCII format, see figure S6). Recordings that contained ABP and Vmca measurements during ICD tests (ventricular fibrillation) were not used for this secondary analysis.

```
FILE      : [redacted]   1994-8-24
SAMPLERATE:   57.400 Hz
START TIME: 10:46:49
CHANNEL:
  1     2     3     5     6
Vli   Vre   ABP   CO2   %O2

DATA:
 32.0   0.0  66.0  31.0  69.0
 32.0   0.0  67.0  30.0  71.0
 32.0   0.0  65.0  31.0  68.0
 30.0   0.0  64.0  31.0  70.0
 30.0   0.0  64.0  31.0  69.0
 30.0   0.0  65.0  31.0  70.0
 27.0   0.0  63.0  31.0  69.0
 27.0   0.0  62.0  31.0  69.0
 30.0   0.0  62.0  27.0  69.0
 30.0   0.0  62.0  31.0  69.0
 30.0   0.0  61.0  31.0  69.0
 27.0   0.0  60.0  31.0  68.0
```

**Figure S6: Exported TCD data-set (ASCII format)**

*CPPe / ZFP analysis*

For the CPPe / ZFP analysis we used dedicated custom-developed software (LabView®, USA, written by Dr. E.G. Mik, Erasmus MC).

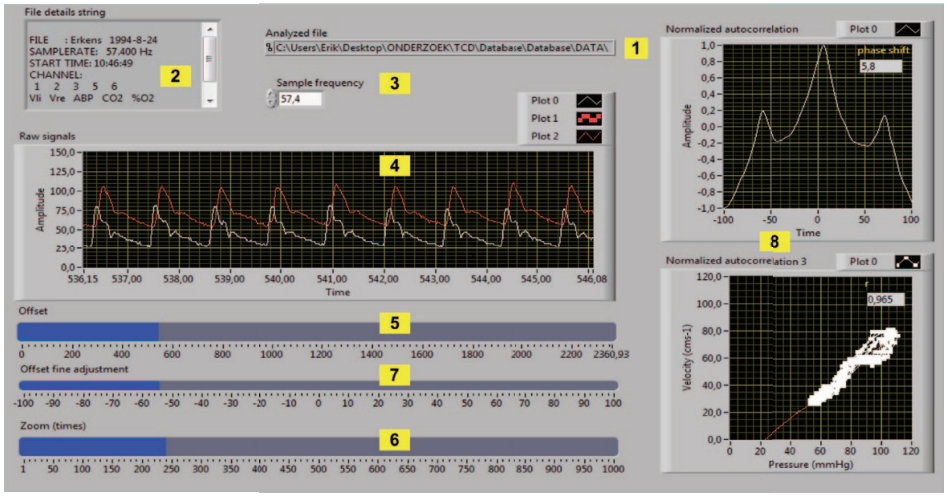



**Figure S7: CPPe estimation software based on LabView® (window 1)**

The following steps were performed (Figures S7 and S8):

1. Import
   An ASCII files was imported.
2. File detail string
   The imported file was checked and verified using the preview window.
3. Sample rate
   The used TCD sample rate was noted.
4. Inspection
   Vmca and ABP waveforms were visually inspected for artifacts or arrhythmias, which could distort further analysis.
5. Determine the start of the measurement period (*Offset*)
   The start of measurement period within the whole data tracings was chosen.
6. Determine the duration of the measuring period (*Zoom function*)
   A data set of 10-12 seconds (two breaths, 9 beats) was selected.
7. Synchronization (*Offset fine adjustment*)
   ABP and Vmca waveforms were synchronized: To compensate for the time delay between ABP and Vmca at the radial and middle cerebral artery, respectively, flow velocity curves have to be shifted.
8. Visual control pressure flow plot
   The correct compensation of time delay was calculated by iterative regression analysis until hysteresis of ABP / Vmca plots completely disappeared. A correlation

coefficient >0.94 was used as a cut-off value to select heartbeats with adequate signal quality.

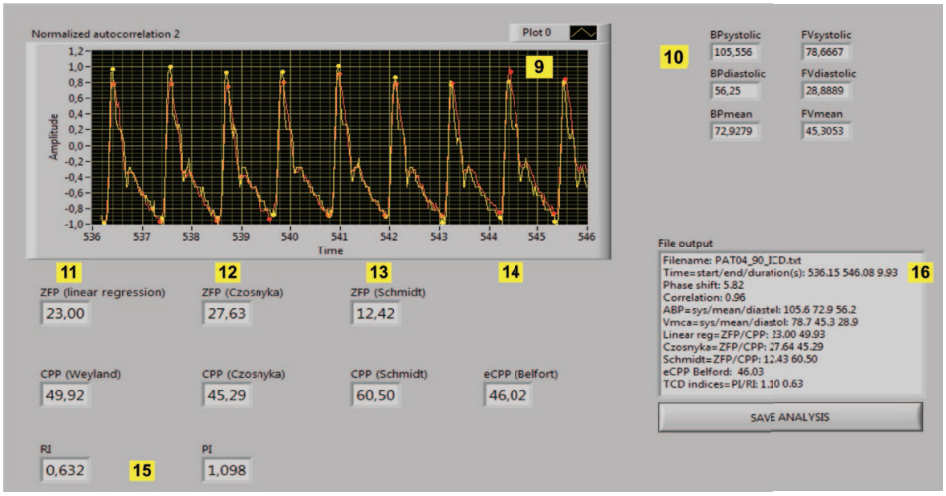



**Figure S8: CPPe estimation software based on LabView® (window 2)**

9. Visual control of the selected measurement period
   On the following screen (window 2) measurement tracings of ABP and Vmca and their synchronization were visually controlled.
10. Verification of ABP and Vmca values
    Systolic, diastolic, and mean values of ABP and Vmca of the selected measurement period were averaged.
11. CPPe, $ZFP_{LR}$ estimation by linear regression of ABP and Vmca
    The pressure axis intercepts of the ABP / Vmca plot of the selected measurement period represent the $ZFP_{LR}$ of the cerebral circulation (step 8 and 9). CPPe was calculated by MAP-$ZFP_{LR}$.[15]
12. CPPe, $ZFP_{CZO}$ calculation by Czosnyka formula
    $ZFP_{CZO}$ was calculated by a formula reported by Czosnyka et al.[38] Here, averaged systolic and diastolic values of ABP and Vmca (step 10) were used. CPPe was calculated by MAP-$ZFP_{CZO}$.

$$ZFP_{CZO} = SAP - Vs \bullet \frac{(SAP - DAP)}{(Vs - Vd)}$$

13. CPPe, $ZPF_{SCH}$ calculation by Schmidt formula
    $ZFP_{SCH}$ was calculated by a formula reported by Schmidt et al.[39 67] Here, averaged mean and diastolic values of ABP and Vmca (step 10) were used. CPPe was calculated by MAP-$ZFP_{SCH}$.

$$ZFP_{SCH} = MAP - (MAP \bullet \frac{Vd}{Vm} + 14)$$

14. CPPe, $ZFP_{BEL}$ calculation by Belfort formula

$ZFP_{BEL}$ was calculated by a formula reported by Belfort et al.[66] Here, averaged mean and diastolic values of ABP and Vmca (step 10) were used. ZFP was calculated by MAP-$CPP_{BEL}$.

$$ZFP_{BEL} = MAP - Vm \bullet \frac{(MAP - DAP)}{(Vm - Vd)}$$

15. Calculations of resistance index (RI) and pulsatility index (PI)

The Resistance index (RI) was calculated by a formula reported by Pourcelot et al.[68] The Pulsatility index (PI) was calculated by a formula reported by Gosling et al.[69 70] Here, averaged systolic, mean and diastolic values of Vmca (step 10) were used. These results were not used in the current manuscript.

$$PI = \frac{Vs - Vd}{Vm}$$

$$RI = \frac{Vs - Vd}{Vs}$$

16. Export of measured data

The results of the analysis were saved and exported as text file (*.txt).

## Additional calculations

All measurements files were imported in a spreadsheet for further calculation and analysis (Excel 2011®, Microsoft Cooperation, USA).

*CPPe, $ZFP_{LR3}$ calculation*

$ZFP_{LR3}$ was calculated by a 3-point intercept estimation (LR3) based on the averaged dataset of systolic, mean and diastolic ABP and Vmca values of each measurement period (from step 10).

The Excel "Intercept function" calculates the intercept (the value at the intersection of the y axis) of the linear regression line through a supplied set of x- and y- values (URL: https://support.office.com/en-US/article/INTERCEPT-function-2A9B74E2-9D47-4772-B663-3BCA70BF63EF)

*RAP calculations*

The $RAP_{LR3}$ was defined as the inverse slope of the linear regression line of ABP and Vmca values. Thus, the $RAP_{LR}$, $RAP_{LR3}$, $RAP_{BEL}$, $RAP_{CZO}$, and $RAP_{SCH}$ were calculated by the quotient of the respective CPPe and mean Vmca. (RAP = (MAP-ZPF) / mean Vmca).

## APPENDIX 3 PRESSURE-VELOCITY RELATIONSHIP ANALYSIS OF LONG DIASTOLES

### Background:

In order to verify the $ZFP_{LR}$ method as suitable reference method in our patients we additionally measured ZFP based on the first long diastole during ICD testing-induced cardiac arrest ($ZFP_{LD}$ and $RAP_{LD}$).

### Methods:

Our own ZFP analysis software (made with LabView ®) could not fit the job. This ZFP analysis of long diastoles has be performed offline with EXCEL and PRISM (see Figure S1). We performed pressure-velocity plots analyses at different durations of the long diastole in 10 patients (1s - 10s, and the whole long diastole).

Normal distribution of data was assessed both visually by inspection of histograms and with the D'Agostino-Pearson omnibus K2 method.[71] Results were presented as mean values (standard deviation, SD) unless otherwise stated.

Values of $ZFP_{LD}$ and $RAP_{LD}$ estimations (1s -10s and the whole LD) were compared to the reference method (LR) by paired tests and ANOVA for repeated measurements with correction for multiple comparison (Dunnett).

### Results:

The first long diastole of patient 4 and patient 13 showed a lot of artifacts regarding the TCD signal. They have been excluded from further analysis of long diastoles)

*Figure S9* showed the measurement phase the first long diastole of patient 8. Figure S10 showed the ZFP analysis at 1s - 10s, and for the whole long diastole.

*Table S1/S2* and *figure S11/S12* show the values of $ZFP_{LD}$ / $RAP_{LD}$ analyses of the first long diastole after induction of ventricular fibrillation of 10 patients.

In our study $ZFP_{LD}$ (3s) was 3 mmHg lower (MD 2.8 (4.), 95% CI -2.7 to 8.3 mmHg, P 0.51) and $ZFP_{LD}$ (4s) was 6 mmHg lower when compared to $ZFP_{LR}$ (MD 5.5 (4.0), 95% CI 1.1 to 9.9, P = 0.016). The analysis of long diastoles of our patients with a duration >4 seconds showed a decrease in $ZFP_{LD}$ when compared to the $ZFP_{LR}$ based on instantaneous pressure-velocity relationships. The longer the duration of the measurement phase, the lower the $ZFP_{LD}$ was. The RAP showed an increase with the similar characteristics.

### Conclusions

Our additional analysis of $ZFP_{LD}$ demonstrated that pressure velocity relationships with a duration of 4 s of longer showed a less linear relationship. Subsequently, the extrapolated $ZFP_{LD}$ (4s or longer) showed lower values when compared to $ZFP_{LR}$.

The use $ZFP_{LR}$ as reference method seems to safe and a good alternative to $ZFP_{LD}$ (2-3s) measurements.

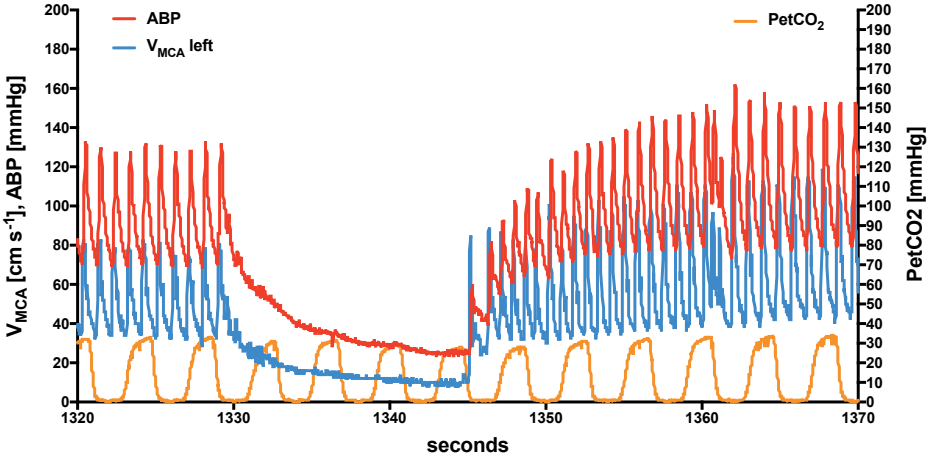



**Figure S9: ZFP and RAP analyses based on long diastoles (patient 8).**
Values of ZFP and RAP by pressure-velocity plots analyses at different durations of the long diastole (1s - 10s, and the whole long diastole).

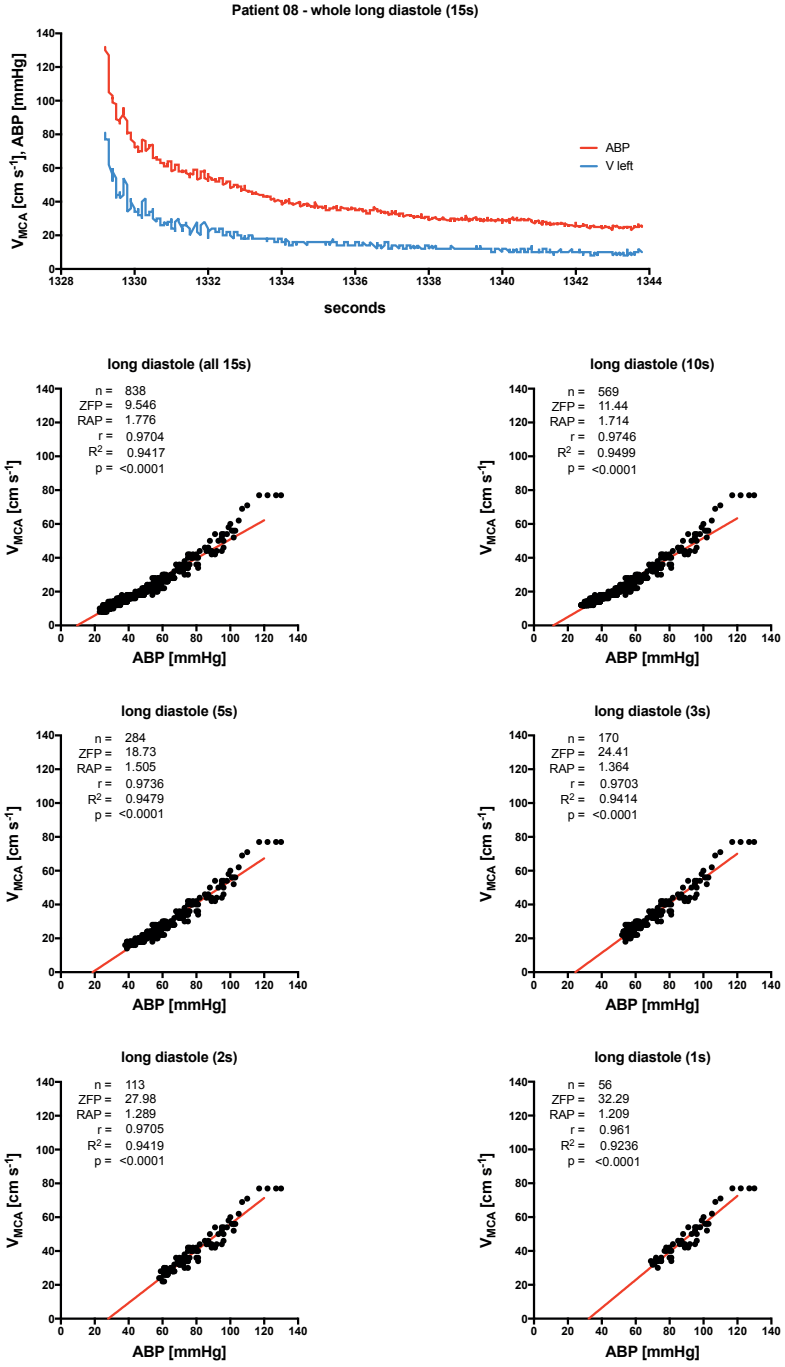



**Figure S10: ZFP and RAP analyses based on long diastoles (patient 8).**
values of ZFP and RAP by pressure-velocity plots analyses at different durations of the long diastole (1 s, 2s, 3s, 5s, 10s, and the whole long diastole).

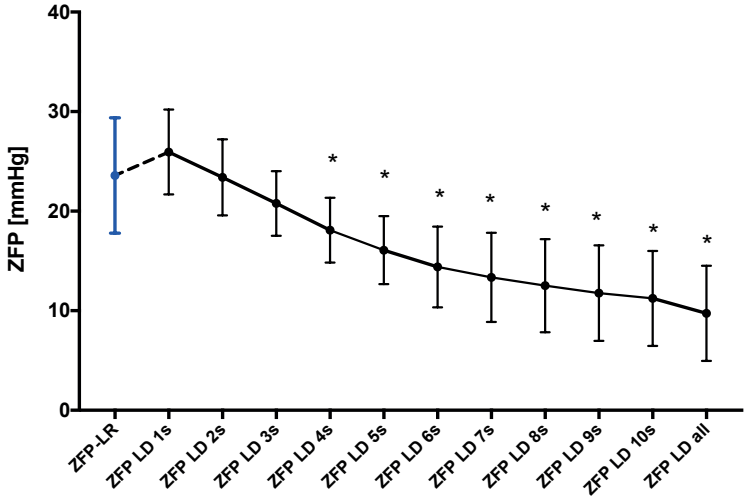



**Figure S11: ZFP analyses based on long diastoles.**

**Table S1: ZFP analyses based on long diastoles.**

| PAT | ZFP-LR | ZFP-LD1s | ZFP-LD2s | ZFP-LD3s | ZFP-LD4s | ZFP-LD5s | ZFP-LD10s | ZFP-LD-all |
|---|---|---|---|---|---|---|---|---|
| PAT_02 | 11.3 | 19.5 | 17.5 | 14.8 | 11.3 | 9.7 | 3.6 | 2.7 |
| PAT_03 | 20.9 | 21.6 | 26.3 | 22.0 | 16.0 | 12.8 | 7.4 | 7.5 |
| PAT_05 | 25.0 | 24.2 | 21.9 | 19.2 | 16.7 | 14.5 | 6.6 | 4.3 |
| PAT_06 | 29.8 | 30.5 | 22.0 | 19.2 | 18.2 | 17.8 | 15.2 | 13.4 |
| PAT_07 | 26.2 | 28.2 | 28.2 | 25.6 | 21.2 | 18.4 | 13.7 | 13.5 |
| PAT_08 | 29.6 | 32.3 | 28.0 | 24.4 | 21.8 | 18.7 | 11.4 | 9.5 |
| PAT_09 | 28.7 | 26.7 | 19.9 | 18.6 | 18.9 | 18.3 | 17.6 | 16.7 |
| PAT_11 | 24.9 | 28.9 | 26.3 | 20.3 | 18.3 | 17.6 | 12.8 | 7.0 |
| PAT_12 | 21.4 | 26.6 | 24.7 | 23.9 | 22.1 | 20.2 | 16.7 | 15.3 |
| PAT_14 | 18.3 | 21.1 | 19.2 | 19.6 | 16.4 | 12.8 | 7.3 | 7.4 |
| Mean (SD) | **23.6 (5.8)** | **25.9 (4.3)** | **23.4 (3.8)** | **20.8 (3.3)** | **18.1* (3.3)** | **16.0* (3.2)** | **11.2* (4.8)** | **9.7* (4.8)** |

**ZFP-LR** = values of zero flow pressure based on 5 "in vivo" instantaneous beat to beat pressure-velocity plot analyses within 2 breaths,

ZFP LD1= values of ZFP pressure-velocity plots analyses at different durations of the long diastole (1 s, 2s, 3s, 5s, 10s, and the whole long diastole). * significant different when compared to ZFP LR (two tailed paired t test and RM ANOVA, $P < 0.05$)

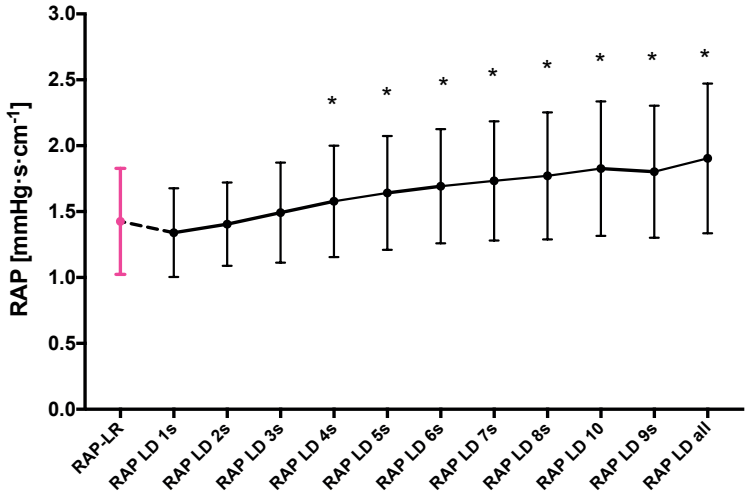


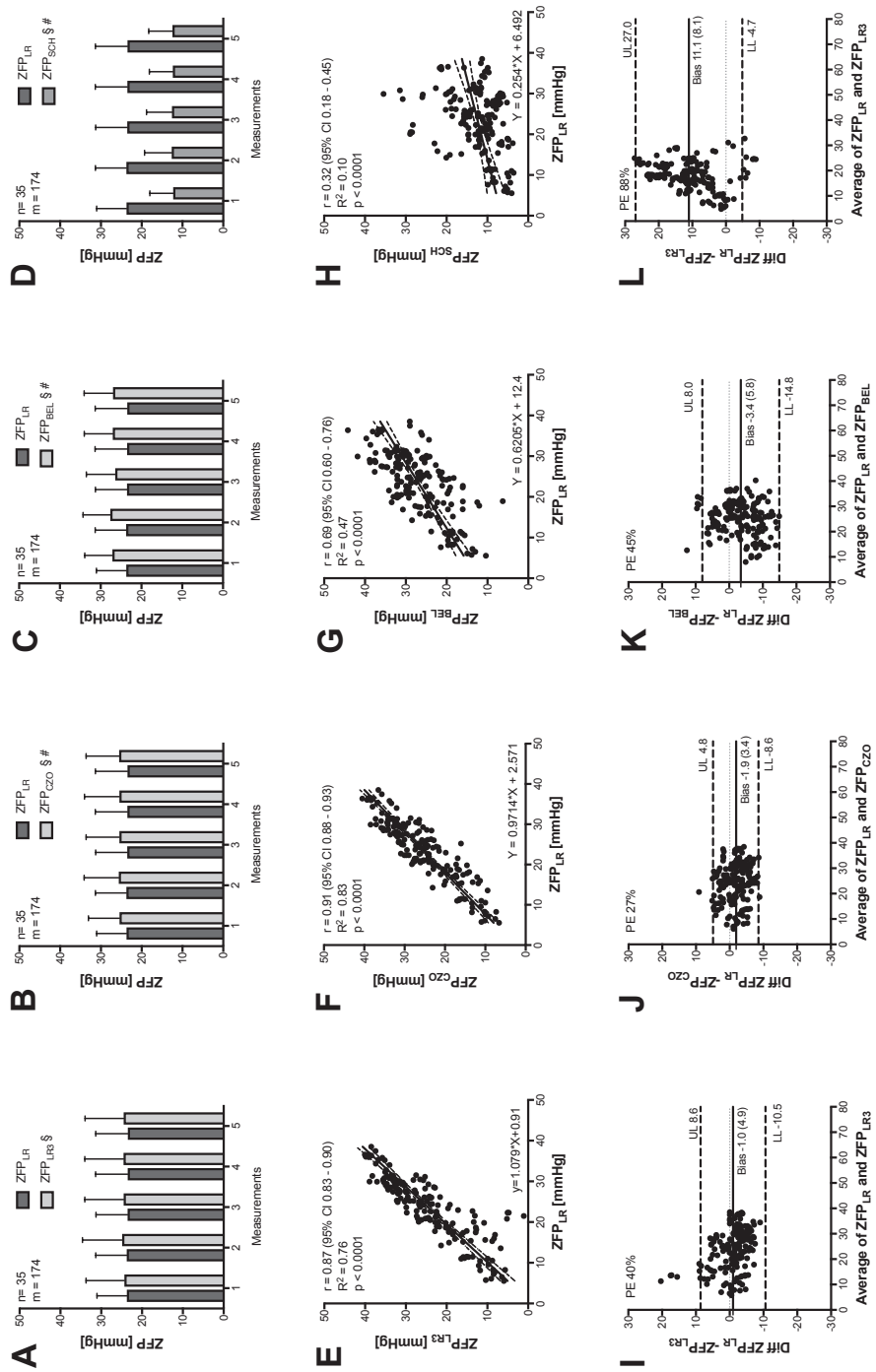

**Figure S12: ZFP analyses based on long diastoles.**

**Table S2: RAP analyses based on long diastoles.**

| PAT | RAP-LR | RAP LD1s | RAP LD2s | RAP LD3s | RAP LD4s | RAP LD5s | RAP LD10s | RAP LD-all |
|---|---|---|---|---|---|---|---|---|
| PAT_02 | 1.79 | 1,67 | 1.72 | 1.82 | 1.94 | 2.00 | 2.24 | 2.29 |
| PAT_03 | 1.89 | 1.87 | 1.75 | 1.89 | 2.11 | 2.23 | 2.46 | 2.46 |
| PAT_05 | 1.69 | 1.49 | 1.59 | 1.64 | 1.73 | 1.81 | 2.13 | 2.25 |
| PAT_06 | 1.28 | 1.32 | 1.57 | 1.70 | 1.71 | 1.73 | 1.85 | 1.94 |
| PAT_07 | 1.69 | 1.39 | 1.39 | 1.47 | 1.63 | 1.73 | 1.93 | 1.94 |
| PAT_08 | 1.27 | 1.21 | 1.30 | 1.36 | 1.43 | 1.51 | 1.71 | 1.78 |
| PAT_09 | 0.92 | 0.84 | 0.95 | 0.98 | 0.97 | 1.00 | 1.01 | 1.04 |
| PAT_11 | 1.81 | 1.62 | 1.72 | 1.98 | 2.08 | 2.11 | 2.40 | 2.79 |
| PAT_12 | 1.16 | 1.12 | 1.15 | 1.17 | 1.21 | 1.26 | 1.37 | 1.41 |
| PAT_14 | 0.76 | 0.89 | 0.91 | 0.90 | 0.96 | 1.04 | 1.16 | 1.16 |
| Mean (SD) | 1.43 (0.40) | 1.34 (0.34) | 1.40 (0.32) | 1.49 (0.38) | 1.58* (0.42) | 1.64* (0.43) | 1.83* (0.51) | 1.90* (0.57) |

**RAP-LR** = values of zero flow pressure based on "in vivo" instantaneous beat to beat pressure-velocity plot analyses within 2 breaths,
ZFP LD1= values of ZFP pressure-velocity plots analyses at different durations of the long diastole (1s -10s, and the whole long diastole). * significant different when compared to ZFP LR (two tailed paired t test and RM ANOVA, P< 0.05)

## APPENDIX 4: ADDITIONAL FIGURES



**⬅ Figure S13: Comparison $ZFP_{LR}$ versus $ZFP_{LR3}$, $ZFP_{CZO}$, $ZFP_{BEL}$, and $ZFP_{SCH}$.**
The cerebral zero flow pressure (ZFP) estimated by four different methods, the 3-point intercept estimation (LR3, systolicmeandiastolic), Czosnyka (CZO, 2 point systolic/diastolic), Belford (BEL, 2 point mean/diastolic), and Schmidt (SCH, 2 point systolic/diastolic) were validated against the reference method (LR, linear regression). One ZFP measurement corresponds to the cumulative analysis of 10-12 cardiac cycles within two breaths. 174 measurements were performed on 35 cardiovascular patients (5 each per patient) under general anesthesia and normocapnia. The figures explain differences (top rows: A-D), correlations (middle rows E-H) and agreement (bottom rows I-L) of the ZFP measurements. All statistical analyses were performed two-sided, and a P value of less than 0.05 was considered to be significant. All results are presented as mean (standard deviation).
Differences between the four tests methods of ZFP estimation (LR3, BEL, CZO SCH) and reference method (LR) were tested by ANOVA with correction for multiple comparison (Dunnett); § significant for all measurements; # significant for subject means.
Pearson *r* correlation coefficients between four ZFP values and the reference method (LR) of all observation were computed to assess their relationship. Agreement was analyzed by Bland-Altman plot analysis with correction for multiple measurements per subject (LL = lower limits of agreement, UL = upper limits of agreement, PE = percentage error).

**➡ Figure S14: Comparison $RAP_{LR}$ versus $RAP_{LR3}$, $RAP_{CZO}$, $RAP_{BEL}$, and $RAP_{SCH}$.**
The resistance area product (RAP) estimated by four different methods, the 3-point intercept estimation (LR3, systolicmeandiastolic), Czosnyka (CZO, 2 point systolic/diastolic), Belford (BEL, 2 point mean/diastolic), and Schmidt (SCH, 2 point systolic/diastolic) were validated against the reference method (LR, linear regression). One RAP measurement corresponds to the cumulative analysis of 10-12 cardiac cycles within two breaths. 174 measurements were performed on 35 cardiovascular patients (5 each per patient) under general anesthesia and normocapnia. The figures explain differences (top rows: A-D), correlations (middle rows E-H) and agreement (bottom rows I-L) of the RAP measurements. All statistical analyses were performed two-sided, and a P value of less than 0.05 was considered to be significant. All results are presented as mean (standard deviation).
Differences between the four tests methods of RAP estimation (LR3, BEL, CZO SCH) and reference method (LR) were tested by ANOVA with correction for multiple comparison (Dunnett); § significant for all measurements; # significant for subject means.
Pearson *r* correlation coefficients between four RAP values and the reference method (LR) of all observation were computed to assess their relationship. Agreement was analyzed by Bland-Altman plot analysis with correction for multiple measurements per subject (LL = lower limits of agreement, UL = upper limits of agreement, PE = percentage error).

A
B
C
D
E
F
G
H
I
J
K
L
n= 35
m = 174
RAP_LR
RAP_LR3 n.s.
RAP_CZO § #
RAP_BEL § #
RAP_SCH § #
Measurements
RAP_LR3 [mmHg·s·cm-1]
RAP_CZO [mmHg·s·cm-1]
RAP_BEL [mmHg·s·cm-1]
RAP_SCH [mmHg·s·cm-1]
r = 0.97 (95% CI 0.97 - 0.98)
R2 = 0.94
p < 0.0001
Y = 0.9832*X + 0.001656
r = 0.99 (95% CI 0.98 - 0.99)
R2 = 0.97
p < 0.0001
Y = 0.9279*X + 0.0511
r = 0.95 (95% CI 0.94 - 0.96)
R2 = 0.91
p < 0.0001
Y = 0.7878*X + 0.1983
r = 0.87 (95% CI 0.82 - 0.90)
R2 = 0.74
p < 0.0001
Y = 0.8726*X + 0.4349
RAP_LR [mmHg·s·cm-1]
PE 16%
PE 12%
PE 22%
PE 31%
UL 0.25
Bias 0.02 (0.12)
LL -0.20
UL 0.21
Bias 0.05 (0.08)
LL -0.11
UL 0.40
Bias 0.10 (0.15)
LL -0.20
UL 0.22
Bias -0.26 (0.24)
LL -0.74
Diff RAP_LR - RAP_CZO
Diff RAP_LR - RAP_BEL
Diff RAP_LR - RAP_SCH
Average of RAP_LR & RAP_CZO
Average of RAP_LR & RAP_BEL
Average of RAP_LR & RAP_SCH

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# Chapter 3

## Carbon dioxide induced changes in cerebral blood flow and flow velocity: role of cerebrovascular resistance and effective cerebral perfusion pressure.

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J Cereb Blood Flow Metab 2015;35:1470–7
German Clinical Trials Register (DRKS00011535).

This article is dedicated in memoriam to our teacher, colleague, and friend Professor Hans Sonntag, who considerably contributed to the concept of this study and died in 2011.

## ABSTRACT

**Background:** In addition to cerebrovascular resistance (CVR) zero flow pressure (ZFP), effective cerebral perfusion pressure (CPPe) and the resistance-area-product (RAP) are supplemental determinants of cerebral blood flow (CBF). Until now, the interrelationship of $PaCO_2$-induced changes in CBF, CVR, CPPe, ZFP, and RAP is not fully understood.
**Materials and methods:** In a controlled crossover trial, we investigated 10 anesthetized patients aiming at PaCO2-levels of 30, 37, 43 and 50 mmHg. CBF was measured with a modified Kety-Schmidt-technique. ZFP and RAP was estimated by linear regression analysis of pressure-flow velocity relationships of the middle cerebral artery. CPPe was calculated as the difference between mean arterial pressure and ZFP, CVR as the ratio CPPe/CBF. Statistical analysis was done by one-way RM-ANOVA.
**Results:** When comparing hypocapnia with hypercapnia CBF showed a significant exponential reduction by 55% and mean VMCA by 41%. CPPe linearly decreased by 17% while ZFP increased from 14 to 29 mmHg. CVR increased by 96% and RAP by 39%; despite these concordant changes in mean CVR and Doppler-derived RAP correlation between these variables was weak (r=0.43).
**Conclusion:** Under general anesthesia hypocapnia-induced reduction in CBF is caused by both, an increase in CVR and a decrease in CPPe, as a consequence of an increase in ZFP.


**Keywords:** carbon dioxide/physiology, cerebrovascular circulation/physiology, resistance, cerebrovascular, ultrasonography, Doppler, transcranial, velocity, blood flow

## INTRODUCTION

Arterial partial pressure of carbon dioxide ($PaCO_2$) is well known to change global cerebral blood flow (CBF) and the flow velocity of the middle cerebral artery ($V_{MCA}$), which can be explained by an increase or decrease of cerebral vascular resistance (CVR) and partly by cerebral perfusion pressure (CPP). Over a range of $PaCO_2$ values of 20-80 mmHg for each mmHg increase or decrease in $PaCO_2$ there is a 2-4% change in CBF or $V_{MCA}$.[1] However, it is still unclear which of both determinants is more affected by hyperventilation and hypoventilation: CPP, CVR, or both. Both variables are thought to be influenced by arteriolar smooth muscle tone and therefore these variables can be expected to change simultaneously when $PaCO_2$ varies.[2]

When calculating the CPP, the mean arterial pressure (MAP) is commonly 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.[3] However, another major component of the effective downstream pressure is the critical closing pressure (CCP), which cannot be directly measured in patients with spontaneous circulation. It has been proven that in vivo pressure-flow relationships are linear for many vascular beds, including the cerebral vessels.[4] Since the introduction of transcranial Doppler ultrasonography (TCD), a number of methods have been developed to assess CCP by extrapolating instantaneous pressure-flow-velocity plots ($ABP/V_{MCA}$) to zero or by calculation of the intercept of diastolic, mean and/or systolic values of pressures and flow-velocity.[2,5-8]

A number of factors other than vascular tone, i.e. central venous pressure (CVP) and ICP, can also influence the EDP in the cerebral circulation. Consequently, the use of the term 'zero flow pressure' (ZFP) is considered more appropriate than CCP.[9] It is suggested that, in patients without increased ICP, ZFP is determined by arteriolar tone. The effective cerebral perfusion pressure (CPPe) is defined by the difference between MAP and ZFP.[5] The inverse of the slope of the ABP - $V_{MCA}$ plot is named the 'resistance area product' (RAP).[10] In several investigations the RAP has been used as index of CVR.[2,11]

Recent studies could demonstrate that ZFP varies inversely with changes of $PaCO_2$.[2,5,6] Furthermore, hypocapnia reduced CBF by decreasing CPPe due to the increase in ZFP, whereas the RAP was unaffected.[7] In contrast, McCulloch and colleagues could demonstrate that hyperventilation significantly increases RAP, which seemed to have a greater effect on $V_{MCA}$ than the increase in ZFP.[2]

It is still unclear, which of both components is more affected by hyperventilation and hypoventilation. Describing 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.[6]

Up to now there is no investigation that combines measurements of CBF and $V_{MCA}$ in order to compare changes of the cerebrovascular $CO_2$-reactivity ($CO_2$-R) of global CBF and of $V_{MCA}$. 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, $V_{MCA}$, CPPe, ZFP, RAP and CVR in patients under intravenous anesthesia.

## MATERIAL AND METHODS

### Design

The prospective study was designed and performed in a controlled, crossover design at the University of Göttingen Medical Center. The main purpose of this study was to evaluate the cerebrovascular reactivity induced by variations in arterial partial pressure of carbon dioxide in anesthetized patients examined by a combination of two cerebral measurements techniques: transcranial Doppler Sonography and Kety-Schmidt technique. Each patient served as his own control. The study followed the recommendations of the Declarations of Helsinki from 1975-1989 and the European Union Commission and European Medicines Agency (Council Directive 91/507/EEC and 75/318/EEC). Approval was obtained from the local institutional review board (Medical Ethical Committee of the Georg-August-University of Göttingen, Göttingen, Niedersachsen, Germany; No. 07/09/90).

### Endpoints

The endpoints of the trial were changes in CBF, $V_{MCA}$, CPPe, ZFP, CVR and RAP.

### Screening, inclusion and informed consent of patients

Due to logistic reasons we could perform only 1-2 measurements per month. Therefore, standard-screening procedures could not be applied in this crossover trial. Patients were eligible for inclusion if scheduled for elective coronary surgery. Exclusion criteria were being older than 80 years of age, female gender, patient refusal, active neurological disease, and a history of cerebrovascular disease, brain injury, or intracranial surgery. All patients were informed of the purpose of the study and provided written informed consent before being enrolled. None of the eligible patients refused inclusion of the trial. There were no dropouts during the study period.

### Sample size calculation

The inter-subject and intra-subject variability of CBF, CPP and CVR has been reported in earlier studies.[12-15] There is paucity of data of CBF and $V_{MCA}$ in humans under general anesthesia, which was necessary for an exact sample size calculation for this crossover trial. We expected a 50% difference of CBF with an estimated effect size of 0.7-0.8. For a statistical power of 0.8-0.9 the sample size had to be between 7-10 patients. Therefore we projected a sample size of 10 patients.

### Anesthesia Procedure

Individual medications were continued until surgery. Intravenous anesthesia was induced and maintained by continuous intravenous administration fentanyl, midazolam and pancuronium. The anesthesia procedure, the details of mechanical ventilation and the methods of catheter insertion have been described in previous reports in detail.[14,16]



### Measurements

CBF was measured using the modified Kety-Schmidt inert gas saturation technique with argon as a tracer gas as described in detail in earlier reports.[14,16] Blood flow velocity in the proximal (M1) segment of the middle cerebral artery ($V_{MCA}$) was measured by TCD as extensively described in earlier reports.[5,14] Because TCD measurements of $V_{MCA}$ from the transtemporal window fail with above average incidence in elderly female patients we included only male patients in this study.[17] Arterial blood pressure was measured invasively in the radial artery, ispilateral to the TCD probe.

Measurements were performed aiming at $PaCO_2$-levels of A) hyperventilation (30mmHg), B) normoventilation I (37mmHg), C) normoventilation II (43mmHg) and D) hypoventilation (50 mmHg) before surgery. All measurements were performed during hemodynamic and respiratory steady-state conditions. The time interval between the measurements was 20 min. Blood samples were drawn twice, at the beginning and end of each argon wash-in period, to measure hemoglobin concentration and variables of blood gas analysis (ABL; Radiometer, Copenhagen, Denmark). For comparisons with CBF measurements, $V_{MCA}$ was averaged over the 10 min period of each argon wash-in maneuver. End-expiratory $CO_2$ concentrations were continuously recorded to ensure a stable $PaCO_2$ during argon saturation.

### Calculations

The analyses of the ZFP, CPPe and RAP have been performed after the study period. Cerebral ZFP was calculated from data at the beginning and end of each CBF measurement from two simultaneous 10-s recordings (two breathing cycles) of the $V_{MCA}$ envelope and arterial pressure curves. Over each 10-s period we first averaged consecutive pairs of diastolic, mean and systolic data of ABP and $V_{MCA}$. These data were used in a pres-

sure/flow velocity plot. ZFP was then extrapolated by linear regression analysis of the ABP-$V_{MCA}$ relationship. A correction of the time delay between ABP and $V_{MCA}$ signal was not necessary. The ABP axis intercept of the regression line determines the ZFP.[5,8] The cerebral ZFP was used as a measure of the effective downstream pressure of the cerebral circulation. In the relationship between ABP and $V_{MCA}$, the RAP is defined as the inverse slope of their linear regression line.[2,4,6,10]

Formulae to calculate CPPe, CVR, and RAP are shown in table 1. The calculation of the carbon dioxide-reactivity was based on the ratio of the individual changes of CBF and $PaCO_2$. To ensure a better comparability with previous studies, we compared CBF and $V_{MCA}$-values of hyperventilation (A) and hypoventilation (D) with standardized normocapnic CBF and $V_{MCA}$-values, extrapolated by regression analysis for each patient at a $PaCO_2$-level of 40mmHg. This calculation of $CO_2$-reactivity indicates of the percentage of the changes in CBF and $V_{MCA}$ per mmHg, which is relatively independent of the particular flow levels and the $PaCO_2$ values.[18]

**Table 1. Formulae to calculate CPPe, CVR, RAP, and $CO_2$-R**

| *Parameter* | *Formula* | *Value* |
|---|---|---|
| Effective cerebral perfusion pressure (CPPe)[5,7] | CPPe = MAP − ZFP | mm Hg |
| Cerebral vascular resistance (CVR)[5] | CVR= CPPe/CBF | mm Hg/ml/100 g/min |
| Resistance area product (RAP)[2,10] | RAP= inverse slope of the relationship of pressure/flow $velocity_{MCA}$ | mm Hg × s/cm |
| Relative carbon dioxide reactivity ($CO_2$-R)[18] | $CO_2$-R = (parameter D–A)/$parameter_{extrapolated\ for\ normocapnia}$ / (Pa $CO_2$ D–A) x 100 | %/mm Hg |

Abbreviations: MAP, mean arterial pressure; $V_{MCA}$, cerebral flow velocity of the middle cerebral artery; ZFP, zero flow pressure.

## Statistical Analysis

The results presented in tables are expressed as mean (standard deviation) unless otherwise stated. Tests for normal distribution of data were done with the D'Agostino-Pearson omnibus K2 method.

The differences between the ventilation steps were assessed using one-way analysis of variance for repeated measures (RM-ANOVA). Multi-comparison analyses between measurements have been done with Holm-Šídák post hoc tests.[19,20]

The differences between D (hypoventilation) and A (hyperventilation), C (normoventilation II) and A (hyperventilation) as well as B (normoventilation I) and D (hypoventilation) were calculated using t-tests for paired data or Welch-test and non-parametric Wilcoxon signed-rank test, if indicated.[21] To provide an estimate of the effect of changes in $PaCO_2$ levels and their clinical meaningfulness, we calculated mean differences (MD) and their 95% confidence intervals (MD; 95% CI upper bound, lower bound; *P*-value).[22] In

order to prevent from type I error, all primary endpoints were tested by one-way ANOVA for repeated measurements followed by Bonferoni multiple comparison tests.[23] All statistical analysis were performed two-sided and a p-value of $p<0.05$ was considered to be significant. Database sheets were done by MS Excel® for Mac 2011 (Microsoft, Redmond, Washington, USA). Statistical procedures and graphs were made using Prism 6.0 (GraphPad Software, La Jolla, California, USA). Sample size calculation was done with G*Power (University of Düsseldorf, Dept. of Psychology, Düsseldorf, Germany).

## RESULTS

The study period was 11 months (February 20th 1991 until January 28th 1992). A total of 10 male patients were included in the study. The mean age of the patients was 56(6) yrs. (median 58, range 48-65 yrs.), mean height 173(6) cm, and mean body weight 77(9) kg. The variability of the four target levels of $PaCO_2$ was small due to the controlled adjustment of mechanical ventilation. Levels of hemoglobin, partial oxygen pressure, blood viscosity and blood temperature were kept constant during the measurements. Cardiac index and stroke volume index changed slightly, which was clinically not relevant. The controlled reduction in $PaCO_2$ caused a small increase of MAP, which could be related to a significant small increase of systemic vascular resistance.

The mean TCD-insonation depth of the MCA was 51(3) mm. TCD signals were of high quality in all patients except one measurement: during the second 10s recording of $V_{MCA}$ and ABP of patient 5 at $PaCO_2$ of 37mmHg showed ABP artifacts. The calculation of the ZFP was thus based on the values at the beginning of the CBF measurement. Hemodynamic and basic metabolic data are presented in table 2. Results of absolute $CO_2$ reactivity of CBF and $V_{MCA}$ are presented in table 3 for the different steps of $PaCO_2$ -variation as well in figure 1A and 1B as exponential function.

The effects of ventilatory changes on the cerebral circulation were substantial. Hyperventilation (A) exponentially reduced CBF, in total by 55%, and $V_{MCA}$ by 41%, when compared with hypoventilation (D). Compared to CBF, the exponential decrease of mean $V_{MCA}$ due to changes in $PaCO_2$ was less pronounced (figure 1A, 1B, table 2 and 3A).

The decrease in CBF and mean $V_{MCA}$ due to hyperventilation was interrelated to an increase of CVR by 96% (figure 1E, table 2 and 3A) and a decrease of CPPe by 17% (figure 1C, table 2 and 3A). As expected, changing $PaCO_2$ levels from hypoventilation to hyperventilation lead to small increase of the MAP by 7.5%, however post-hoc comparison analysis between measurement (D) and (A) did not reach level of significance (MD 5 (8) mmHg, P=0.25). The CPPe decrease was thus primarily caused by an evident linear increase of ZFP by 15(6) mmHg (figure 1C and 1D, table 2, and table 3A). Hyperventilation (A) increased RAP only by 39%, when compared with hypoventilation (D) (figure

**Table 2. Hemodynamic and metabolic variables**

| *Variable* | *Dimension* | *$PaCO_2$ level* | | | | *ANOVA* | *MC* |
|---|---|---|---|---|---|---|---|
| | | *A* | *B* | *C* | *D* | *P value* | *post hoc* |
| $PaCO_2$ | mm Hg | 29 (2) | 37 (2) | 44 (2) | 52 (2) | < 0.001 | s; 1–6 |
| CBF[a] | mL/100 g/min | 31 (6) | 35 (7) | 45 (13) | 73 (22) | < 0.001 | s; 1–6 |
| $V_{MCA}$ mean[a] | cm/s | 31 (8) | 34 (10) | 40 (14) | 52 (15) | < 0.001 | s; 1–6 |
| ZFP[a] | mm Hg | 29 (5) | 24 (4) | 18 (4) | 14 (5) | < 0.001 | s; 2–5 |
| CPPe[a] | mm Hg | 47 (10) | 52 (11) | 54 (14) | 56 (12) | 0.002 | s; 2,3 |
| CVR[a] | mm Hg/mL/100 g/min | 1.53 (0.38) | 1.52 (0.40) | 1.28 (0.50) | 0.83 (0.28) | < 0.001 | s; 3,5,6 |
| RAP[a] | mm Hg × s/cm | 1.60 (0.52) | 1.69 (0.62) | 1.49 (0.58) | 1.17 (0.41) | < 0.001 | s; 3,5,6 |
| CI | $L/min/m^2$ | 2.1 (0.4) | 2.1 (0.3) | 2.3 (0.3) | 2.4 (0.3) | 0.063 | ns |
| SVI | $mL/beat/m^2$ | 38 (10) | 39 (10) | 41 (9) | 42 (9) | 0.059 | ns |
| MAP | mm Hg | 76 (11) | 74 (11) | 71 (11) | 71 (11) | 0.045 | ns |
| SVRI | $mL/beat/m^2$ | 2,741 (771) | 2,668 (710) | 2,298 (621) | 2,217 (583) | 0.030 | s; 5 |
| Hb | mg/dL | 12.1 (1.2) | 12.0 (1.3) | 12.3 (1.1) | 12.2 (1.3) | 0.197 | ns |
| $PaO_2$ | mm Hg | 118 (17) | 119 (22) | 119 (25) | 117 (26) | 0.908 | ns |
| Visc | mPa × s | 4.3 (0.5) | 4.2 (0.6) | 4.4 (0.5) | 4.3 (0.5) | 0.345 | ns |
| Temp | C | 35.3 (0.3) | 35.2 (0.2) | 35.3 (0.3) | 35.2 (0.3) | 0.159 | ns |

Abbreviations: CBF, cerebral blood flow; CI, cardiac index; CPPe, effective cerebral perfusion pressure; CVR, cerebrovascular resistance; Hb, hemoglobin concentration; MAP, mean arterial pressure; ns, non significant; $PaCO_2$, arterial partial pressure of $CO_2$; $PaO_2$, arterial partial pressure of $O_2$; RAP, resistance area product; s, significant; ; SVI, stroke volume index; SVRI, systemic vascular resistance; Temp, blood temperature; Visc, blood viscosity; $V_{MCA}$, blood flow velocity of the middle cerebral artery; ZFP, zero flow pressure. Effect of the $PaCO_2$ level (RM-ANOVA = analysis of variance for repeated measures $P < 0.05$). MC = multiple group comparison (Holm–Sidak, $P < 0.05$): Significant difference between means between: 1 = A versus B, 2 = A versus C, 3 = A versus D, 4 = B versus C, 5 = B versus D, 6 = C versus D. [a]End points.

**Table 3. Effect of changes in $PaCO_2$ levels on primary end points**

| *Variable* | *Dimension* | *MD (s.d.)* | *CI limits** | *P** |
|---|---|---|---|---|
| *(A) Comparison between D ($PaCO_2$ = 50 mm Hg) versus A ($PaCO_2$ = 29 mm Hg)* | | | | |
| $PaCO_2$ §* | mm Hg | 23 (2) | 20 to 25 | < 0.0001 |
| CBF §$#* | mL/100 g/min | 42 (18) | 22 to 62 | 0.0003 |
| $V_{MCA}$ mean §$#* | cm/s | 21 (8) | 13 to 30 | < 0.0001 |
| ZFP §* | mm Hg | −15 (6) | −22 to −8 | 0.0002 |
| CPPe §* | mm Hg | 10 (8) | 1 to 18 | 0.0210 |
| CVR §* | mm Hg/mL/100 g/min | −0.70 (0.33) | −1.06 to -0.34 | 0.0007 |
| RAP §* | mm Hg × s/cm | −0.42 (0.29) | −0.74 to −0.10 | 0.0097 |
| *(B) Comparison between C ($PaCO_2$ = 44 mm Hg) versus A ($PaCO_2$ = 29 mm Hg)* | | | | |
| $PaCO_2$ §* | mm Hg | 15 (2) | 13 to 16 | < 0.0001 |
| CBF §$#* | mL/100 g/min | 14 (12) | 1 to 27 | 0.0330 |
| $V_{MCA}$ mean §$#* | cm/s | 9 (6) | 2 to 16 | 0.0116 |
| ZFP §* | mm Hg | −11 (6) | −17 to −5 | 0.0010 |
| CPPe § | mm Hg | 7 (7) | −0,3 to 14 | 0.0650 |
| CVR § | mm Hg/mL/100 g/min | −0.24 (0.33) | −0.60 to 0.11 | 0.2689 |
| RAP | mm Hg × s/cm | −0.11 (0.25) | −0.38 to 0.16 | 0.7940 |
| *(C) Comparison between D ($PaCO_2$ = 50 mm Hg) versus B ($PaCO_2$ = 37 mm Hg)* | | | | |
| $PaCO_2$ §* | mm Hg | 15 (2) | 13 to 17 | < 0.0001 |
| CBF §$#* | mL/100 g/min | 38 (17) | 20 to 56 | 0.0004 |
| $V_{MCA}$ mean §$#* | cm/s | 19 (5) | 13 to 25 | < 0.0001 |
| ZFP §* | mm Hg | −10 (6) | −17 to −3 | 0.0047 |
| CPPe | mm Hg | 4 (7) | −3 to 12 | 0.5271 |
| CVR §* | mm Hg/mL/100 g/min | −0.69 (0.22) | −0.85 to −0.53 | < 0.0001 |
| RAP §* | mm Hg × s/cm | −0.52 (0.34) | −0.76 to −0.28 | 0.0062 |

Abbreviations: CBF, cerebral blood flow; CI, confidence interval; CPPe, effective cerebral perfusion pressure; CVR, cerebrovascular resistance; MD, mean difference; $PaCO_2$, arterial partial pressure of $CO_2$; RAP, resistance area product; s.d., standard deviation; $V_{MCA}$ = blood flow velocity of the middle cerebral artery; ZFP, zero flow pressure. The *P* values, which refer to the difference between two measurement points, were calculated using two-sided *t*-test for paired data (§). Because the variances of some outcome variables differed between two measurement points, these parameters were additionally examined by Welch test (#) and nonparametric Wilcoxon signed-rank test ($), which showed that the differences persist ($P < 0.05$). To prevent from type I error, statistical analysis of end points was adjusted by one-way ANOVA for repeated measurements with Bonferoni multicomparison procedure (*).

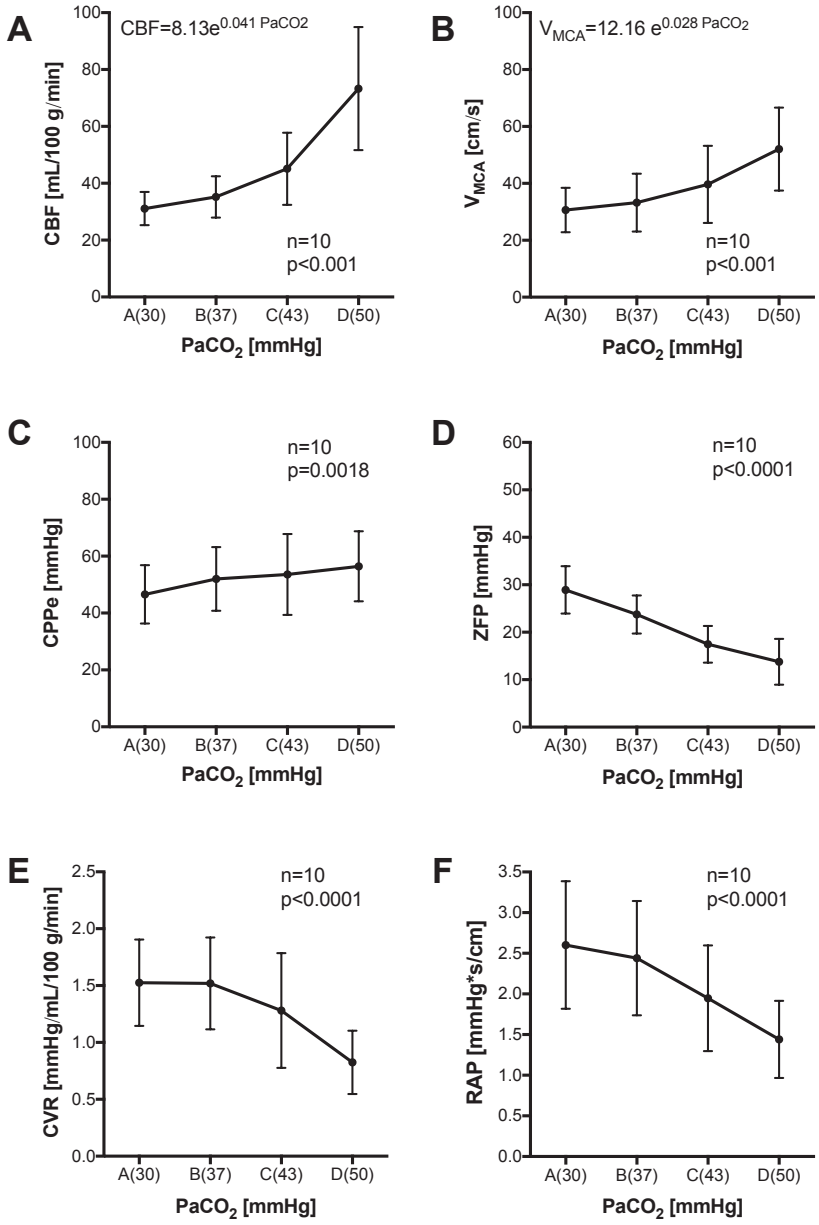


**Figure 1: Cerebral hemodynamic variables under different levels of $PaCO_2$**

Values of CBF (figure 1A), mean $V_{MCA}$ (figure 1B), CPPe (figure 1C), ZFP (figure 1D), CVR (figure 1E) and RAP (figure 1F) under four different levels of $PaCO_2$. Data are mean (SD) for each measurement. The P values were calculated using analysis of variance for repeated measures ($p< 0.05$).

CBF = cerebral blood flow, CI = confidence interval, CPPe = effective cerebral perfusion pressure, CVR = cerebrovascular resistance, MD = mean differences, $PaCO_2$ = arterial partial pressure of $CO_2$, RAP = resistance area product, SD = standard deviation, $V_{MCA}$ = blood flow velocity of the middle cerebral artery, ZFP = zero flow pressure.

1F, table 2 and table 3A). The changes in mean CVR and RAP were thus concordant, nevertheless the correlation analysis of individual data showed only a weak linear connection (Pearson r = 0.43, CI 0.14 to 0.66, P = 0.005).

The curves of CBF, $V_{MCA}$, CVR and RAP showed an exponential slope (figure 1). Thus, percent changes between the ventilation-steps might be quantitatively different. For statistical analysis we consequently compared C (normoventilation II) versus A (hyperventilation) and B (normoventilation I) versus D (hypoventilation) of all endpoints.

When comparing level C (normoventilation II) with A (hyperventilation) CBF was reduced by 28% and mean $V_{MCA}$ by 21% (table 3B). The decrease of CPPe by 12% was caused by an increase of ZFP by 74%, which exceeded the small increase in MAP. CVR increased by 0.24(0.30) mmHg/mL/100 g/min and RAP by 0.11 (0.25) mmHg*s/cm (table 3B), which were not significant.

When comparing level D (hypoventilation) with B (normoventilation I) the CBF was decreased by 50% and mean $V_{MCA}$ by 36% (table 3C). Here the relative increase of ZFP was high (93%) but absolute changes were small which lead only to a small reduction in CPPe by 7%. The RAP showed a less pronounced increase (by 46%) than the CVR, which increased by 91% (table 3C).

Cerebrovascular $CO_2$-reactivity of CBF was 1.88 (0.89) mL/100 g/min/mmHg, corresponding to a relative change of 4.13 (1.27) %/mmHg. The cerebrovascular $CO_2$-reactivity of mean $V_{MCA}$ was 0.95(0.36) cm/s/mmHg, corresponding to a relative change of 2.47 (0.48) %/mmHg, which was significantly lower than the relative $CO_2$-reactivity of CBF (MD -1.67; 95% CI: -2.46, -0.87; p=0.001).



## DISCUSSION

We investigated the effects of variations in $PaCO_2$ on cerebral blood flow, blood flow velocity, effective cerebral perfusion pressure, cerebrovascular resistance, zero flow pressure and resistance area product in cardiovascular patients undergoing fentanyl-midazolam anesthesia. The three most prominent results of our study are:

(i) hypocapnia-induced reduction in CBF under general anesthesia was the effect of both, an increase in CVR and a decrease in CPPe, as a consequence of an increase in ZFP;

(ii) the increases of mean CVR and RAP associated with hypocapnia were concordant. Nevertheless, correlation analysis showed only a weak linear relationship;

(iii) variation of $PaCO_2$ within a range of 30-50 mmHg induced changes in CBF and $V_{MCA}$, which both followed an exponential function. However, $V_{MCA}$ systematically underestimated changes in global cerebral blood flow resulting in a discrepancy between cerebrovascular $CO_2$ reactivity measured by CBF and $V_{MCA}$.

Examining the functional capacity of the cerebrovascular autoregulatory system by altering blood pressure is difficult and possibly hazardous to be performed as a routine clinical procedure. Therefore, Bloor and colleagues introduced $CO_2$-reactivity measurements to evaluate cerebral vascular reactivity.[24]

In our study we could demonstrate that the cerebrovascular $CO_2$-reactivity (within a $PaCO_2$ range of 30-50 mmHg) of CBF as well as $V_{MCA}$ followed an exponential shape. Other authors described the cerebral $CO_2$-reactivity response curve of CBF in humans as a linear or exponential function.[1,15,25,26] Correspondingly, $CO_2$-response curves of the $V_{MCA}$ measured by TCD have been described as a linear, logarithmic, exponential or as a sigmoid function.[26,27]

Today, $V_{MCA}$ and its indices are routinely used to assess components of cerebral circulation and cerebrovascular resistance. A good correlation between changes in $V_{MCA}$ and changes in CBF has been found during carotid endarterectomy.[28] During cardiopulmonary bypass and in patients with cerebrovascular diseases, correlations between CBF and $V_{MCA}$ values are rather weak with wide between-patient variation.[14,29]

In a number of previous studies relative changes in CBF were reflected by changes in $V_{MCA}$ in a proportional manner, suggesting that MCA diameter remains constant.[30] Nevertheless, other investigations could demonstrate that illness and interventions as orthostasis, migraine attacks, $CO_2$-rebreathing or vasoactive medicine could change the MCA diameters by 5-12%.[31-34]

Reports of cerebrovascular $CO_2$-reactivity of CBF and $V_{MCA}$ in humans give inconsistent results. Additionally, comparisons between cerebrovascular $CO_2$-reactivity of CBF and $V_{MCA}$ in humans under general anesthesia are very rare. In our study we could demonstrate that the cerebrovascular $CO_2$-reactivity (within a range of 30-50mmHg) of CBF as well as $V_{MCA}$ showed an exponential function. However, the relative cerebrovascular $CO_2$-reactivity measured by TCD was lower when compared to measurements of CBF by the Kety-Schmidt technique, especially under hypercapnia. 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. A similar phenomenon had been described during hypothermic CPB.[14]

Our study is the first report that combines measurement of global CBF with the determination of ZFP and CPPe. The CVR is commonly defined by the law of Darcy as the quotient between the driving blood pressure and CBF ("classical model" CVR=(MAP-ICP)/CBF). This model has limitations, because it assumes that flow or flow velocity only reaches zero when the driving pressure is zero, which is unlikely, at least in the absence of intracranial hypertension.[6] Patients without cerebrovascular disease are expected to have a normal ICP between 7-15 mmHg in supine position.[35] Hyperventilation reduces cerebral blood volume and consequently decreases ICP.[36] But the reduction of ICP in-

duced by hyperventilation in patients without cerebrovascular disease is expected to be small. Thus, the main determinant of the driving pressure would be the MAP. Our patients showed only a small increase of MAP and SVRI, which was in accordance with previous findings.[37] Nevertheless, measures of MAP do not directly reflect the *effective* CPP because the CPP may be modified by factors other than MAP and ICP.[6]

Studies of other organs have shown, that the EDP can be determined by a Starling resistor located at arteriolar level.[38] These studies verified the theory of Permutt and Riley[39] showing that two forces, the extramural pressure (ICP in the case of the brain) and arteriolar wall tension determine CCP. Arteriolar wall tension arises from a combination of the stretched elastic components of the vessel wall and active contraction of vascular smooth muscle. 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 CCP.



The CCP of the cerebral circulation cannot be directly measured in patients with spontaneous circulation. It has been confirmed that in vivo pressure-flow relationships are straight lines for many vascular beds and for the cerebral vessels as well.[4] Since the introduction of TCD, a number of methods have been developed to assess CCP non-invasively by extrapolating instantaneous pressure-flow velocity plots ($ABP/V_{MCA}$) to zero from continuous recordings or by extrapolation of the ZFP from a linear function given by diastolic, mean and/or systolic values of pressures and flow-velocity.[2,5-7]

In a former investigation we suggested the hypothesis of two Starling resistors in a series connection, one (proximal) at the precapillary level of cerebral resistance vessels ($CCP_{art}$) and a second (distal) at the level of collapsible cerebral veins ($CCP_{ven}$). The effective downstream pressure of the cerebral circulation may be determined by either $CCP_{art}$, $CCP_{ven}$ (i.e. ICP), or jugular venous pressure, depending on which one is highest.[5] Thus, a number of factors other than vascular tone, i.e. CVP and ICP, can also influence EDP in the cerebral circulation. Consequently, the use of the term 'zero flow pressure' (ZFP) is considered more appropriate than CCP.[9]

Using the difference between MAP and ZFP as the driving pressure of the cerebral circulation offers advantages in understanding pathophysiology, because changes of the effective downstream pressure will be reflected by this kind of calculation ("alternative model" CVR=(MAP-ZFP)/CBF). The reduction of CPPe due to hyperventilation in our patients was clinically relevant, which is in accordance with previous findings.[2,5-7,40]

When using TCD, an estimate of vascular resistance can be derived from the ratio between blood pressure and blood flow velocity, which equals the product of the peripheral resistance and the cross-sectional area of the vessel at the site of insonation, the resistance area product (RAP).[10] Up to now, there is no investigation that compared measurements of global CBF and $V_{MCA}$ in order to compare changes in CVR with RAP. In our study the increase of mean CVR and RAP due to changes of $PaCO_2$ was concordant.

Nevertheless, correlation analysis of individual data showed only a weak linear relationship. There are only a few trials about variations of $PaCO_2$ and its effect on CBF and CVR as well as on $V_{MCA}$ and RAP in patients or volunteers without cerebral disease. They all showed an inverse reaction of CBF and CVR.[1,26] Recent TCD-studies could demonstrate that the RAP varies inversely with changes in $PaCO_2$.[2,40] Thus, the RAP might have potential to reflect $CO_2$-induced changes of vascular resistance. Some investigations showed that hypocapnia increases ZFP, whereas the RAP seems to be unaffected.[7,41] Conversely, McCulloch and colleagues found that RAP increased significantly with hypocapnia, and the increase in RAP appeared to have a greater effect on $V_{MCA}$ than the increase in ZFP.[2] In the relationship between flow velocity and arterial blood pressure, the RAP has been defined as the inverse slope of their linear regression line.[2,4,6,10] RAP can thus be expressed as RAP=(MAP-ZFP)/$V_{MCA}$. The CVR is defined "classically" as CVR=(MAP-ICP)/CBF or in our study "alternatively" as CVR=(MAP-ZPF)/CBF. In our patients, the $CO_2$-reactivity-curve of the $V_{MCA}$ showed a smaller increase than CBF when comparing levels from hyperventilation to hypoventilation, which affects the slope of the pressure-flow (velocity) relationship and consequently also limits the validity of RAP as an index of CVR. Recently, 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 $CO_2$.[42] Our data, however, could not explain the regulatory mechanism between these two factors.

Some methodological aspects of our study have to be considered. First, the *a priori* sample size calculation was based on estimation of the effect size, because of a lack of data regarding CBF and $V_{MCA}$ under general anesthesia in humans. A post-hoc calculation showed a statistical power of 99% for the CBF and $V_{MCA}$ (n=10, α error probability = 0.05; effect size CBF of 2.3 and effect size $V_{MCA}$ 2.6).

Furthermore, the type of anesthesia may have potential influence on the results of our study. Induction of anesthesia with fentanyl and midazolam leads to a moderate, but proportional reduction of CBF and cerebral metabolism.[14] The cerebrovascular $CO_2$ reactivity in our patients favorably compared with data in conscious patients. Although we thus have no reason to assume, that intravenous anesthesia with fentanyl and midazolam *per se* may have affected the $PCO_2$-induced changes in CBF and $V_{MCA}$ in our patients, the results of this study cannot *a priori* be extrapolated to other types of anesthesia.

Similarly, the external validity of our data could be limited by the fact that our patients were suffering from coronary artery disease and concomitant asymptomatic cerebrovascular disease cannot completely be excluded despite normal cerebrovascular $CO_2$-reactivity. Therefore, the conclusions from our study results should be limited to this patient population.

## CONCLUSIONS

Hypocapnia-induced reduction in CBF under general anesthesia is caused by both, an increase in CVR and a decrease in CPPe, as a consequence of an increase in ZFP. The increases in CVR and RAP associated with hypocapnia were concordant. Nevertheless, correlation analysis showed only a weak linear relationship. Using the RAP as an index of CVR has thus limitations. The cerebrovascular $CO_2$ reactivity of $V_{MCA}$ was lower when compared to CBF. The most probable explanation is that changes of $PaCO_2$ do not only cause changes in vascular diameter at the arteriolar level but might also cause minor changes in MCA main trunk diameter, resulting in a slight systematic difference between relative changes in flow and flow velocity.



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# Chapter 4

## Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux.

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Anesthesiology 2014; 120: 335–42
German Clinical Trials Register (DRKS00011535).

## ABSTRACT

**Background:** Hyperventilation is known to decrease cerebral blood flow (CBF) and to impair cerebral metabolism, but the threshold in patients undergoing intravenous anesthesia is unknown. We hypothesized that reduced CBF associated with moderate hyperventilation might impair cerebral aerobic metabolism in patients undergoing intravenous anesthesia.

**Methods:** Thirty male patients scheduled for coronary surgery were included in a prospective, controlled crossover trial. Measurements were performed under fentanyl/midazolam anesthesia in a randomized sequence aiming at partial pressures of carbon dioxide of 30 and 50 mmHg. Endpoints were CBF, blood flow velocity in the middle cerebral artery, and cerebral metabolic rates for oxygen, glucose, and lactate. Global CBF was measured using a modified Kety-Schmidt technique with argon as inert gas tracer. Cerebral blood flow velocity of the middle cerebral artery was recorded by transcranial Doppler sonography. Data were presented as mean (standard deviation). Two-sided paired t-tests and one-way ANOVA for repeated measures were used for statistical analysis.

**Results:** Moderate hyperventilation significantly decreased CBF by 60%, blood flow velocity by 41%, cerebral oxygen delivery by 58%, and partial pressure of oxygen of the jugular-venous bulb by 45%. Cerebral metabolic rates for oxygen and glucose remained unchanged, however, net cerebral lactate efflux significantly increased from -0.38 (2.18) to -2.41 (2.43) $\mu mol \bullet min^{-1} \bullet 100g^{-1}$.

**Conclusions:** Moderate hyperventilation, when compared with 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, suggesting partial impairment of cerebral aerobic metabolism at clinically relevant levels of hypocapnia.

## INTRODUCTION

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.[1] Despite routine end-tidal carbon dioxide monitoring, periods of inadvertent hyperventilation occur frequently during mechanical ventilation under general anesthesia, which may be associated with unfavorable side effects such as cognitive dysfunction and increased length of hospital stay.[2]

Patients with Alzheimer disease are predisposed to post-operative cognitive dysfunction. This group of patients has an increased vasoconstrictive response to hypocapnia and concomitantly a greater increase in oxygen extraction fraction (OEF) than control patients.[3] In patients with traumatic injury, vascular disorders, or meningitis hyperventilation is associated with impaired aerobic cerebral metabolism, reflected by an increase in net cerebral lactate efflux (cerebral metabolic rate [CMR] of lactate [CMRL]).[4-8]

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. A recent report about moderate and profound hyperventilation in anesthetized young pigs without cerebral disorder showed a reduction of regional CBF and oxygen availability, resulting in tissue hypoxia as reflected by an increase in markers of anaerobic metabolism.[9] Similarly, investigations using magnetic resonance spectroscopy or the Kety-Schmidt-technique in awake volunteers undergoing hyperventilation showed an increase innet cerebral lactate efflux.[8,10,11]

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.[1] In humans induction of intravenous anesthesia even may reduce cerebral lactate efflux.[12-14] But moderate hyperventilation during anesthesia also showed a trend to increase net cerebral lactate efflux though not reaching significance.[13,15,16] The relevance of this finding, however, may be limited, because of the small number of patients, which have been included in these studies.

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 variation in arterial carbon dioxide partial pressure on cerebral hemodynamics and metabolism in 30 cardiac surgical patients undergoing intravenous anesthesia. We hypothesized that moderate hyperventilation, when compared with moderate hypoventilation, will reduce CBF and $cDO_2$ to an extent which might impair cerebral aerobic metabolism.

## MATERIAL AND METHODS

### Design

The prospective study was designed and performed in a controlled, crossover design at the University of Göttingen Medical Center aiming at changes in CBF, cerebral blood flow velocity (V), and the metabolic effects of hyper- vs. hypoventilation in anesthetized patients. Each patient served as his own control. Approval was obtained from the local institutional review board (Medical Ethical Committee of the Georg-August-University of Göttingen, Göttingen, Niedersachsen, Germany; No. 07/09/90). Study period was 27 months (February 20th 1991 until May 10th 1993).

### Endpoints

The primary endpoints of the trial were changes in CBF, blood flow velocity of the middle cerebral artery ($V_{MCA}$), $cDO_2$, CMRL, cerebral metabolic rates of oxygen ($CMRO_2$) and glucose (CMRG). The secondary endpoints were changes in cerebral zero-flow pressure (ZFP), effective cerebral perfusion pressure ($CPP_{eff}$), and CVR.

### Screening and inclusion of patients

Due to logistic reasons, we could perform only 1-2 measurements per month. Thus, standard screening procedures could thus not be applied in this crossover trial. Patients were eligible for inclusion if scheduled for elective coronary surgery. Exclusion criteria were being older than 80 years of age, female gender, patient refusal, active neurological disease, and a history of cerebrovascular disease, brain injury, or intracranial surgery. All patients were informed of the purpose of the study and provided written informed consent before being enrolled. None of the eligible patients refused inclusion of the trial. There were no dropouts during the study period.

### Sample size calculation

The intersubject and intrasubject variability of CBF and cerebral lactate metabolism has been reported in earlier studies.[10,13,15,16] However, there was a lack of data regarding the variance of the CMRL measurement method in anesthetized patients, which was necessary for an exact sample size calculation for this crossover trial. We expected a 50% difference of CMRL with an estimated effect size of 0.7-0.8. For a statistical power of 0.8-0.9 the sample size had to be between 24-30 patients. Therefore, we projected a sample size of 30 patients.

### Anesthesia Procedure

Individual medications were continued until surgery. Anesthesia was induced by intravenous administration of 7 $\mu g \cdot kg^{-1}$ fentanyl, 0.2 $mg \cdot kg^{-1}$ midazolam, and 0.1 $mg \cdot kg^{-1}$

pancuronium. Anesthesia was maintained with 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl and 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$ midazolam. The anesthesia procedure, the details of mechanical ventilation and the methods of catheters insertion have been described in a previous report in detail.[14]

## Measurements

CBF was measured using the modified Kety-Schmidt inert gas saturation technique with argon as a tracer gas.[14,17,18] The wash-in period was 10 min. Blood samples were obtained simultaneously from the arterial and jugular bulb catheters at a constant rate of 0,5ml/min by a high-precision aspiration pump with gas-tight Hamilton glass syringes. The withdrawal rate for probes of the argon end concentration was 5ml/20s. A brain/blood partition coefficient of 1.10 was used to calculate CBF.[19,20]

Blood flow velocity in the proximal (M1) segment of the middle cerebral artery was measured by transcranial Doppler sonography as extensively described in earlier reports.[14,21,22] Because transcranial Doppler measurements of $V_{MCA}$ from the transtemporal window fail with above average incidence in elderly female patients we included only male patients in this study.[23,24]

Measurements were performed at two different $PaCO_2$ levels, approximately 50 mmHg and 30 mmHg, in a randomized sequence before surgery. All measurements were performed during hemodynamic and respiratory steady-state conditions. The time interval between the measurements was 20 min. Blood samples were drawn twice, at the beginning and end of each argon wash-in period, to measure hemoglobin concentration, blood gas analysis (ABL; Radiometer, Copenhagen, Denmark), and blood glucose and lactate concentrations (enzymatic tests kids, Boehringer Mannheim, Germany). For comparisons with CBF measurements, $V_{MCA}$ was averaged over the 10 min period of each argon wash-in maneuver. End-expiratory concentrations of carbon dioxide were continuously recorded to ensure a stable $PaCO_2$ during argon saturation.

## Calculations

Cerebral zero-flow pressure was calculated at the beginning and end of each CBF measurement from two simultaneous 10-s recordings (two breathing cycles) of the $V_{MCA}$ envelope and arterial pressure curves. Over each 10-s period we first averaged diastolic, mean and systolic data of arterial blood pressure (ABP) and $V_{MCA}$ to obtain a pressure/flow velocity plot. Cerebral ZFP was then extrapolated by linear regression analysis of the ABP/$V_{MCA}$ relationship. The ABP axis intercept of the regression line determines the ZFP.[22,25] The cerebral ZFP was used as a measure of the effective downstream pressure of the cerebral circulation. Consequently, $CPP_{eff}$ and CVR were calculated as $CPP_{eff}$ = mean ABP-ZFP and CVR = $CPP_{eff} \cdot CBF^{-1}$, respectively. Cerebrovascular $CO_2$-reactivity was calculated from the slope of the linear regression line of the relationship between CBF and $PaCO_2$ as well as $V_{MCA}$ and $PaCO_2$. Relative $CO_2$-reactivity was calculated as the percentage of change in CBF or $V_{MCA}$ per mmHg change in $PaCO_2$.[26]

$CMRO_2$, CMRG, and CMRL were calculated using the reversed Fick principle, multiplying CBF by the difference in arterio-jugularvenous content of oxygen ($AJVDO_2$), lactate (AJVDL) and glucose.[8] By definition, positive CMR values indicate consumption or net influx, and negative values indicate production or net efflux. For AJVDL and CMRL, we thus expected negative values in case of cerebral lactate production.

The OEF was calculated as the ratio between $AJVDO_2$ and arterial oxygen content. The lactate-oxygen index (LOI), which relates cerebral lactate production to oxygen extraction, was defined as LOI [ ] = AJVDL[$mmol \cdot l^{-1}$] · $AJVDO_2^{-1}$[$mmol \cdot l^{-1}$]. The lactate-glucose index (LGI), i.e. the fraction of glucose consumption that is metabolized and excreted from brain as lactate, was defined as the ratio between the arterio-jugularvenous content differences of lactate and glucose. For these calculations contents of oxygen and glucose concentrations have been converted in to $mmol \cdot l^{-1}$. Because one molecule of glucose is metabolized to two molecules of lactate, an LGI of e.g. -0.1 indicates, that 5% of the cerebral glucose consumption have been metabolized to lactate.[5,8,27]

### Statistical Analysis

The results presented in tables are expressed as mean (standard deviation) unless otherwise stated. To provide an estimate of the effect of hypocapnia and its clinical meaningfulness, we calculated mean differences (MD) and their 95% confidence intervals (mean difference; 95% CI: lower bound, upper bound; p-value).[28] The difference between hyperventilation and hypoventilation were calculated using t tests for paired data or Welch test and nonparametric Wilcoxon signed-rank tests, if indicated. To prevent from type I error-inflation all primary endpoints were tested by one-way ANOVA for repeated measurements followed by Bonferoni's multiple comparison tests. All statistical analysis were performed two-sided and a p-value of $p<0.05$ was considered to be significant.

Calculations were performed using SPSS 17 (IBM SPSS Statistics, Armonk, NY), and graphs were made using Prism 6.0c (GraphPad Software, La Jolla, CA).

Sample size calculation was done with G*Power 3 (University of Düsseldorf, Dept. of Psychology, Düsseldorf, Germany).[29]

## RESULTS

A total of 30 male patients were included in the study. The mean age of the patients was 56(8) yrs. (median 58, range 41-78 yrs.), mean height 173(6) cm, and mean body weight 77(9) kg. In one patient, CBF could not be measured during hypoventilation, because of technical problems during jugular venous blood sampling. Hemodynamic and metabolic data are presented in table 1.

**Table 1: Hemodynamic and metabolic data during moderate changes in $PaCO_2$ in patients without cerebral disease under intravenous anesthesia.**

| Parameters (n=30) | Units | Hyper-ventilation mean (SD) | Hypo-ventilation mean (SD) | Mean differences (CI 5%; 95%) | P |
|---|---|---|---|---|---|
| $PaCO_2$ | [mmHg] | 31 (3) | 51 (3) | 20 (19; 21) | <0.001 |
| CBF*§ | [ml·min$^{-1}$·100g$^{-1}$] | 27 (6) | 68 (24) | 41 (28; 53) | <0.001 |
| $V_{MCA}$ mean*§ | [cm·s$^{-1}$] | 34 (12) | 58 (17) | 24 (19; 28) | <0.001 |
| MAP | [mmHg] | 76 (12) | 71 (11) | -5 (-8; -2) | 0.003 |
| ZFP§ | [mmHg] | 24 (9) | 11 (11) | -13 (-16; -9) | <0.001 |
| $CPP_{eff}$ | [mmHg] | 51 (11) | 59 (14) | 8 (4; 12) | <0.001 |
| CVR§ | [mmHg·ml$^{-1}$·min·100g] | 1.93 (0.52) | 0.95 (0.32) | -0.95 (-1.11; -0.75) | <0.001 |
| Hb | [mg·dl $^{1}$] | 12.7 (1.5) | 12.4 (1.4) | -0.3 (-0.5; 1.0) | 0.505 |
| $Temp_{Blood}$ | [°C] | 35.3 (0.4) | 35.3 (0.5) | -0.06 (-0.15; 0.03) | 0.166 |
| $pH_{art}$ | [ ] | 7.48 (0.03) | 7.30 (0.03) | -0.18 (-0.19; -0.16) | <0.001 |
| $SaO_2$§ | [%] | 96 (1) | 95 (2) | -1.6 (-2.4; -0.7) | <0.001 |
| $SjvO_2$§ | [%] | 41 (8) | 72 (5) | 31 (28; 34) | <0.001 |
| $PaO_2$ | [mmHg] | 121 (31) | 109 (28) | -11 (-23; 0) | 0.047 |
| $PjvO_2$§ | [mmHg] | 30 (9) | 46 (5) | 16 (13; 19) | <0.001 |
| $AJVDO_2$§ | [mg·dl $^{1}$] | 9.7 (1.6) | 3.9 (0.9) | -5.8 (-6.3; -5.3) | <0.001 |
| AJVDG | [mg·dl $^{1}$] | 11.2 (2.7) | 5.6 (2.3) | -5.6 (-4.4; -6.9) | <0.001 |
| AJVDL§ | [mmol·l$^{-1}$] | -0.080 (0.079) | -0.003 (0.033) | 0.077 (0.047; 0.107) | <0.001 |
| $cDO_2$*§ | [ml·min$^{-1}$·100g$^{-1}$] | 4.61 (0.83) | 11.08 (4.01) | 6.49 (4.42; 8.51) | <0.001 |
| $CMRO_2$* | [ml·min$^{-1}$·100g$^{-1}$] | 2.64 (0.68) | 2.51 (0.77) | -0.14 (-0.20; 0.48) | >0.999 |
| CMRG* | [mg·min$^{-1}$·100g$^{-1}$] | 3.10 (1.23) | 3.56 (1.49) | 0.46 (1.43; 0.51) | >0.999 |
| CMRL* | [µmol·min$^{-1}$·100g$^{-1}$] | -2.41 (2.43) | -0.38 (2.18) | 2.03 (0.60; 3.48) | 0.003 |
| OEF | [ ] | 0.57 (0.09) | 0.24 (0.05) | -0.34 (-0.36; -0.31) | <0.001 |
| LOI | [ ] | -0.014 (0.014) | -0.004 (0.016) | 0.011 (0.004; 0.018) | <0.001 |
| LGI | [ ] | -0.13 (0.13) | -0.03 (0.15) | 0.11 (0.04; -0.18) | 0.003 |

AJVDG = arterio-jugular venous difference in glucose, AJVDL = arterio-jugular venous difference in lactate, $AJVDO_2$ = arterio-jugular venous difference in oxygen, CBF = cerebral blood flow, $cDO_2$ = cerebral oxygen delivery, CI = 5%, 95% confidence interval, CMRG = cerebral metabolic rate of glucose, CMRL = cerebral metabolic rate of lactate, $CMRO_2$ = cerebral metabolic rate of oxygen, $CPP_{eff}$ = effective cerebral perfusion pressure, CVR = cerebrovascular resistance, Hb = hemoglobin concentration, LGI = lactate glucose index. LOI = lactate oxygen index, MAP = mean arterial pressure, OEF = oxygen extraction fraction, $PaCO_2$ = arterial partial pressure of carbon dioxide, $PaO_2$ = arterial partial pressure of oxygen, $pH_{art}$ = negative logarithm of $H^+$ concentration (molarity) of arterial blood, $PjvO_2$ = jugular venous partial pressure of oxygen, SD = standard deviation, $SaO_2$ = arterial blood saturation, $SjvO_2$ = venous blood saturation of the jugular bulb, $Temp_{Blood}$ = blood temperature, $V_{MCA}$ mean = mean blood flow velocity of the middle cerebral artery, ZFP = zero flow pressure. The p-values, which refer to the difference between hyperventilation and hypoventilation, were calculated using two-sided t-test for paired data (n=30).

(*) Statistical analyses of primary endpoints were adjusted by one-way ANOVA for repeated measurements with Bonferoni's multiple comparisons procedure (n=29).

(§) Because the variances of some outcome variables substantially differed between hyperventilation versus hypoventilation, these parameters were additionally examined by Welch test and non-parametric Wilcoxon signed-rank tests, which showed that the differences persist.

Due to the controlled adjustment of mechanical ventilation, the variability of $PaCO_2$ at both target levels was small. The blood temperature of the patients was effectively kept constant. Only one of our patients had diabetes mellitus. None of the patients showed elevated levels of blood glucose.

The effects of ventilatory changes on the cerebral circulation were substantial. Hyperventilation reduced CBF by 60%, and $V_{MCA}$ by 41%, when compared to hypoventilation. This reduction was predominantly caused by increased CVR (MD, 0.95; 95% CI: 0.75, 1.11 mmHg·ml$^{-1}$·min·100g; p<0.001) and decreased $CPP_{eff}$ (-14%). The decrease in $CPP_{eff}$ during hyperventilation occurred because of a significant increase in the cerebral ZFP

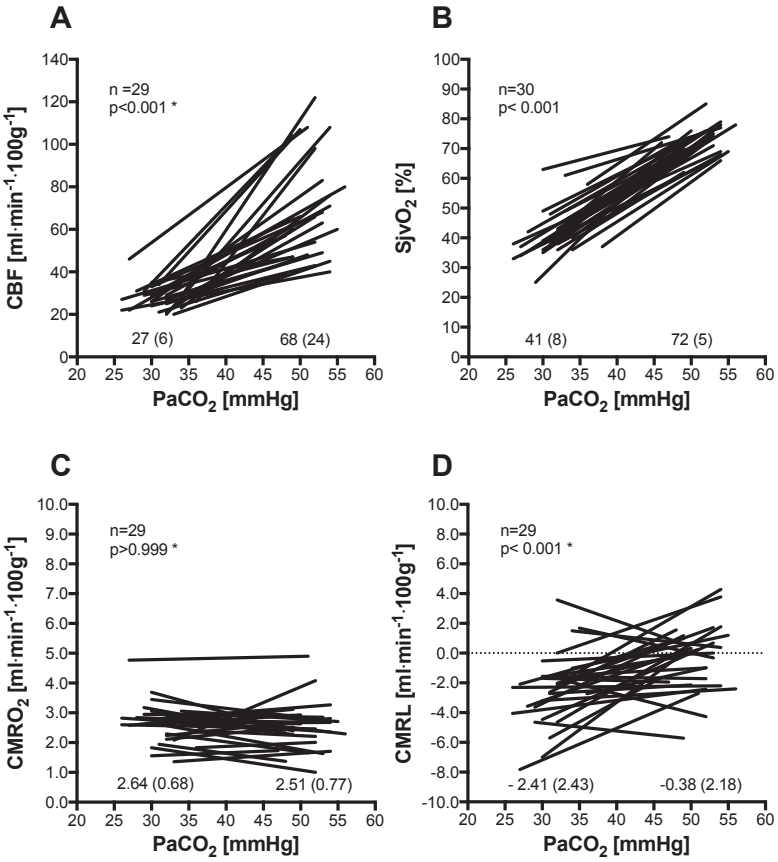


**Fig. 1. A-D. Values of cerebral blood flow (CBF), jugular-venous partial pressure of oxygen ($PjvO_2$), cerebral metabolic rate of oxygen ($CMRO_2$), and lactate (CMRL) during moderate hyperventilation compared with moderate hypoventilation.**

Straight lines link individual values for each subject. Data are mean (standard deviation) for each measurement. The p-values, which refer to the difference between hyperventilation and hypoventilation, were calculated using two-sided t-tests for paired data. P-values of primary endpoints were adjusted by Bonferoni's multiple comparisons procedure (*).

(MD, 13; 95% CI: 9, 16 mmHg; p<0.001), which exceeded the small increase in mean arterial pressure (MD, 5; 95% CI: 2, 8 mmHg; p=0.003). The decrease in CBF and $cDO_2$ (by 58%) during hyperventilation was associated with a pronounced decrease in the venous jugular bulb oxygen saturation (MD, 31; 95% CI: 34, 28 %; p<0.001) and venous jugular bulb partial pressure of oxygen ($PjvO_2$; MD, 21; 95% CI: 19, 22 mmHg; p<0.001; Fig. 1). The $cDO_2/CMRO_2$ ratio changed from 4.5:1 to 1.8:1; that is, the OEF during hyperventilation markedly increased from 0.24 to 0.57.

Mean arterial-jugular venous difference of oxygen, glucose and lactate changed significantly during moderate hyperventilation when compared to hypoventilation (table 1). The mean cerebral efflux of lactate significantly increased, by 2.0 $\mu mol \cdot min^{-1} \cdot 100g^{-1}$, whereas mean $CMRO_2$ and CMRG remained constant. LOI and LGI significantly decreased, that is, became more negative.

Cerebrovascular $CO_2$ reactivity of CBF was 2.02 (1.18) $ml \cdot min^{-1} \cdot 100^{-1} \cdot mmHg^{-1}$, corresponding to a relative change of 2.79 (0.77) $\% \cdot mmHg^{-1}$. The cerebrovascular $CO_2$ reactivity of mean $V_{MCA}$ was 1.18(0.48) $cm \cdot s^{-1} \cdot mmHg^{-1}$, corresponding to a relative change of 2.03 (0.50) $\% \cdot mmHg^{-1}$, which was significantly lower than the relative $CO_2$-reactivity of CBF (MD, -0.76; 95% CI: -0.96,-0.56; p<0.001).



## DISCUSSION

We investigated the effects of variations in arterial carbon dioxide partial pressure on cerebral hemodynamics and metabolism in cardiac surgical patients undergoing fentanyl/midazolam anesthesia. Compared to hypoventilation, moderate hyperventilation was associated with a significant reduction in CBF, $cDO_2$ and $PjvO_2$. The mean cerebral efflux of lactate significantly increased, whereas mean $CMRO_2$ and CMRG remained constant.

Hyperventilation reduces $PaCO_2$ and decreases extracellular $H^+$, leading to cerebral vasoconstriction and consecutively to reduced CBF and $cDO_2$.[1] An associated increase in net cerebral efflux of lactate at low $PaCO_2$ levels in principle may be explained by different mechanisms:

- Dissociation of oxygen-bindings curve to the left as a result of the respiratory alkalosis, (Bohr-effect)[30-32]
- Alkalosis induced change of redox-systems of lactate/pyruvate and NADH/NAD+[16,33-35], and
- Severe cerebral hypoperfusion with tissue hypoxia.[9,36,37]

Recent investigations of lactate kinetics and oxygenation using lactate isotopes demonstrate simultaneous lactate uptake and release in the brain.[38] In addition to glucose and ketone bodies, lactate is known to be an essential part of cerebral energy metabolism. Recent trials have shown that the glucose taken up by astrocytes is converted to lactate,

and that the lactate released from astrocytes may be taken up by neurons and used as energy, especially in activated neurons, referred to as the astrocyte–neuron lactate shuttle hypothesis.[39] Thus, partial metabolic compartmentalization appears to exist between astrocytes and neurons, with astrocytes feeding the neurons with lactate generated from glycolysis upon cerebral activation.[40]

The magnitude of change in mean CMRL of our patients' was 2.0 µmol·min$^{-1}$·100g$^{-1}$, which was greater than expected. Previous studies have shown that, absolute levels of CMRL may considerably vary depending on the group of patients and the level of consciousness.[14,15,41,42] Absolute values of net cerebral lactate efflux in our patients thus have to be interpreted with care. A slight lactate efflux at hypocapnia may not necessarily indicate tissue hypoxia. However, the increase in AJVDL and net cerebral lactate efflux associated with hypocapnia and the concomitant decrease in CBF might be suspicious for anaerobic metabolism in relatively ischemic brain regions.

It seems unlikely, that the increase of net cerebral lactate efflux at low $PaCO_2$ levels might solely be caused by alkalosis-induced enzymatic effects. There are no oxygen stores in the brain in contrast to myoglobin that stores oxygen in the muscle. Thus, the rate of oxygen delivery from the blood to brain tissue critically depends on the vessel-to-tissue oxygen partial pressure ($P_{ti}O_2$) gradient and the efficiency of oxygen transfer from the capillary bed.[43,44] A definite ischemic threshold for brain tissue oxygenation has not yet been defined. Jones and colleagues demonstrated that CBF less than18 ml·min$^{-1}$·100g$^{-1}$ in awake monkeys results in irreversible brain tissue infarction.[45] Michenfelder and colleagues reported critical CBF values of about 10-20 ml·min$^{-1}$·100g$^{-1}$ in patients with ischemic changes in electroencephalography during carotid endarterectomy.[46] In awake humans under normocapnic conditions, the $cDO_2/CMRO_2$ ratio is approximately 3:1 corresponding to an OEF of 0.33.[8,47] An OEF of greater than 0.4 in patients with traumatic head injury corresponded to a critically elevated microdialysis lactate/pyruvate ratio which might reflect a mismatch between substrate demand and delivery on a cellular level.[48] In our patients, the OEF considerably exceeded the threshold of 0.4 during hyperventilation, mainly caused by a reduction of $cDO_2$ while $CMRO_2$ remained unchanged.

Most investigators have considered jugular-venous $PO_2$ below 20 mmHg and tissue $PO_2$ values below 10 mmHg as pathological. Clausen and colleagues showed that even moderate hyperventilation ($PaCO_2$ = 30 mmHg) leads to a critical reduction of regional CBF below 18 ml·min$^{-1}$·100g$^{-1}$ in 22% of observed pigs; the tissue oxygen pressure fell below 10 mmHg in 30% of the animals undergoing moderate hyperventilation.[9] Furthermore, recent investigations showed that the final diffusion gradient from the microcirculation to the mitochondria is quite small.[49] Then, oxygen tension might play an essential role in mitochondrial cellular oxygen sensing and oxygen-regulated gene expression in clinical situations of low $cDO_2$.[50,51]

Although net cerebral lactate efflux during hyperventilation increased in our patients, $CMRO_2$ did not significantly change. Similarly, several prior studies found a reduction of tissue or cerebral venous oxygen tensions during moderate hyperventilation, but no decrease in $CMRO_2$ could be demonstrated.[8,10,15,16,52,53]

In contrast, other investigations could demonstrate that hyperventilation leads to a substantial decrease in $CMRO_2$ [35,54] or tissue oxygen pressure.[9] However, investigations of CBF and cerebral metabolism with variations of $PaCO_2$ in anesthetized patients or volunteers without cerebral disease are scarce and also showed an unchanged $CMRO_2$ at moderately low $PaCO_2$ levels.[8,13,15,55] The Kety-Schmidt method measures only global CBF and metabolism. In case of regional hypoperfusion with increased $CMRO_2$ in other regions of the brain, global $CMRO_2$ may be unaffected. Only when global oxygen availability decreases below oxygen demand, $CMRO_2$ will fall. The results of our report demonstrate that moderate hyperventilation, when compared to hypoventilation, leads to a significant decrease in venous jugular bulb oxygen saturation, $PjvO_2$, $AJVDO_2$, CBF and thus $cDO_2$. Net cerebral lactate efflux increased, which was associated with more negative LOI and LGI. Thus, our data do not indicate a severely disordered energy metabolism after a short phase of moderate hyperventilation, but it suggests that cerebral aerobic metabolism may partly be impaired. However, the clinical significance of these findings remains unclear, because in humans without cerebrovascular or traumatic brain injury detrimental effects of hyperventilation in terms of morphologic or histologic changes have not yet been demonstrated.

For the analysis of our data different methodological aspects have to be considered:

First, the *a priori* sample size calculation was based on estimation of the effect size, because of a lack of data regarding CMRL. A post-hoc calculation, however, showed a statistical power of 97% (n=30, α error probability = 0.05; effect size of 0.73).

Furthermore, the type of anesthesia may have potential influence on the results of our study. Induction of anesthesia with fentanyl and midazolam leads to a moderate, but proportional reduction of CBF and cerebral metabolism.[12,14,56] The cerebrovascular $CO_2$-reactivity in our patients favorably compared with data in conscious patients. Although we thus have no reason to assume, that intravenous anesthesia with fentanyl and midazolam *per se* may have affected the $PCO_2$-induced changes in CMRL in our patients, the results of this study cannot *a priori* be extrapolated to other types of anesthesia.

Similarly, the external validity of our data could be limited by the fact that our patients were suffering from coronary artery disease and concomitant asymptomatic cerebrovascular disease cannot completely be excluded despite normal cerebrovascular $CO_2$-reactivity. Therefore, the conclusions from our study results should be limited to this patient population.

The changes in CBF induced by hyperventilation and hypoventilation are related to changes in CVR and CPP. The calculation of these variables commonly requires measure-

ments of intracranial pressure. We used a minor-invasive method to estimate cerebral ZFP and $CPP_{eff}$ by extrapolating pressure-flow-velocity plots using recordings of arterial blood pressure and $V_{MCA}$. This technique, however, is well established and may even provide a more meaningful quantification of the cerebral downstream pressure than intracranial pressure, particularly in the absence of intracranial hypertension.[6,22,57,58] The finding that moderate hyperventilation leads to a small but significant reduction of $CPP_{eff}$ due to a significant increase in ZFP is in accordance with previous trials investigating the effects of hyperventilation on the effective downstream pressure of the cerebral circulation.[6,22,57,58]

The Kety-Schmidt method has been considered a reference method for estimating global CBF.[59-61] In contrast to positron emission tomography or single-photon emission computed tomography, the Kety-Schmidt technique is largely independent of assumptions regarding tracer kinetics, but might slightly overestimate global CBF in case of incomplete cerebral tracer saturation. Because of the crossover design of our study, a slight systematic overestimation of CBF has minor importance for the interpretation of hemodynamic and metabolic changes.

In our investigation we studied cerebral blood flow and metabolism aiming at $PaCO_2$ levels of 30 and 50 mmHg. We chose these $PaCO_2$ levels because they roughly reflect the range of unintended variations of $PaCO_2$ that often occur in routine clinical practice. The lack of data during normocapnia is a potential limitation of our study. Individual extrapolation of CBF at a $PaCO_2$ of 40 mmHg gave a mean CBF under normocapnia of 48(10) $ml \cdot min^{-1} \cdot 100g^{-1}$. The absolute and relative $CO_2$-reactivity of CBF is in accordance with previous studies on the cerebral circulation during general anesthesia. This underlines the validity of our hemodynamic measurements.[8,13,18,55,62] Interestingly, the relative cerebrovascular $CO_2$-reactivity of CBF was significantly higher than cerebrovascular $CO_2$-reactivity of $V_{MCA}$. The most probable explanation is that changes of $PaCO_2$ do not only cause changes in vascular diameter at the arteriolar level but might also cause minor changes in diameter of the middle cerebral artery, resulting in a slight systematic difference between relative changes in flow and flow velocity. A similar phenomenon previously had been described during hypothermic cardiopulmonary bypass.[14]

In conclusion, moderate hyperventilation, when compared to hypoventilation, increased net cerebral lactate efflux and decreased LOI and LGI in cardiovascular patients undergoing fentanyl-midazolam anesthesia. These metabolic changes suggest that the observed decrease in CBF, $cDO_2$ and $PjvO_2$ may partly impair cerebral aerobic metabolism at clinically relevant levels of hypocapnia.

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# Chapter 5

## Is hyperventilation during general anesthesia potentially hazardous?

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J Anaesth Intensivbehandl 2015; 21: 72–8

## INTRODUCTION

The normal range of the partial pressure of carbon dioxide ($PaCO_2$) is 36–45 mmHg (4.8 – 6.0 kPa). However, there are various situations, when anesthesiologists accept or clinically tolerate hypocapnia ($PaCO_2$ <36 mmHg) or hypercapnia ($PaCO_2$ >45 mmHg). This mini review aims to summarise the physiological effects, potential harms and consequences of hyperventilation/hypocapnia.

## PHYSIOLOGIC BACKGROUND

Carbon dioxide ($CO_2$) is the end-product of aerobic metabolism. For a normal gas exchange with a balanced $CO_2$-production and output, an amount of 10-20 breaths per min at rest are needed. The term tachypnea is commonly described by an increased respiratory rate >20/min, which could be induced by exercise, pregnancy, pain, fever, and respiratory failure. In contrast, **hyperventilation is defined an exaggerated output of $CO_2$**. Increased alveolar ventilation by hyperventilation will lead to a small rise in alveolar partial pressure of oxygen. Due to the sigmoid shape of the oxygen binding curve levels of arterial oxygen content and mixed venous oxygen saturation are nearly unchanged. The slope of the $CO_2$-binding curve is steeper at hypocapnic conditions when compared to normocapnia, which results in a reduced venous-to-arterial carbon dioxide partial pressure difference. So, in basic conditions hyperventilation reduces the tissue pressure of $CO_2$ and will lead to respiratory alkalosis. Then the equilibrium of the $CO_2/HCO_3^-$ buffer system ($CO_2 + H_2O \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$) is shifted to the left, the content of $H^+$ ions in the blood is reduced and pH is increased. Subsequent changes in Base Excess are effected by renal mechanisms, which take hours to develop.[1,2]

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.[3]

### Systemic circulation

Under conditions of spontaneous circulation, hyperventilation will increase systemic vascular resistance and mean arterial pressure with a concomitant decrease in cardiac output.[4] Within $PaCO_2$ levels from 30 to 50 mmHg, these changes are small and in most cases clinically of minor relevance.[3]

## Pulmonary circulation

Ventilatory management may markedly affect pulmonary vascular resistance (PVR). Alveolar hypoxia is a potent pulmonary vasoconstrictor and use of high-inspired oxygen concentrations may result in additional pulmonary vasodilation in some patients. Hypercapnia is a potent pulmonary vasoconstrictor, and hypocapnia is a pulmonary vasodilator. The relationship between lung volume and PVR during mechanical ventilation is U-shaped with PVR. At low lung volumes, alveolar hypoxia and hypercapnia cause hypoxic pulmonary vasoconstriction whereas hyperinflation of the lungs per se leads to compression of the intra-alveolar vessels with marked increases in PVR.[5]

## Cerebral circulation

Global cerebral blood flow (CBF) averages 50ml/min for each 100g of brain tissue. Due to autoregulation, CBF is kept constant within a wide range of hemodynamic conditions. Nevertheless, regional changes in blood distribution occur in response to changing patterns of neuronal activity. Examining the functional capacity of the cerebrovascular autoregulatory system by altering blood pressure is difficult and possibly hazardous to be performed as a routine clinical procedure. Therefore, Bloor and colleagues introduced $CO_2$-reactivity measurements to evaluate cerebrovascular reactivity.[1,6]

Changes in $PaCO_2$ (induced by hyper- or hypoventilation) are well known to change global CBF and the flow velocity of the middle cerebral artery ($V_{MCA}$), which can be explained by an increase or decrease of cerebral vascular resistance (CVR) and partly by cerebral perfusion pressure (CPP). Over a range of $PaCO_2$ values of 20-80 mmHg for each mmHg increase or decrease in $PaCO_2$ there is a 2-4% change in CBF or $V_{MCA}$.[6] Here, two mechanisms control CBF flow by changing blood vessel diameter and CVR: autoregulation maintains flow in the face of CPP changes, and brain metabolism adjusts flow to meet metabolic requirements.[7]

CPP usually is defined as the difference between MAP and intracranial pressure (ICP). Since the introduction of transcranial Doppler ultrasonography (TCD), a number of methods has been developed to assess the cerebral effective downstream pressure (EDP) by extrapolating instantaneous pressure-flow-velocity plots ($ABP/V_{MCA}$) to zero - the zero flow pressure (ZFP).[8] Thus, the effective CPP is defined by the difference between MAP and ZFP.

Comparisons between cerebrovascular $CO_2$-reactivity of CBF and $V_{MCA}$ in humans under general anesthesia are very rare. Recent studies of our group could demonstrate that ZFP varies inversely with changes of $PaCO_2$. The effects of ventilatory changes on the cerebral circulation were substantial. Hyperventilation (30mmHg) exponentially reduced CBF, in total by 60%, and $V_{MCA}$ by 41%, when compared with hypoventilation (50 mmHg). The hypocapnia-induced reduction in CBF under general anesthesia was

caused by both, an increase in CVR and a decrease in CPPe, as a consequence of an increase in ZFP (figure 1).[8,9]

The metabolic consequences of hyperventilation, when compared to hypoventilation, are substantial too. Hyperventilation reduces CBF, tissue $CO_2$ tension, jugular venous oxygen tension ($PjvO_2$), and thus cerebral oxygen delivery ($cDO_2$) (figure 2).[9] The $CO_2$-mediated alteration of brain cellular pH is the initial step leading to changes in vascular tone. The effect of pH on the cerebrovascular tone is mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and intracellular calcium. Hyperventilation is associated with an increase in net cerebral efflux of lactate, which may be explained by different mechanisms:

- Dissociation of oxygen-bindings curve to the left as a result of the respiratory alkalosis, (Bohr-effect)
- Alkalosis induced change of redox-systems of lactate/pyruvate and NADH/NAD+, and
- Severe cerebral hypoperfusion with tissue hypoxia.

Recent investigations of lactate kinetics and oxygenation using lactate isotopes demonstrate simultaneous lactate uptake and release in the brain. These trials have shown that the glucose taken up by astrocytes is converted to lactate, and that the lactate released from astrocytes may be taken up by neurons and used as energy, especially in activated neurons, referred to as the astrocyte–neuron lactate shuttle hypothesis. Thus, partial metabolic compartmentalization appears to exist between astrocytes and neurons, with astrocytes feeding the neurons with lactate generated from glycolysis upon cerebral activation. A slight lactate efflux at hypocapnia may not necessarily indicate tissue hypoxia. However, the increase in net cerebral lactate efflux associated with hypocapnia and the concomitant decrease in CBF might be suspicious for anaerobic metabolism in relatively ischemic brain regions.[9]



## HYPERVENTILATION IN CLINICAL PRACTICE AND OUTCOME

### General Anesthesia

Intravenous anesthetics reduce CBF in a dose-dependent way that is coupled to the reduction in metabolism. However, large doses of propofol may cause vasodilation, which may overcome the response to $CO_2$. Ketamine appears to preserve CBF, but blunts the response to $CO_2$ Thiopental or midazolam appears to be the best choices of intravenous anesthesia if preservation of cerebrovascular reactivity to $CO_2$ is needed.

Inhalation anesthetics generally increase CBF in a dose-dependent manner that is uncoupled to the reduction in metabolism. Cerebrovascular autoregulation, including the response to $CO_2$, is maintained up to 1.0–1.5 MAC. Isoflurane best preserves the

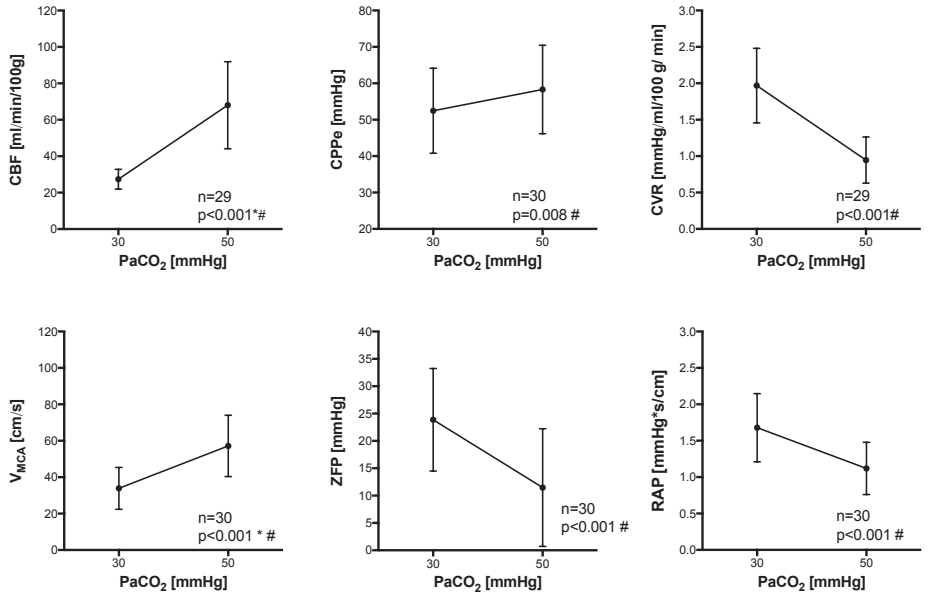


**Figure 1**

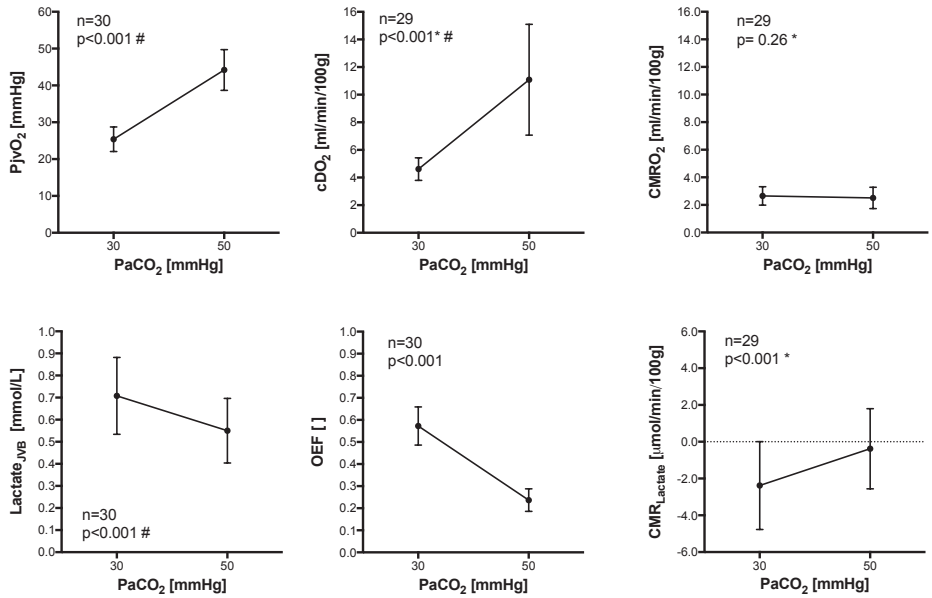


**Figure 2**

Modified from Grüne et al 2014[9] The P values, which refer to the difference between hyperventilation and hypoventilation, were calculated using two-sided t test for paired data (n=30).
* Statistical analyses of primary endpoints were adjusted by one-way ANOVA for repeated measurements with Bonferoni multiple comparison procedure (n=29).
# Because the variances of some outcome variables substantially differed between hyperventilation *vs.* hypoventilation, these parameters were additionally examined by Welch test and nonparametric Wilcoxon signed-rank tests, which showed that the differences persist.
CBF = cerebral blood flow; $cDO_2$ = cerebral oxygen delivery; CMRL = cerebral metabolic rate of lactate; $CMRO_2$ = cerebral metabolic rate of oxygen; CPPe = effective cerebral perfusion pressure; CVR = cerebrovascular resistance; OEF = oxygen extraction fraction; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PaO_2$ = arterial partial pressure of oxygen; $PjvO_2$ = jugular venous partial pressure of oxygen; RAP = resistance area product; $V_{MCA}$ mean = mean blood flow velocity of the middle cerebral artery; ZFP = zero-flow pressure.[9]

response to $CO_2$, when compared to other inhalational anesthetics. Sevoflurane appears to increase CBF slightly more than other inhalation anesthetics. Nitrous oxide increases both CBF and metabolism, but preserves the response to $CO_2$.[6]

The anesthetized brain might be less vulnerable to ischemia than the non-anesthetized brain as anesthesia reduces cerebral electric activity, metabolism, and flow. However, results of our study suggest that moderate hyperventilation, when compared to hypoventilation, in patients undergoing fentanyl-midazolam anesthesia partly impair cerebral aerobic metabolism at clinically relevant levels of hypocapnia.[9] Hyperventilation does not only reduce the total cerebral blood flow, but also changes the distribution of blood flow within the brain. Recent studies reveal that blood flow to the frontal, occipital, and parieto-occipital cortex, as well as the hippocampus is reduced relative to other areas of the brain within seconds to minutes of commencing hyperventilation. Alzheimer disease patients are predisposed to postoperative cognitive dysfunction. This group of patients has an increased vasoconstrictive response to hypocapnia and concomitantly a greater increase in oxygen extraction fraction (OEF) than control patients. So hyperventilation is associated with cognitive changes such as disturbed mentation, impaired concentration, and poor memory, which may be explained by reduced frontal cortical function.[1]

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.[3,10]



### Traumatic brain injury

Aggressive hyperventilation (arterial $PaCO_2$ < 25 mm Hg) formerly has been a cornerstone in the management of severe traumatic brain injury (TBI) for more than 20 years because it reduces cerebral blood volume and thus ICP. However, cerebral auto-

regulation is often abolished in the area surrounding damaged brain tissue or after an acute cerebral infarction. These blood vessels are often maximally dilated, presumably reflecting accumulation of acidic metabolic products. As a result, CBF to this area is already maximal (luxury perfusion), and changes in $PaCO_2$ have nearly no effect on its local blood distribution. Then, hypercapnia induced cerebral vasodilation of normal vessels could shunt blood away from the diseased area. Conversely, hyperventilation induced vasoconstriction theoretically could divert CBF to diseased areas (Robin Hood phenomenon). Based upon these competing concerns, recent guidelines on traumatic injury recommend to avoid hyperventilation, especially in the acute phase (the first 24 to 48 hours) following TBI. Mild to moderate hyperventilation can be considered at later stages, but $PaCO_2$ of less than 30 mmHg should always be avoided. If hyperventilation is used, jugular venous oxygen saturation ($SjvO_2$) or brain tissue oxygen tension ($PbrO_2$) measurements are recommended to monitor oxygen delivery.[11]

## CONCLUSIONS

Up to now, there is no evidence to support the therapeutic or prophylactic use of induced hypocapnia in any therapeutic context. 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. It is recommended to anesthesiologists to be familiar with the physiological effects of $CO_2$ and manage it according to their patient's situation.

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# Chapter 6

## The relationship between cerebral blood flow and the cerebral blood flow velocity: Influence of halothane and cerebral $CO_2$ reactivity.

[Zusammenhang zwischen zerebralem Blutfluss (CBF) und der zerebralen Blutflussgeschwindigkeit ($V_{MCA}$): Einfluss von Halothan und der zerebralen $CO_2$-Reaktivität]

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Anasthesiol Intensivmed Notfallmed Schmerzther 2001; 36: 538 – 44
Translated by Laura Perotto (MD) and Frank Grüne.

NB.
*This manuscript refers to the following trial: Validation of transcranial Doppler sonography as a monitoring technique of the cerebral circulation during general anaesthesia (Validierung der transkraniellen Dopplersonographie als Überwachungsverfahren der zerebralen Hämodynamik unter anästhesiologischen Bedingungen). The trial was planned and done before CONSORT initiative. German and Dutch laws did not require international registration of this type of clinical trial at that time. We registered the trial retrospectively at the German Clinical Trials Register (DRKS00011535).*

## ABSTRACT

**Objective:** This controlled study was designed to investigate 1.) the effects of 0,8% halothane and 2.) the effects of a variation in $PaCO_2$ on the relationship between global cerebral blood flow (CBF) and middle cerebral artery flow velocity ($V_{MCA}$).

**Method:** With ethical committee approval and informed patient consent we investigated 10 patients undergoing coronary artery bypass surgery. Measurements were performed under fentanyl/midazolam anesthesia prior to the start of surgery. First, during a baseline period, ventilation was changed in a random sequence to achieve two different levels of arterial $PCO_2$ (30 and 50 mmHg, respectively). Consequently, measurements were repeated during application of 0.8% halothane at identical $PaCO_2$ levels. Measurements of global CBF were performed by modified Kety-Schmidt-technique using argon gas as an indicator. Simultaneously, $V_{MCA}$ was recorded by use of a 2-Mhz transcranial Doppler system.

**Results:** Application of 0.8% halothane caused a significant decrease in cerebrovascular resistance (CVR) both at hypocapnia and hypercapnia by 36% and 23%, respectively. Because of a concomitant reduction in cerebral perfusion pressure ($CPP_{JVB}$), however, CBF remained unchanged during application of halothane. The relationship between CBF and $V_{MCA}$ was not altered when compared to the baseline period. Similarly, $CO_2$ reactivity of CBF and $V_{MCA}$ remained unchanged. $CO_2$ reactivity of CBF significantly exceeded $CO_2$ reactivity of $V_{MCA}$.

**Conclusion:** The results of this clinical study demonstrate that Doppler-sonographic estimation of relative changes in CBF is not altered by application of 1 MAC halothane indicating that the decrease in CVR is not associated with a vasodilation of the proximal segments of basal cerebral arteries. The difference between $CO_2$ reactivity of CBF and $V_{MCA}$, however, suggests that $CO_2$-induced changes in CBF are slightly underestimated by TCD monitoring of $V_{MCA}$.


**Keywords:** Cerebral blood flow, cerebral blood flow velocity, cerebrovascular $CO_2$ reactivity, halothane, transcranial Doppler sonography

## INTRODUCTION

Transcranial Doppler sonography (TCD) is a non-invasive and continuous method for monitoring brain perfusion, which is used in anesthesia in operative settings as well as in intensive care medicine.[1] A fundamental problem, however, limits the significance of the TCD as a monitoring method of cerebral hemodynamics: the blood flow of cerebral vessels (CBF), according to Hagen-Poiseuille's law, is a function of the cerebral blood flow velocity (V) as well as the vessel cross-section. Thus, proportional changes in the cerebral blood flow velocity with varying cerebral perfusion are only to be expected if the diameter of the vascular lumen is largely constant during the examination period.[2] This assumption is the basis for the interpretation of most Doppler sonographic examinations for perfusion monitoring available to-date.[3-6] However, the effects and relevance of possible caliber changes of basal brain arteries on the relationship between global CBF and V can only be assessed by a direct comparison of methods.[7]

Although there are indications that the diameter of the cerebral vessels close to the base are not significantly affected by carbon dioxide induced changes in the cerebral resistance, only a few comparative studies exist on the relationship between flow velocity measurements and reference measurements of cerebral blood flow.[8,9]

A further problem with the validation of TCD with regard to cerebral blood flow changes is the possible pharmacological influence of anesthetics and vasoactive substances. For example, a discrepancy between CBF and V was observed under the influence of nitroglycerine, indicating a pharmacologically induced change in the cross section of the sonicated vessel, thus making the interpretation of the TCD findings more difficult.[10,11]

In addition to its narcotic effect, the inhalational anesthetic agent halothane is known for its vasodilatory effects on cerebral circulation. Previous studies showed a clear reduction in cerebrovascular resistance under halothane exposure.[12,13] However, the exact mechanisms are not yet fully understood. Animal experimental studies have shown that basal brain arteries are also subject to vasodilatation by halothane, thus making interpretation of TCD studies more difficult.

The present clinical study was conducted to determine: 1.) The effects of halothane and 2.) The influence of a variation in $PaCO_2$ on the relationship between global cerebral blood flow and blood flow velocity in basal brain arteries.

## METHODS

The study was carried out after approval of the local ethics committee and with the written consent of the patients. In a prospective and controlled study design, we included 10

male patients scheduled for cardiac surgery. Measurements were done after anesthetic induction and before start of surgery. Cerebrovascular diseases were not detected in all study patients by assessing their medical history and by preliminary examinations with duplex sonography of the extracranial cerebral vessels and transcranial Doppler. The mean age of the patients was 54 (6) years, the mean body height was 174 (6) cm and the mean body weight was 82.3 (7.8) kg. Preoperative medication with calcium antagonists and nitrates was continued until the evening before the operation. β-blockers were applied further until immediately before surgery. For premedication, 2 mg flunitrazepam were administered per os on the preoperative evening as well as one hour before the anesthetic induction.

Anesthesia was induced with 200 $\mu g \cdot kg^{-1}$ midazolam, 7 $\mu g \cdot kg^{-1}$ fentanyl and 0.1 $mg \cdot kg^{-1}$ pancuronium after placing a permanent venous catheter and cannulation of the radial artery to measure the blood pressure. After nasotracheal intubation, patients were ventilated using a volume-controlled respirator controlled with an air / oxygen mixture corresponding to an inspiratory $O_2$ fraction ($FIO_2$) of 0.3. Anesthesia was maintained by continuous infusion of 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$ midazolam and 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl via a drop-controlled infusion pump (Schiwamatic 3000, Schiwa) and pancuronium injections in intervals at a dose of 0.03 $mg \cdot kg^{-1}$. Subsequently, a 7.5 F introducer sheath (Arrow International Inc., USA) was introduced into the left subclavian vein using the Seldinger technique and, under continuous registration of the corresponding pressure curves, a 4 lumen pulmonary arterial introducer catheter was placed. Furthermore, the placement of a catheter (6 F Goodale-Lubin, USCI, Bard Inc., USA) in the right venous jugular bulb was performed after retrograde puncture of the right internal jugular vein via a corresponding introducer sheath (Arrow International Inc., USA). The technique used corresponded largely to the method described by *Jacobsen and Enevoldsen*.[14] The correct position of the catheter tip in the jugular bulb was controlled by means of an X-ray image intensifier in order to prevent contamination of the cerebral venous blood samples by veins merging further distally from the facial region. Subsequently, a pulsed monitoring ultrasonic probe (IMP-2, EME) was placed in the area of the right temporal bone. After identification of the proximal middle cerebral artery (MCA), the probe was fixed to the patient's head in a constant position by means of a probe holder (IMP-2 Monitoring Probe Holder, EME) provided for this purpose.

The measurements of the global CBF were carried out using the Kety-Schmidt technique using argon gas as an indicator, as described elsewhere.[15] The $V_{MCA}$ was determined by using the posterior temporal "bone window" by means of a 2 MHz ultrasound system (TC 2000, EME). The mean depth of insonation for the treatment of the proximal main trunk of the MCA was 50 (3) mm. All other individually adjusted ultrasound variables, such as enhancement, intensity and target volume, were kept constant throughout the study. The determination of the flow rate in the MCA was based on the maximum intra-

vascular erythrocyte velocity as the envelope curve of the Doppler frequency spectrum. The temporal averaging of the $V_{MCA}$ was achieved by integrating the envelopes continuously recorded on a microcomputer at 52 Hz. For comparison with the simultaneous CBF measurements, the $V_{MCA}$ was averaged over the 10-minute period of the corresponding inert gas saturation phase. During these phases the end-expiratory $CO_2$ concentration was continuously monitored to ensure a stable arterial partial pressure of carbon dioxide ($PaCO_2$).

First, the hemodynamic measurements were performed during a control phase using two different $PaCO_2$ levels ($PaCO_2 \approx 30$ mmHg and $PaCO_2 \approx 50$ mmHg). The order of the ventilation changes was randomized. After saturation to an end-expiratory halothane level of 0.8 Vol.%, the measurements were repeated with largely identical $PaCO_2$ values in the reverse order of the ventilation changes (study phase).

The variation of the respiratory minute volume was performed with a constant breathing frequency of 10 $min^{-1}$ and an inspiratory / expiratory ratio of 1: 1 with adjustment of the tidal volume. All measurements were performed under hemodynamic and ventilatory steady-state conditions. After a new $PaCO_2$ level had been reached, a waiting period of 20 minutes with constant end-expiratory $CO_2$ concentration was completed before the corresponding measurement was taken. Measurements during the study phase were carried out at the earliest 30 minutes after the start of the halothane supply under end-expiratory control of the inhalation anesthetic concentration.

In addition to the determination of CBF and $V_{MCA}$, the heart rate, the nasopharyngeal temperature as well as the arterial, central venous and jugular venous pressures in the jugular bulb were recorded on a multichannel recorder at each measurement time. The determination of cardiac output (CO) was carried out by using the thermodilution technique by administering three injections of cold Ringer solution (Polymed CO computer module, System 1281, Siemens) distributed randomly over the respiratory cycle. The calculation of cardiac index and systemic vascular resistance was performed using standard formulas. The cerebral perfusion pressure ($CPP_{JVB}$) was calculated approximately from the difference between mean arterial pressure (MAP) and the pressure in the jugular bulb ($P_{JVB}$), which served as an approximation of the downstream pressure in the cerebral circulation. The CVR was calculated from the quotient of $CPP_{JVB}$ and CBF. The cerebrovascular $CO_2$ reactivity was expressed as a percentage change in perfusion per mmHg $PaCO_2$ change. Immediately before and after each CBF measurement, blood samples were taken to determine blood viscosity, hematocrit, as well as $O_2$ and $CO_2$ partial pressures.

Statistical analysis of the data was carried out by means of a microcomputer using the SPSS program package. All results are presented as mean values (standard deviation). In order to investigate the influence of halothane exposure as well as the $CO_2$ variation, a two-factor analysis of variance was carried out for repeated measures (RM-ANOVA).

In the case of significant interactions between the two factors, additional *t*-tests were performed for paired samples, in addition to the post-hoc comparison of the mean values. In this case, the level of significance of $\alpha < 0.05$ was adjusted by means of a sequentially rejective test method for multiple mean value comparisons.[16] The percentage cerebrovascular $CO_2$ reactivity was compared with the Wilcoxon test for paired samples.

## RESULTS

By varying the respiratory minute volume, a $PaCO_2$ of 32.8 (2.6) mmHg was achieved under hypocapnia, whilst a $PaCO_2$ of 50.7 (2.1) mmHg was achieved under hypercapnia during the control phase. The $PaCO_2$ values obtained during repetition of the respiration maneuvers under halothane influence differed from the corresponding control values on average by only 0.2 and 2.3 mmHg, respectively. The difference during hypercapnia was significant. This small difference in $PaCO_2$ is to be taken into account when comparing the hemodynamic changes between control and study phases (Table 1).

The mean nasopharyngeal temperature showed no change during the entire course of the examination. However, the mean hematocrit and the viscosity decreased slightly in comparison to the control phase due to the chronological order of the measurement periods during halothane exposure.

The heart rate under halothane was slightly lower than during the control period. The MAP and the $CPP_{JVB}$ also decreased as a result of exposure to halothane at both ventilation levels, whereas the reduction under hypocapnia was more pronounced than under hypercapnia (MAP 27% and 14%, $CPP_{JVB}$ 27% and 20%, respectively). The central venous pressure as well as the pressure in the bulb of the jugular vein showed slightly higher values during the study phase compared to the control phase. Halothane led to a significant decrease in the peripheral vascular resistance (32% and 22%, respectively), especially in hypocapnia, and to a consecutive increase in the cardiac output and stroke volume.

Under halothane, only minimal changes were seen in global CBF and $V_{MCA}$ during hypocapnia as well as hypercapnia. During the control phase the mean CBF increased from 26 (5) to 52 (9) $ml \cdot min^{-1} \cdot 100g^{-1}$ by varying the $CO_2$ level. The corresponding mean values of CBF under halothane tended to be higher (around 14%) than those of the control phase (30 (5) and 60 (22) $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively), but did not differ significantly (Figure 1). A similarly slight increase under halothane exposure occurred when the $V_{MCA}$ increased by 4% under hypocapnia (33 (14) $cm \cdot s^{-1}$ to 34 (16) $cm \cdot s^{-1}$) and by 10% under hypercapnia (52 (18) $cm \cdot s^{-1}$ to 57 (17) $cm \cdot s^{-1}$ (Figure 2).

Neither the CBF nor the $V_{MCA}$ showed a significant change in cerebrovascular $CO_2$-reactivity as a result of halothane intake (Table 2). The mean $CO_2$-reactivity of the MCA-flow rate, however, was significantly lower than that of the global cerebral perfusion.

**Table 1: Hemodynamic and metabolic data during moderate changes in $PaCO_2$ in patients without cerebral disease with intravenous anesthesia.**

| | Control | | 0.8 Vol.% Halothane | | |
|---|---|---|---|---|---|
| | A | B | A´ | B´ | |
| $PaCO_2$ * # § | 32.8 (2.6) | 50.7 (2.1) | 33.0 (2.1) | 53.0 (3.0) | [mmHg] |
| $SaO_2$ * | 95.4 (1.7) | 93.5 (3.4) | 94.9 (2.7) | 93.8 (2.8) | [%] |
| $PaO_2$ * | 106 (25) | 92 (20) | 95 (28) | 92 (19) | [mmHg] |
| $S_{JVB}O_2$ * | 45.9 (9.8) | 70.7 (4.8) | 46.9 (7.9) | 73.6 (3.8) | [%] |
| $P_{JVB}O_2$ * # | 26.7 (4.1) | 45.2 (3.9) | 28.4 (2.9) | 51.2 (10.1) | [mmHg] |
| CBF * | 26 (5) | 52 (9) | 30 (5) | 60 (22) | [ml·min$^{-1}$·100g$^{-1}$] |
| Mean $V_{MCA}$* # | 33 (14) | 52 (18) | 34 (16) | 57 (17) | [cm·s$^{-1}$] |
| $CPP_{JVB}$* # § | 74 (10) | 65 (10) | 54 (12) | 53 (6) | [mmHg] |
| $CVR_{JVB}$* # § | 2.87 (0.66) | 1.24 (0.23) & | 1.84 (0.50) $ | 0.95 (0.24) & $ | [mmHg·ml$^{-1}$·min$^{-1}$·100g$^{-1}$] |
| $P_{JVB}$ # | 10.6 (3.3) | 10.3 (3.4) | 12.1 (4.3) | 12.8 (4.5) | [mmHg] |
| MAP * # § | 84 (10) | 75 (9) & | 66 (12) $ | 65 (9) $ | [mmHg] |
| CVP # | 7.1 (2.2) | 6.5 (4.1) | 9.0 (1.3) | 7.7 (1.3) | [mmHg] |
| HR # § | 60 (10) | 59 (11) | 57 (11) | 59 (12) | [min$^{-1}$] |
| CO * # | 4.3 (1.9) | 4.9 (2.1) | 4.6 (1.6) | 5.2 (2.1) | [l·min$^{-1}$] |
| SV * # | 72.4 (24.5) | 81.9 (24.4) | 81.5 (21.8) | 87.7 (22.5) | [ml] |
| SVR * # § | 1642 (652) | 1283 (456) & | 1121 (543) $ | 1001 (372) $ | [dyn·s·cm$^{-5}$] |
| Hb # | 12.9 (1.2) | 12.7 (1.2) | 11.3 (1.2) | 11.8 (1.3) | [g·dl$^{-1}$] |
| Tnp | 35.4 (0.6) | 35.5 (0.6) | 35.4 (0,8) | 35.5 (0.7) | [°C] |
| Visc # | 4.2 (0.6) | 3.9 (0.7) | 3.5 (0.6) | 3.7 (0.7) | [mPa·s] |

A : hypocapnia (control); B: hypercapnia (control); A´: hypocapnia (halothane); B´: hypercapnia (halothane); * significant influence of the $PaCO_2$ level (RM-ANOVA, p< 0,05); # significant influence of halothane (RM-ANOVA, p< 0,05); § significant Interaction between $PaCO_2$ level and halothane (RM-ANOVA, p< 0.05); & significant differently from corresponding values under hypocapnia (*t* test, p< 0,05); $ Significantly different from the corresponding $PaCO_2$ level of the control phase (t test, p< 0.05).

CBF = cerebral blood flow; CO = cardiac output; $CPP_{JVB}$ = cerebral perfusion pressure expressed as the difference between mean arterial pressure and jugular bulb pressure; CVP = central venous pressure; $CVR_{JVB}$ = cerebral vascular resistance pressure expressed as the quotient between $CPP_{JVB}$ and CBF; Hb = hemoglobin concentration; HR = heart rate; MAP = mean arterial pressure; mean $V_{MCA}$ = mean cerebral blood flow velocity of the mean cerebral artery; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PaO_2$ = arterial partial pressure of oxygen; $P_{JVB}$ = jugular bulb pressure; $P_{JVB}O_2$ = jugular venous partial pressure of oxygen; $SaO_2$ = arterial blood oxygen saturation; $S_{JVB}O_2$ = venous blood oxygen saturation of the jugular bulb; SV = stroke volume; SVR = systemic vascular resistance; $T_{np}$ = nasopharyngeal body temperature; Visc = blood viscosity

The administration of halothane resulted in a reduction of the global cerebrovascular resistance from 2.87 (0.66) to 1.84 (0.50) mmHg·ml$^{-1}$·min·100 g under hypocapnia and from 1.24 (0.23) to 0.95 (0.24) mmHg·ml$^{-1}$·min·100 g under hypercapnia. Here, the halothane-induced decrease in $CVR_{JVB}$ under hypocapnia was more pronounced than under hypercapnia (36% and 23%, respectively).

**Table 2: Mean $CO_2$ reactivity of cerebral blood flow and blood flow velocity of the mean cerebral artery.**

| $CO_2$-Reactivity | CBF [%] | $V_{MCA}$ [%] |
|---|---|---|
| Control period | 3.9 (1,5) | 2.8 (0.9)* |
| 0.8 Vol % Halothane | 3.7 (2.3) | 3.0 (1.7)* |

The data represent the percent change per mmHg $PaCO_2$ increase; * significant difference compared to the $CO_2$ reactivity of CBF (Wilcoxon-test, $p<0.05$)

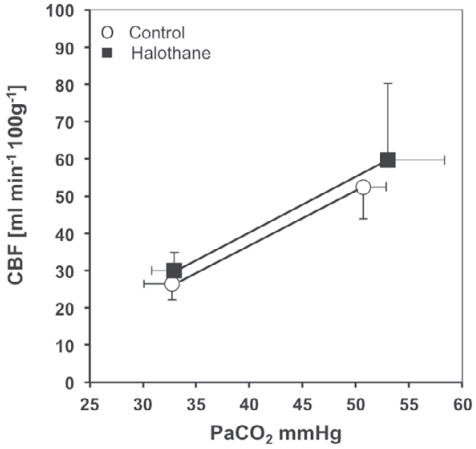


**Figure 1: Cerebral blood flow (CBF) as a function of arterial $PaCO_2$.**
Administration of 1 MAC halothane does not significantly alter cerebral blood flow. The cerebrovascular $CO_2$ reactivity of CBF remains unchanged.

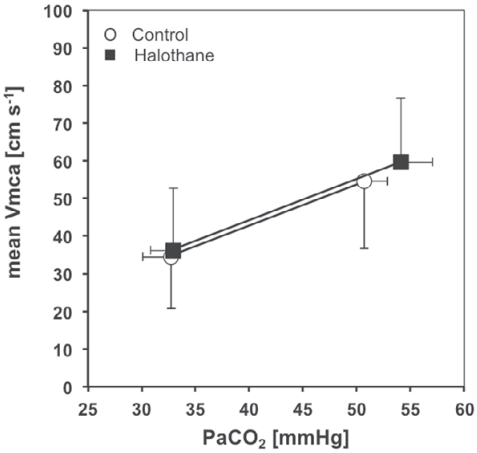


**Figure 2: Mean cerebral blood flow velocity of the mean cerebral artery ($V_{MCA}$) as a function of arterial $PaCO_2$.**
The administration of 1 MAC halothane does not result in any significant change in mean $V_{MCA}$ measured by transcranial Doppler sonography. The cerebrovascular $CO_2$ reactivity of $V_{MCA}$ remains unchanged.

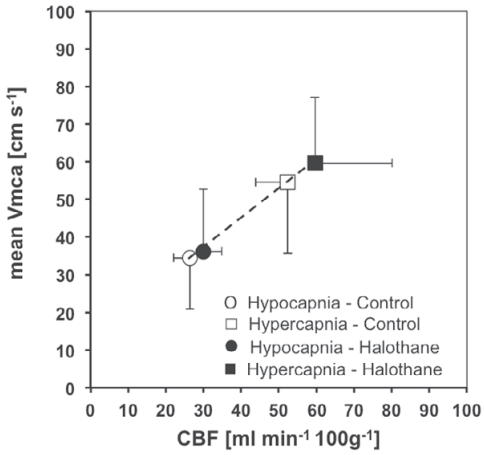


**Figure 3: Relationship between cerebral blood flow (CBF) and mean blood flow velocity in the mean cerebral artery (Vmca) with variation of $PaCO_2$.**
The application of 1 MAC halothane does not shift the relationship of flow and flow velocity, so that defined CBF values correspond to the same $V_{MCA}$ values as before halothane supply.

## DISCUSSION

The present clinical study shows, on the one hand, that 0.8 Vol.% of halothane, in addition to fentanyl/midazolam anesthesia, does not increase global CBF nor $V_{MCA}$, despite a decrease in cerebrovascular resistance. This is mainly related to reduction in mean arterial pressure. The cerebrovascular $CO_2$-reactivity remains unchanged. On the other hand, the results of the method comparison carried out during halothane adminstration revealed an unchanged relationship between the $V_{MCA}$ and the CBF compared to the control period. This means that $CO_2$-induced changes of the $V_{MCA}$ indicate similar changes in global cerebral perfusion before and after the administration of halothane, despite a systematic underestimation (Figure 3).



### General hemodynamic effects

In the present study, a significant decrease in SVR (32% and 22%, respectively) and MAP (22% and 14%, respectively) could be observed under the influence of 1 MAC halothane under hypocapnia and hypercapnia. These changes were accompanied by a significant but small increase in cardiac output and stroke volume. This observation is in contradiction to earlier studies that showed a decrease in cardiac output during approximately constant SVR during halothane administration.[17,18] This finding was interpreted as a halothane-induced impairment of the myocardial pump function. Whereas, *Rouby et. al.* observed a SVR reduction of 20% in patients with mechanical heart replacement and

fixed cardiac output during halothane exposure of 0.75 Vol %.[19] However, it should be noted that these changes have been recorded under mono-anesthesia with halothane. In the present study, halothane was applied additively to a fentanyl / midazolam anesthesia. According to the study protocol, a decrease of the MAP below 60 mmHg was counteracted with infusions of a balanced electrolyte solution. In this context, the slight increase in CVP is less likely to be interpreted as a result of right ventricular myocardial depression but rather as an expression of an increased preload, which was responsible for a slight increase in the stroke volume index in connection with the reduced vessel resistance.

**Influence on global cerebral perfusion**

No increase in cerebral perfusion was observed in the investigated patients under the influence of 0.8Vol.% halothane. This finding is in contradiction with previous studies, which showed a significant increase in CBF when administered with different dosages of halothane.[12,13,20-25] This discrepancy can partly be explained by the influence of a halothane-induced regional redistribution of cerebral blood flow on the different CBF measurement procedures. Using regional CBF measurement techniques, the groups of *Hansen*[26] and *Young*[27] demonstrated that halothane induces a selective increase in cortical cerebral perfusion. In combination with nitrous oxide, these effects were even more pronounced.[26] At the same time, it should be borne in mind that $^{133}$Xenon-clearance-measurements to determine the CBF assign overproportionate weight to cortical blood flow. Under these circumstances, the mentioned studies seemed to overestimate the halothane-induced changes in global cerebral perfusion. In studies with the Kety-Schmidt technique, a cortical weighting of the CBF measurements is unlikely. The gas dilution method represents the global cerebral blood flow as the mean value of the perfusion of white and gray brain matter. On the basis of the methodological principles, only slight differences in the weighting of the basal and cortical brain regions are to be assumed. In a study using the Kety-Schmidt method, *Wollmann et al.* found that the global CBF increased by 14% when administering 1.2 Vol % halothane.[28] Under similar conditions, *Alexander et al.* found a middle CBF value, which did not differ from the normal values accepted for conscious patients.[29]

The comparative assessment of previous studies should also take the accompanying changes of the $CPP_{JVB}$ into account. Halothane leads to an impairment of the autoregulation depending on the dose, so that a decrease in $CPP_{JVB}$ can also cause a reduction of CBF at a level of more than 50 mmHg.[12,30,31] On the basis of the present study , we assume that the halothane-induced reduction in CVR was not an expression of an autoregulatory response to the $CPP_{JVB}$ reduction; a moderate increase in the global CBF was prevented by lowering the $CPP_{JVB}$ through direct vasodilatory effects. Similar results were obtained in animal experimental studies by using the microsphere technique, which under 0.87

Vol % halothane intake and an accompanying decrease in $CPP_{JVB}$ did not show any increase in cerebral perfusion.[32] CBF was also unchanged during controlled hypotension at even higher halothane concentrations.[33]

**Effect on MCA blood flow rate**

Comparative simultaneous measurements of the MCA flow rate showed a completely analogous behavior to the CBF in the present study. This constant relationship between $V_{MCA}$ and CBF implies that the diameter of the insonated vessel segment did not change under administration of the inhalation anesthetic, since in the case of halothane-induced vasomotion a non-proportional or even divergent response of the flow velocity would have been expected. However, the conclusions from the present results contradict experimental investigations on the resistance changes of large brain base arteries. *Schregel et al.* was able to show in dogs that 0.87 Vol.% halothane causes a reduction in the vascular resistance of extraparenchymal arteries of the brain, and this result was attributed to a corresponding vasodilatation.[32] In comparison with the results obtained, one must bear in mind that the findings obtained in animals characterize the entire resistance between the common carotid artery and the vertebral artery, and thus only allow indirect statements about the section of the middle cerebral artery detected by the TCD. This limitation seems to be relevant in that different segments of basal brain arteries have heterogeneous responses to vasodilators[10,34,35] and reactions of extracranial vessels are not to be assigned to cerebral arteries.[36] While the majority of in vitro studies on vascular rings under halothane described a reduction of the myogenic tone[34,36] some deviating findings also showed an unexpected vasoconstriction for pre-contracted segments of basal brain arteries under halothane.[37] Under in vivo conditions, it is important to note that basal brain arteries can also participate in autoregulatory mechanisms.[10, 15, 38, 39] In view of these complex interactions, the present results show that experimental studies on the vasomotion of basal brain arteries alone do not allow a sufficient prediction of the validity of TCD measurements under clinical conditions.

In previous TCD studies the influence of halothane on caliber fluctuations of the middle cerebral artery could only be derived indirectly. Thus, *Schregel et al.* found that supplementing a nitrous oxide/opiate base anesthesia with an average 0.77 Vol% of halothane in the inspiration mixture increased MCA flow rate significantly.[40] They attributed this finding, however, to an increase in CBF under assumption of a constant MCA diameter. In a later study with a supply of 1.5 Vol.% halothane, however, the same group showed an increase in a Doppler sonographic "MCA area index".[32] The cause of this effect was thought to be an increase in the diameter of the middle cerebral artery. The significance of the Doppler-sonographically derived area index with regard to possible cross-sectional changes of basal brain arteries is not sufficiently determined yet due to a lack of validation of this parameter. On the basis of the present results and with the use

of significantly higher halothane concentrations, however, the possibility of a relevant vasomotion of the sonicated MCA cannot be completely excluded.

### Influence on $CO_2$ reactivity

In addition to the assessment of the pharmacologically induced effects of halothane, the present results allow us to investigate the relationship between global CBF and $V_{MCA}$, especially with regard to the influence of the $PaCO_2$ variations. To date, it has generally been assumed that changes in the $PaCO_2$ have no effect on the diameter of basal brain arteries. This assumption was based primarily on radiological studies using angiographies[8] and on indirect comparisons of the $CO_2$ reactivity of the $V_{MCA}$ with earlier data with regard to the $CO_2$ reactivity of cerebral blood flow.[9] In animal experiments, however, it was found that the large cerebral arteries also undergo a change in the cross-section when the variation in $PaCO_2$ is pronounced.[38] The analysis of the $CO_2$-induced changes in CBF and $V_{MCA}$ first shows that the cerebrovascular $CO_2$ reactivity remains unchanged under halothane. This finding is consistent with previous studies on $CO_2$ reactivity, which under halothane anesthesia demonstrated a CBF response unchanged compared to control periods or control studies.[25,41,42] In the present study, the $CO_2$ reactivity of the $V_{MCA}$ showed significantly lower values than the $CO_2$ reactivity of the CBF. A $CO_2$ -induced vasomotion in the area of the basal brain arteries is presumably the primary cause for this discrepancy. An increase in the vessel diameter with increasing $PaCO_2$ results in a change in the flow velocity that is underproportional compared to the volume flow and can thus explain the differences between the CBF- and $V_{MCA}$-responses. This finding confirms the results of our own investigations that $CO_2$-induced changes in brain perfusion are generally underestimated by TCD monitoring.[10,43]

## CONCLUSIONS

The present clinical study shows that 0.8 Vol% halothane in addition to a fentanyl/midazolam base anesthesia does not lead to an increase in the global CBF or the $V_{MCA}$. The relationship between $CO_2$-induced changes of the CBF and the $V_{MCA}$ remains unchanged compared to control conditions. Thus, the Doppler sonographic assessment of relative CBF changes is not expected to be affected by the supply of halothane. This interpretation is of clinical relevance especially for the intraoperative TCD monitoring of cerebral hemodynamics since changes in operative stimuli require a frequent adjustment of the concentrations of inhalation anesthetics. Furthermore, it can be concluded from a pathophysiological point of view that a reduction in global CVR by halothane concentrations of up to 0.8 Vol% is not associated with a corresponding vasodilatation in the region of the proximal basal brain arteries and can thus be predominantly localized at the arteriolar level.

The cerebrovascular $CO_2$ reactivity under the influence of halothane was unchanged in both methods, but the $CO_2$ reactivity of the $V_{MCA}$ showed significantly lower values than the $CO_2$ reactivity of the CBF. The primary cause of this discrepancy is presumably a $CO_2$-induced vasomotion in the area of the basal brain arteries. This finding suggests that $CO_2$-induced changes in brain perfusion tend to be underestimated by TCD monitoring.

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## ADDENDUM CHAPTER 6:

## The relationship between cerebral blood flow and the cerebral blood flow velocity: Influence of halothane on zero flow pressure, effective cerebral perfusion pressure and resistance area product.

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Anasthesiol Intensivmed Notfallmed Schmerzther 2001; 36: 538 – 44
(This addendum has been submitted to AINS)

NB.
*This manuscript refers to the following trial: Validation of transcranial Doppler sonography as a monitoring technique of the cerebral circulation during general anaesthesia (Validierung der transkraniellen Dopplersonographie als Überwachungsverfahren der zerebralen Hämodynamik unter anästhesiologischen Bedingungen). The trial was planned and done before CONSORT initiative. German and Dutch laws did not require international registration of this type of clinical trial at that time. We registered the trial retrospectively at the German Clinical Trials Register (DRKS00011535).*
*In the method and results section of this addendum we added supplemental information as requested from the CONSORT group.*

### INTRODUCTION

In the primary report we investigated the effects of 0.8 vol% Halothane on cerebral circulation during hypocapnia and hypercapnia in cardiovascular patients under fentanyl-midazolam anesthesia. We demonstrated that:

1) Hypocapnia-induced reduction in cerebral blood flow (CBF) under general anesthesia was the effect of both, an increase in cerebrovascular resistance ($CVR_{JVB}$) and cerebral perfusion pressure ($CPP_{JVB}$). However, the increase in $CPP_{JVB}$ was more related by an increase of the mean arterial pressure due to systemic vasoconstriction (SVR). The pressure of the jugular venous bulb ($P_{JVB}$) was nearly unchanged.
2) 0.8 vol% halothane in addition to a fentanyl/midazolam base anesthesia did not lead to an increase in the global CBF or the mean blood flow velocity of the mean cerebral artery ($V_{MCA}$). The relationship between $CO_2$-induced changes of the CBF and the $V_{MCA}$ remains unchanged compared to control conditions.

In the primary report, we defined the cerebral perfusion pressure (CPP) as difference between mean arterial pressure and pressure of the jugular venous bulb ($P_{JVB}$). The mean arterial pressure (MAP) has been used as effective upstream pressure (EUP). The effective downstream pressure (EDP) of the cerebral circulation is commonly defined as the intracranial pressure (ICP), because of a Starling resistor phenomenon located at the level of cerebral veins ('classical model' CPPi = MAP-ICP).[1] In supine position the pressure in the jugular bulb ($P_{JVB}$) could be used as an approximation of the downstream pressure in the cerebral circulation. However, the "classical model" to define CPP has limitations. Using solely the ICP or $P_{JVB}$ as effective downstream pressure (EDP) of the cerebral circulation, would neglect vascular tone properties of cerebral arteries.[2-4]

Studies of other organs have shown, that the effective downstream pressure can be determined by a Starling resistor located at arteriolar level.[5] These studies verified the theory of Permutt and Riley[6] showing that two forces, the extramural pressure (ICP in the case of the brain) and arteriolar wall tension determine the critical closing pressure (CrCP). Arteriolar wall tension arises from a combination of the stretched elastic components of the vessel wall and active contraction of vascular smooth muscle. 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 CrCP. However, the CrCP of the cerebral circulation cannot be directly measured in patients with spontaneous circulation.

In vivo pressure-flow relationships are approximately straight lines in many vascular beds such as the cerebral vessels. Thus, the pressure when flow ceases, the zero flow pressure (ZFP), can be extrapolated by linear regression of instantaneously obtained data pairs of pressure and flow (velocity). The ZFP represents the vasomotor tone.[2 6-12] The inverse slope of the pressure-flow plot represents vascular bed resistance and is named resistance area product (RAP).[13] 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).[4 14] The cerebral zero flow pressure (ZFP), effective cerebral perfusion pressure (CPPe) and the resistance area product (RAP) are thus supplemental determinants of cerebral blood flow.

In contrast to intravenous anesthesia, volatile anesthetics cause a partial uncoupling of CBF and metabolism because of a direct cerebral vasodilatatory effect, which could increase cerebral blood volume, intracranial pressure and impair cerebral autoregulation and vascular reactivity.[15-18]

In a secondary analysis we therefore investigated the effects of 1 MAC Halothane (0.8 vol%) under of variations in $PaCO_2$ on CVRe, CPPe, ZFP, and RAP in patients under intravenous anesthesia. Furthermore, reference calculations of CVRe based on quantitative CBF measurements and calculation of CPPe by determination of ZFP have not yet been compared to changes in RAP.

## METHODS

Our research group performed a series of prospective controlled studies about cerebral circulation, $CO_2$-reactivity and cerebral metabolism in the perioperative setting at the University Medical Center of Göttingen. The main purpose of the primary analysis of this study was to evaluate changes in cerebrovascular reactivity induced by halothane and by variations in arterial partial pressure of carbon dioxide in anesthetized patients examined by a combination of two cerebral measurements techniques: transcranial Doppler Sonography and Kety-Schmidt technique. Later, our team gathered more experience with the concept of the ZFP/CPPe model of the cerebral circulation. This secondary analysis of the ZFP, CPPe and RAP was performed after the study period. In this method section we added supplemental information as advised by the CONSORT group.

The study followed the recommendations of the Declarations of Helsinki from 1975-1989 and the European Union Commission and European Medicines Agency (Council Directive 91/507/EEC and 75/318/EEC). Approval was obtained from the local institutional review board (Medical Ethical Committee of the Georg-August-University of Göttingen, Germany; No. 07/09/90).

### International Research Project Registration:

The trial was planned and done before CONSORT 2010. German and Dutch laws did not require international registration of this type of clinical trial at that time. We registered the trial retrospectively at the German Clinical Trials Register (DRKS00011535).

### Study design

The prospective study was designed and performed in a controlled, crossover design at the University of Göttingen, Medical Center. Each patient served as his own control.

### Endpoints

The primary endpoints of the primary analysis of the study were changes in the mean CBF, mean $V_{MCA}$, $CPP_{JBV}$, and $CVR_{JVB}$.

In this secondary analysis we investigated the effects of 1 MAC Halothane under variations in $PaCO_2$ on CVRe, CPPe, ZFP, and RAP in patients under intravenous anesthesia.

### Sample size calculation

Calculation of the sample size was difficult. The inter-subject and intra-subject variability of CBF, and $V_{MCA}$ has been observed in earlier studies.[19-21] The magnitude of changes differs in patients' population, level of consciousness and intervention. When planning the study, there was a lack of data of anesthetized patients regarding sample size calculation of CBF and $V_{MCA}$ under administration of halothane. For the CBF, $V_{MCA}$ and CVR

we expected a 50% difference between hypocapnia and hypercapnia with an effect size between 2-3. For a statistical power of 80-90% the sample size had to be 7- 9 patients. Therefore we projected a sample size of 10 patients.

**Inclusion**

Due to logistical reasons and funding we could perform only 1-2 measurements per month. Thus, standard-screening procedures could not be applied in this cross-over trial. Patients were eligible for inclusion if scheduled for elective coronary surgery. Exclusion criteria were: age older than 80 years, active neurological disease, and a history of cerebrovascular disease, brain injury, or intracranial surgery. Because transcranial Doppler measurements of $V_{MCA}$ from the transtemporal window fail with above average incidence in elderly female patients, we included only male patients in this study.

In the included patients, both anamnestic data and preoperative duplex sonography of extracranial brain vasculature and TCD showed no evidence of cerebrovascular disease. All patients were informed about the purpose of the study and provided written informed consent before being enrolled. None of the eligible patients refused inclusion in the trial.

**Anesthesia Procedure**

The preoperative medication with calcium antagonists and nitrates was continued until the evening before the operation. β-blockers were applied further until immediately before surgery. For premedication, 2 mg flunitrazepam were administered orally on the preoperative evening as well as one hour before the induction of anesthesia.

Anesthesia was induced with 200 $\mu g \cdot kg^{-1}$ midazolam, 7 $\mu g \cdot kg^{-1}$ fentanyl and 0.1 $mg \cdot kg^{-1}$ pancuronium after placing a central venous catheter and cannulation of the radial artery for continuous measurements of the blood pressure. After nasotracheal intubation, patients were ventilated using a volume-controlled anesthesia respirator controlled with an air / oxygen mixture corresponding to an inspiratory $O_2$ fraction ($FIO_2$) of 0.3. Anesthesia was maintained by continuous infusion of 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$ midazolam and 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl via a drop-controlled infusion pump (Schiwamatic 3000, Schiwa) and pancuronium injections in intervals at a dose of 0.03 $mg \cdot kg^{-1}$.

Then, a 7.5 F introducer sheath (Arrow International Inc., USA) was introduced into the left subclavian vein using the Seldinger technique and a 4-lumen pulmonary arterial introducer catheter was placed under continuous registration of the corresponding pressure curves. Furthermore, the placement of a catheter (6 F Goodale-Lubin, USCI, Bard Inc., USA) in the right bulb jugular vein was performed after retrograde puncture of the right internal jugular vein via a corresponding introducer sheath (Arrow International Inc., USA). The technique used corresponded largely to the method described by *Jakobsen and Enevoldsen*.[22] The correct position of the catheter tip in the jugular bulb

was controlled by means of an X-ray image intensifier in order to prevent contamination of the cerebral venous blood samples by veins merging further distally from the facial region.

## Measurements and calculations

The measurements of the global CBF were carried out using the Kety-Schmidt technique using argon gas as an indicator, as described elsewhere.[20 23 24]

First measurements were performed under 70%$N_2$/ 30%$O_2$, then ventilation was switched to 70% argon/30%$O_2$ gas mixture for 15 minutes. All patients have been ventilated by two identical anesthesia machines. When starting the argon-wash-in-period we changed the ventilators, which had been prefilled with the respective gas mixture, using identical respiratory settings and identical inspired oxygen fraction. The ventilator settings have been adjusted following to our study protocol. End-expiratory $CO_2$ concentrations were continuously recorded to ensure a stable $PaCO_2$ during argon ventilation.

Blood samples were drawn twice, at the beginning (baseline) and end of the argon wash-in period (argon), to measure variables of blood gas analysis (ABL; Radiometer, Copenhagen, Denmark), glucose and lactate. Withdrawing blood from the jugular catheter was performed using a high-precision aspiration pump with gas-tight Hamilton glass syringes (Braun, Melsungen, Germany). We used 2 syringes of 5 ml in parallel for jugular venous blood sampling over 10 min to enable in-duplicate analysis. During the saturation phase the total withdrawal rate thus was 10 ml/10min. The withdrawal rate of blood samples used for blood gas analysis, metabolic tests and for gas chromatographic determination of the argon concentration at the end of the saturation period was 5 mL/20 s.

Arterial blood pressure (ABP) was monitored via a cannula placed in the radial artery with the transducer positioned at the level of the base of the skull/ear. A pulsed monitoring ultrasonic probe (IMP-2, EME) was placed in the area of the right temporal bone. After identification of the proximal middle cerebral artery (MCA), the probe was fixed to the patient's head in a constant position by means of a probe holder (IMP-2 Monitoring Probe Holder, EME) provided for this purpose. The $V_{MCA}$ was determined by using the posterior temporal "bone window" by means of a 2 MHz ultrasound system (TC 2000, EME). All other individually adjusted ultrasound variables, such as enhancement, intensity and target volume, were kept constant throughout the study. The determination of the flow rate in the MCA was based on the maximum intravascular erythrocyte velocity as the envelope curve of the Doppler frequency spectrum. The temporal averaging of the $V_{MCA}$ was achieved by integrating the envelopes continuously recorded on a microcomputer at 52 Hz. For comparison with the simultaneous CBF measurements, the $V_{MCA}$ was averaged over the 10-minute period of the corresponding inert gas saturation phase. During

these phases the end-expiratory $CO_2$ concentration was continuously monitored to ensure a stable arterial partial pressure of carbon dioxide.

Measurements were performed in 10 patients after induction of general anesthesia and before surgery during hemodynamic and respiratory steady-state conditions. First, the hemodynamic measurements were performed during a control phase using two different $PaCO_2$ levels ($PaCO_2 \approx 30$ mmHg and $PaCO_2 \approx 50$ mmHg). The order of the ventilation changes was randomized. After saturation to an end-expiratory halothane level of 0.8 vol%, the measurements were repeated with largely identical $PaCO_2$ values in the reverse order of the ventilation changes (study phase).

The variation of the respiratory minute volume was performed with a constant breathing frequency of 10 $min^{-1}$ and an inspiratory / expiratory ratio of 1: 1 with adjustment of the tidal volume. All measurements were performed under hemodynamic and ventilatory steady-state conditions. After a new $PaCO_2$ level had been reached, a waiting period of 20 minutes with constant end-expiratory $CO_2$ concentration was completed before the corresponding measurement was taken. Measurements during the study phase were carried out at the earliest 30 minutes after the start of the halothane supply under end-expiratory control of the inhalation anesthetic concentration.

In addition to the determination of CBF and $V_{MCA}$, the heart rate, the nasopharyngeal temperature as well as the arterial, central venous and jugular venous pressures in the jugular bulb were recorded on a multichannel recorder at each measurement time. The determination of cardiac output (CO) was carried out by using the thermodilution technique by administering three injections of cold Ringer solution (Polymed CO computer module, System 1281, Siemens) distributed randomly over the respiratory cycle. The calculation of cardiac index and systemic vascular resistance was performed using standard formulas.

The cerebral perfusion pressure ($CPP_{JVB}$) was estimated from the difference between mean arterial pressure (MAP) and the pressure in the jugular bulb ($P_{JVB}$), which served as an approximation of the downstream pressure in the cerebral circulation. The $CVR_{JVB}$ was calculated from the quotient of $CPP_{JVB}$ and CBF. The cerebrovascular $CO_2$ reactivity was expressed as a percentage change in perfusion per mmHg $PaCO_2$ change. Immediately before and after each CBF measurement, blood samples were taken to determine blood viscosity, hematocrit, as well as $O_2$ and $CO_2$ partial pressures.



**Additional calculations of ZFP, CPPe and RAP (second analysis)**

Cerebral ZFP was calculated from data at baseline of each argon gas saturation phase from two simultaneous 10-s recordings (two breathing cycles) of the $V_{MCA}$ curves and arterial pressure curves. Over each 10-s period we first averaged consecutive pairs of diastolic, mean and systolic data of arterial blood pressure (ABP) and $V_{MCA}$.

The ZFP was estimated by x-axis intercept determination from the linear regression line based on corresponding data pairs of systolic, mean and diastolic values of ABP and $V_{MCA}$.[14 25] The cerebral ZFP was used as a measure of the effective downstream pressure of the cerebral circulation. Consequently, CPPe was calculated as CPPe = MAP - ZFP.

When using transcranial Doppler sonography, an estimate of vascular resistance has been defined as the inverse slope of a linear regression line of the driving blood pressure and flow velocity, the resistance area product (RAP).[4 11 13 26] Thus, we calculated the RAP as RAP = (MAP - ZFP) / mean $V_{MCA}$. Formulae to calculate CPPe, CVR, and RAP are summarized in table 1.

**Table A1: Formulae to calculate CPPe, CVR, and RAP**

| Parameter | Formula | Value |
|---|---|---|
| **Effective cerebral perfusion pressure (CPPe)** | CPPe= MAP – ZFP | [mmHg] |
| **Cerebral vascular resistance (CVR)** | CVR = CPPe / CBF | [mmHg/mL/100 g/min] |
| **Resistance area product (RAP)** | RAP = (MAP – ZFP) / $V_{MCA}$ | [mmHg*s/cm] |

CBF = cerebral blood flow, MAP = mean arterial pressure, $V_{MCA}$= cerebral flow velocity of the middle cerebral artery, ZFP = zero flow pressure

## Statistical Analysis

Each patient served as his own control. All results are presented as mean values (standard deviation). Normal distribution of data was assessed both visually with inspection of histograms and with the Shapiro-Wilk normality test. In order to investigate the influence of halothane exposure as well as the $CO_2$ variation, a two-factor variance analysis was carried out for measurement repetitions (RM-ANOVA). In the case of significant interactions between the two factors, additional t-tests were performed for paired samples, in addition to the post-hoc comparison of the mean values. In this case, the level of significance of $\alpha < 0.05$ was adjusted by means of a sequentially rejective test method for multiple mean value comparisons. The percentage cerebrovascular $CO_2$ reactivity was compared with the Wilcoxon test for paired samples. All statistical analyses were performed two-sided and a p-value of $p < 0.05$ was considered to be significant.

Statistical procedures and graphs for the second analysis were made using Prism 7.0 (GraphPad Software, La Jolla, California, USA). Power-analysis and sample size calculation was done with G*Power (University of Düsseldorf, Dept. of Psychology, Düsseldorf, Germany).

## RESULTS

The study period was 5 months (February, 14th until July 7th 1992) A total of 10 male patients were included in the study. The mean age of the patients was 54 (6) years, the

mean body height was 174 (6) cm and the mean body weight was 82.3 (7.8) kg. The TCD signals were of high quality in all patients. The mean depth of insonation for the treatment of the proximal segment of the MCA was 50 (3) mm. In one patient, CBF could not be measured during hypoventilation (patient 9, baseline, B), because of technical problems during the jugular venous blood sampling. For further results regarding patient data, vital parameters, metabolic and hemodynamic data we refer to the results section of the first report.

### Effects of $PaCO_2$

As expected, changing $PaCO_2$ levels from hypercapnia to hypocapnia lead to small significant increase of the MAP by 12% (MD -9 (5) mmHg, CI -13 to -5, P 0.0007).

The $P_{JVB}$ values were nearly unaffected by changes of carbon dioxide (Figure A1-A). When changing from hypercapnia to hypocapnia, the ZFP increased by 61% (MD -8.3 (9.4) mmHg, 95%CI -15 to -2, P 0.021, Figure A1-B). However, CPPe under hypocapnia when compared with hypercapnia remained nearly unchanged due to a concomitant increase of MAP and ZFP (Figure A2-B).

When changing from hypercapnia to hypocapnia CBF was reduced by 50% (MD 26* (9) $ml \cdot min^{-1} \cdot 100g^{-1}$, 95% CI 19 to 33, P <0.0001) and mean $V_{MCA}$ by 35% (MD 19 (10) $cm \cdot s^{-1}$, 95%CI 11 to 26, P = 0.0002), which was interrelated to an increase of CVRe by 102 % (MD -1.09* (0.39) $mmHg \cdot ml^{-1} \cdot 100g^{-1} \cdot min^{-1}$, 95%CI -1.39 to -0.79, P <0.0001, Figure A3B,). Hypocapnia increased RAP only by 43% (MD -0.57 (0.29) $mmHg \cdot s \cdot cm^{-1}$, 95%CI -0.78 to -0.37, P 0.001), when compared with hypercapnia (Figure A4). The changes in mean CVRe and RAP after from hypercapnia to hypocapnia, were thus concordant. Their correlation analysis of individual data showed a moderate linear connection (r = 0.61, 95%CI 0.22 to 0.84, P 0.005).

### Effects of halothane

Administration of 1 MAC halothane resulted in a slight but not significant increase in CBF of 14% under hypocapnia (MD -4 (3) $ml \cdot min^{-1} \cdot 100g^{-1}$, 95%CI -7 to 1, P 0.06) and 14% under hypercapnia (MD -2* (14) $ml \cdot min^{-1} \cdot 100g^{-1}$, 95%CI -13 to 9, P 0.99). Thus, changing $PaCO_2$ levels from hypercapnia to hypocapnia under halothane resulted in an equivalent CBF reduction of 50% (MD 30 (23) $ml \cdot min^{-1} \cdot 100g^{-1}$, 95%CI 14 to 46, P 0.008), which was identical to $PCO_2$-induced changes during the baseline (Table A2, first report Figure 1).

The $V_{MCA}$ under halothane administration was slightly but not significant increased by 4% under hypocapnia (MD -3 (7), 95%CI -8 to 2, P = 0.56) and by 10% under hypercapnia (MD -5 (7), 95%CI -10.02 to 0.02, P 0.51). When changing from hypercapnia to hypo-

* Patient 9 was excluded due missing data of control/hypercapnia phase. RM ANOVA was here done with n = 9

capnia under halothane, $V_{MCA}$ was reduced by 35%, which was in line with the baseline measurements (MD 20 (16) cm $s^{-1}$, 95%CI 9 to 32, P 0.01).

During measurements under halothane, patients showed a significant decrease in MAP by 22% under hypocapnia (MD 9 (5) mmHg, 95%CI 5 to 18, P 0.003) and 14% under hypercapnia (MD 11 (5) mmHg, 95%CI 6 to 15, P 0.003). The MAP values during hypocapnia and hypercapnia under halothane were nearly identical.

The $P_{JVB}$ increased under halothane during hypocapnia by 14% (MD -1.5 (3.2) mmHg, 95%CI - 4.7 to 1.7 to, P 0.542) and under hypercapnia by 20% (MD -2.5 (1.9) mmHg, 95%CI -4.4 to -0.64, P 0.01, Figure A1-A). When comparing hypercapnia versus hypocapnia during the halothane phase, $P_{JVB}$ was nearly unchanged, which was comparable to the control phase.

The ZFP values were nearly unchanged after halothane exposition. Changing $PaCO_2$ levels from hypercapnia to hypocapnia under halothane lead to an increase of ZFP by about 55 % (MD -8.1 (8.0) mmHg, 95%CI -15.9 to 0.3, P 0.04, Figure A1-B), which was comparable to the control phase.

Halothane induced a decrease of CPPe under hypocapnia of about 31% (MD 19 (12) mmHg, 95%CI -7 to 31, P 0.004), which tended to be slightly higher than under hypercapnia (29%, MD 14 (8) mmHg, 95%CI -6 to 22, P 0.002). The CPPe values, however, showed no significant reactivity to $CO_2$ under halothane (Figure A2-B1). This was mainly related to a concomitant decrease of MAP and an increase of ZFP.

Halothane induced a reduction in CVRe by 39% under hypocapnia (MD 0.92 (0.42), 95%CI 0.43 to 1.37, P 0.001) and by 26% under hypercapnia (MD 0.26† (0.19), 95%CI 0.05 to 0.46, P 0.046). The halothane-induced decrease in CVRe under hypocapnia was thus more pronounced than under hypercapnia (Figure A3-B). When changing from hypercapnia to hypocapnia under halothane CVRe increased by 41 % (MD -0.45 (0.53), 95%CI -0.78 to -0.12, P 0.01), which was significantly lower when compared to the control phase.

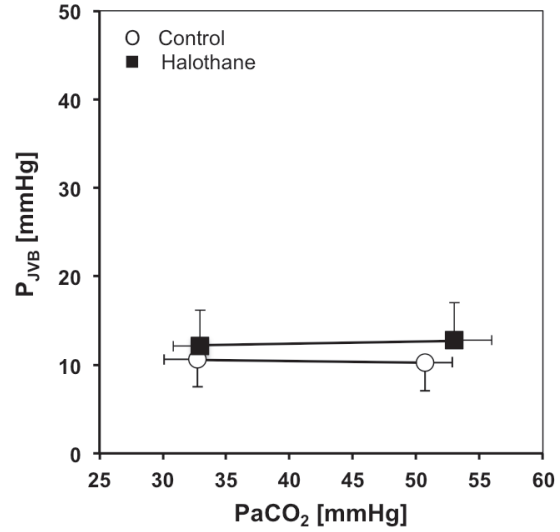
The RAP also showed a reduction after halothane administration. Under hypocapnia RAP was reduced by 27 %, (MD 0.53 (0.39), 95%CI 0.13 to 0,90, P 0.01) and under hypercapnia by 37% (MD 0.53 (0.31), 95%CI 0.19 to 1.80, P 0.03). When changing from hypercapnia to hypocapnia under halothane RAP increased by 67% (MD -0.57 (0.69), 95%CI -1.06 to -0.06, P 0.03, Figure A4). The reduction of RAP due to halothane administration was less pronounced when compared to $CVR_{JVB}$ and CVRe. The $CO_2$-induced changes in mean CVRe and RAP after from hypercapnia to hypocapnia, were thus concordant, the correlation analysis of individual data showed a moderate linear connection (r = 0.68, 95%CI 0.34 to 0.86, P 0.001).

† Patient 9 was excluded due missing data of control/hypercapnia phase. RM ANOVA was here done with n = 9

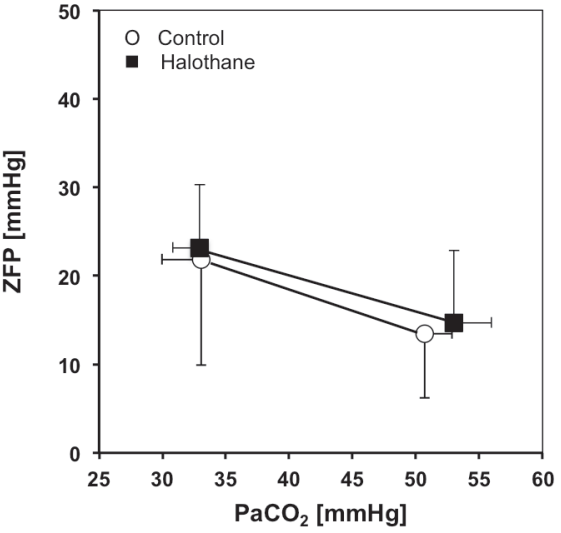
**Table A2: Cerebrovascular effects of 1 MAC halothane (0.8 vol%) and moderate changes in $PaCO_2$ in 10 patients without cerebral disease with intravenous anesthesia.**

| Variable | Control | | 0.8 vol% halothane | | Dimension |
|---|---|---|---|---|---|
| | A | B | A´ | B´ | |
| $PaCO_2$ * # § | 32.8 (2.6) | 50.7 (2.1) | 33.0 (2.1) | 53.0 (3.0) | [mmHg] |
| CBF * | 26 (5) | 52 (9) | 30 (5) | 60 (22) | [ml·min$^{-1}$·100g$^{-1}$] |
| Mean $V_{MCA}$ * # | 33 (14) | 52 (18) | 34 (16) | 57 (17) | [cm·s$^{-1}$] |
| MAP * # § | 84 (10) | 75 (9) & | 66 (12) $ | 65 (9) $ | [mmHg] |
| $P_{JVB}$ # | 10.6 (3.3) | 10.3 (3.4) | 12.1 (4.3) | 12.8 (4.5) | [mmHg] |
| ZFPe * | 21.8 (12.6) | 13.5 (7.5) | 22.7 (7.7) | 14.6 (8.6) | [mmHg] |
| $CPP_{JVB}$ * # § | 74 (10) | 65 (10) | 54 (12) | 53 (6) | [mmHg] |
| CPPe # § | 62 (16) | 62 (10) & | 43 (13) | 48 (7) | [mmHg] |
| $CVR_{JVB}$ * # § | 2.87 (0.66) | 1.24 (0.23) & | 1.84 (0.50) $ | 0.95 (0.24) & $ | [mmHg·ml$^{-1}$·100g$^{-1}$·min$^{-1}$] |
| CVRe * # § | 2.38 (0.58) | 1.18 (0.21) | 1.46 (0.38) | 0.87 (0.21) | [mmHg·ml$^{-1}$·100g$^{-1}$·min$^{-1}$] |
| RAP * # | 1.91 (0.49) | 1.34 (0.43) | 1.40 (0.68) | 0.84 (0.20) | [mmHg·s·cm$^{-1}$] |

**A**: hypocapnia (control); **B**: hypercapnia (control);
**A´**: hypocapnia (halothane); **B´**: hypercapnia (halothane)
Statistical analyses of all data were adjusted by two-way ANOVA for repeated measurements with Holm-Sidak's multiple comparison procedure (n = 9). Difference between hypoventilation versus hyperventilation (A vs. B; A' vs. B') and control versus halothane (A vs. A' and B vs. B') were calculated using two-sided *t* test for paired data (n = 10).
* = significant influence of $PaCO_2$ (RM-ANOVA, p< 0,05)
# = significant influence of halothane (RM-ANOVA, p< 0,05)
§ = significant Interaction between $PaCO_2$ level and halothane (RM-ANOVA, p< 0.05)
& = significant different von corresponding values under hypocapnia (*t* test, p< 0,05)
$ = significant different from the corresponding $PaCO_2$ level of the control phase (t test, p< 0.05)
**CPPe** = effective cerebral perfusion pressure expressed as the difference between mean arterial pressure and zero flow pressure; **$CPP_{JVB}$** = cerebral perfusion pressure expressed as the difference between mean arterial pressure and jugular bulb pressure; **CVRe** = cerebral vascular resistance pressure expressed as the quotient between CPPe and CBF; **$CVR_{JVB}$**= cerebral vascular resistance pressure expressed as the quotient between $CPP_{JVB}$ and CBF; **MAP** = mean arterial pressure; **$PaCO_2$** = arterial partial pressure of carbon dioxide; **$P_{JVB}$** = jugular bulb pressure; **RAP** = resistance area product expressed as de quotient between CPPe and mean $V_{MCA}$.



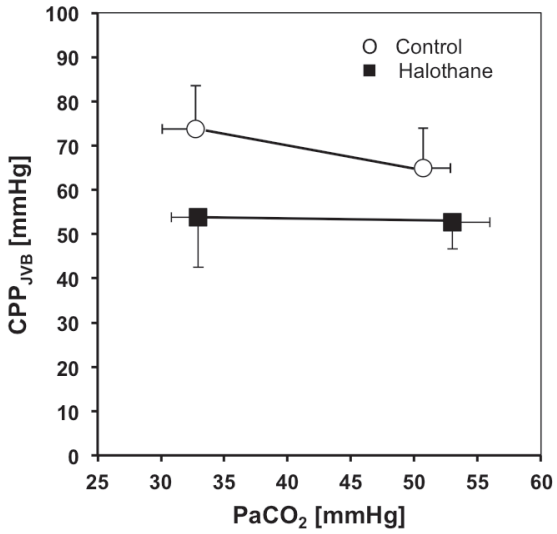

A



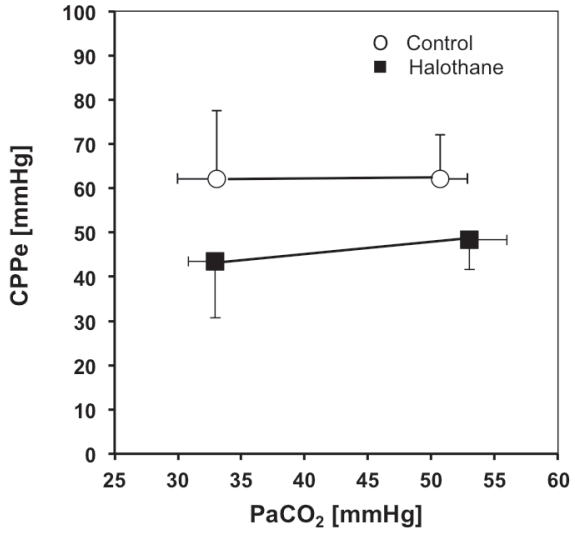

B

**Figure A1: Effective downstream pressure (EDP) of the brain as a function of arterial $PaCO_2$ and 1 MAC Halothane.**

In the first report we defined the jugular bulb pressure ($P_{JVB}$) as EDP of the cerebral circulation (A). In the second analysis we used the zero flow pressure (ZFP), the pressure when flow ceases, as EDP (B). Changes of $PaCO_2$ did not affect $P_{JVB}$ but hypocapnia showed an increase of vasomotor tone (ZFP) of the cerebral circulation. Administration of 1 MAC halothane showed a slight significant increase of $P_{JVB}$. The cerebrovascular $CO_2$ reactivity of the ZFP under Halothane remained unchanged.



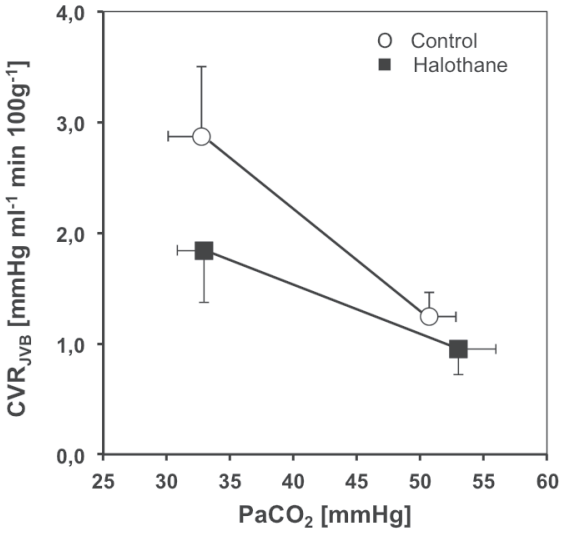

A



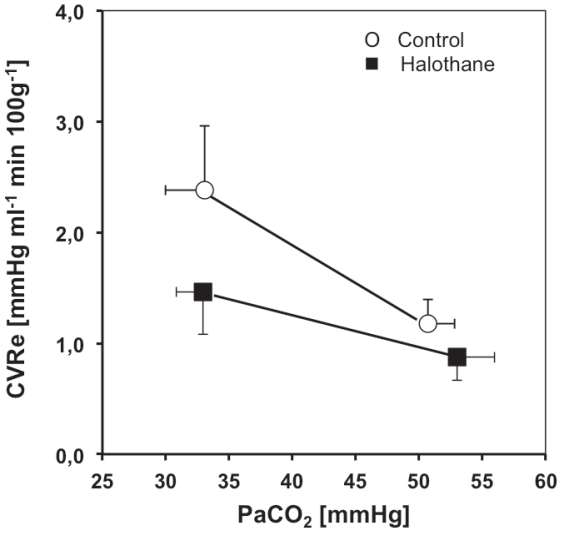

B

**Figure A2: Cerebral perfusion pressure of the brain as a function of arterial $PaCO_2$ and 1 MAC Halothane.**

In the first report, we used the jugular bulb pressure ($P_{JVB}$) instead of the ICP to calculate the CPP. Other model used the difference between the MAP and the zero flow pressure, taking vasomotor properties of the vascular bed more into account. Hypocapnia lead to an increase of $CPP_{JVB}$, which was related to by an increase of the mean arterial pressure due to systemic vasoconstriction (SVR). The effective CPPe was unchanged within hypocapnia and hypercapnia unless increase in cerebral vasomotor tone (ZFP). Administration of 1 MAC halothane showed a significant decrease of $CPP_{JVB}$. The reduction of CPPe under hypocapnia was more pronounced than under hypercapnia.




A




B

**Figure A3: Cerebral vascular resistance as a function of arterial $PaCO_2$ and 1 MAC Halothane.**
Hypocapnia lead to a strong increase of $CVR_{JVB}$, which was related to a decrease of cerebral blood flow (CBF) and increase of $CPP_{JBV}$, mean arterial pressure and systemic vasoconstriction. The increase of the CVRe was less prominent due to the increase in cerebral vasomotor tone (ZFP). Halothane reduced the cerebrovascular $CO_2$ reactivity of the $CVR_{JVB}$ and CVRe.

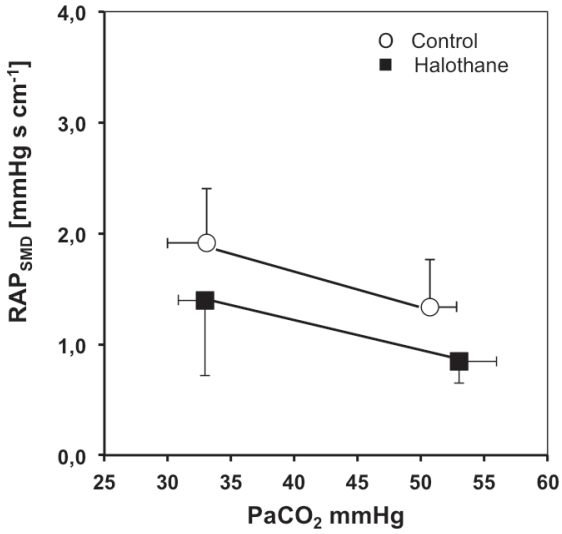



**Figure A4: Resistance area product as a function of arterial $PaCO_2$ and 1 MAC Halothane.**
Analog to the effects on CVRe induced halothane administration also a strong reduction in RAP. The reactivity to changes in $PaCO_2$ was unchanged.

## DISCUSSION

In the secondary analysis we investigated the effects of 1 MAC Halothane during hypocapnia and hypercapnia on CVRe, CPPe, ZFP, and RAP. The most noticeable results are:

1) Hypocapnia-induced reduction in CBF under general anesthesia was the effect of both, an increase in CVRe and an increase in ZFP
2) The increases of mean CVRe and RAP associated with hypocapnia were concordant.
3) 1 MAC halothane reduced the slope of the pressure flow relationship (RAP). The vasomotor tone (ZFP) was nearly unchanged.
4) 1 MAC Halothane did not affect the $CO_2$-reactivity of the ZFP.

### Effects of $PaCO_2$

Recent reports of healthy volunteers and cardiovascular patients have shown that hypercapnia increased the effective cerebral perfusion pressure presumably by decreasing the vascular tone (ZFP); hypocapnia had the opposite effect.[27-29] These findings were counterintuitive to the conventional understanding in which hypercapnia is expected to decrease CPP and hypocapnia is expected to increase it by increasing or decreasing the cerebral blood volume, and hence intracranial pressure. However, these studies

provided evidence that vasomotor tone has a major role in determining CPP in subjects without intracranial hypertension.

In the present halothane study, changes in CPPe and ZFP are similar in nature to those seen during hypocapnia and hypercapnia, suggesting that the effects on vasomotor tone have a predominant role in determining effective downstream pressure.

### Effects of 1 MAC halothane

Volatile anesthetics exert complex effects on the systemic and cerebral circulation. The reduction in mean arterial pressure of 14 to 22% in our study is in line with former investigations.[30 31] Volatile anesthetics increase intracranial pressure due to vasodilation, resulting in an increase in cerebral blood flow and cerebral blood volume.[32 33] Thus, volatile anesthetics can narrow the driving pressure range over which autoregulation occurs and can raise the level of perfusion over the range of autoregulation.

A part of the effects of volatile anesthetics on cerebral blood flow may result from their effects on cerebral activity and metabolism. In a former investigation patients under deep intravenous anesthesia (isoelectric encephalography activity) received 0.5 MAC and 1.5 MAC halothane, desflurane or isoflurane. All volatile anesthetics increased CBF in a dose-related manner. Thus, volatile anesthetics appear to cause a vasodilatation independent of their effect on cerebral metabolic rate (neurovascular uncoupling).[16]

Up to now investigations regarding the effects on volatile anesthetics on CPPe and ZFP are rare. *Strebel et al*. found that $V_{MCA}$ was not changed from control by 0.5 MAC or 1.5 MAC desflurane or isoflurane but was markedly decreased by propofol in patients with orthopedic procedures.[34] In a former investigation, *Marval et al*. could show that the ZFP decreased significantly during sevoflurane anesthesia. Sevoflurane showed also a moderate reduction in MAP and $V_{MCA}$. The proportional reduction of ZFP was thus counterbalanced by a reduction in MAP, which lead to a preserved CPPe.[35]

In our study, 1 MAC halothane caused a reduction of $CVR_{JVB}$ and $CPP_{JBV}$. This prevented a moderate increase in CBF. In the primary analysis, we assumed that this was not an expression of an autoregulatory response, but rather was caused by direct vasodilatory effects. The results of our secondary analysis on the effects of 1 MAC halothane showed similarly a decrease of CPPe, which was mainly caused by a decrease in MAP. The ZFP was nearly unchanged while RAP was reduced by 27% (hypocapnia) and 37% (hypercapnia). Our data suggest now, that halothane has a larger effect on the slope of the pressure flow relationship rather than the vasomotor tone. *Panerai et al.* were able to show that the RAP is related to myogenic properties of the cerebrovascular system, while ZFP reflects metabolism and cerebrovascular reactivity to $CO_2$.[36] Our data, however, could not explain the regulatory mechanism between these two factors.

1 MAC halothane reduced $CVR_{JVB}$, CPPe and RAP. However, the reduction of RAP under hypocapnia was less prominent when compared to $CVR_{JVB}$ and CVRe. This might

be related to a reduced cerebrovascular $CO_2$-reactivity of cerebral blood flow versus blood flow velocity. Earlier trials have shown that relative changes in CBF were reflected by changes in $V_{MCA}$ in a proportional manner, suggesting that MCA diameter remains constant.[37] However, other studies were able to show that illness and interventions as migraine attacks, orthostasis, $CO_2$-rebreathing or vasoactive medicine could alter the MCA diameters by 5-12%.[38-41] In another trial, we could demonstrate that the cerebrovascular $CO_2$-reactivity (within a range of 30-50mmHg) of CBF as well as $V_{MCA}$ showed an exponential function. Conversely, there was a slight systematic difference between relative changes in flow and flow velocity, especially under hypercapnia. The most probable reason 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.[29]

**Limitations**

A possible limitation of the second analysis study may arise from the linear extrapolation method of ABP and $V_{MCA}$, which has been used to estimate ZFP. Capacitance effects of the middle cerebral artery may have changed, during variation of carbon dioxide, which in turn may have weakened the accuracy of our extrapolation of ZFP. The linearity of pressure-flow velocity relationships have not been influenced by $PaCO_2$ in an earlier study.[14] Thus, possible effects on MCA compliance are assumed to be of minor methodological importance.

The Kety-Schmidt method has been considered as a reference method for quantifying global CBF.[42 43] When compared to PET or SPECT, the Kety-Schmidt technique is largely independent of assumptions concerning tracer kinetics, but might slightly overestimate global CBF in case of incomplete cerebral tracer saturation. Because of the crossover design of our study, a slight systematic overestimation of CBF has minor importance for the interpretation of hemodynamic changes.



## CONCLUSIONS

In the secondary analysis we could demonstrate that hypocapnia-induced reduction in CBF under general anesthesia was the effect of both, an increase in CVRe and an increase in ZFP. The increase of mean CVRe and RAP associated with hypocapnia were concordant.

0.8 vol% Halothane in addition to a fentanyl/midazolam based anesthesia reduced the slope of the pressure flow relationship (RAP). The vasomotor tone (ZFP) was nearly unchanged. Furthermore, halothane did not affect the $CO_2$-reactivity of the ZFP.

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# Chapter 7

## Argon does not affect cerebral circulation or metabolism in male humans.

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PLoS ONE Public Library of Science; 2017;12: 1–13
German Clinical Trials Register (DRKS00011535).

## ABSTRACT

**Background:** Accumulating data have recently underlined argon´s neuroprotective potential. However, to the best of our knowledge, no data are available on the cerebrovascular effects of argon (Ar) in humans. We hypothesized that argon inhalation does not affect mean blood flow velocity of the middle cerebral artery (Vmca), cerebral flow index (FI), zero flow pressure (ZFP), effective cerebral perfusion pressure (CPPe), resistance area product (RAP) and the arterio-jugular venous content differences of oxygen ($AJVDO_2$), glucose (AJVDG), and lactate (AJVDL) in anesthetized patients.

**Materials and methods:** 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 anaesthesia before coronary surgery. Vmca was measured by transcranial Doppler sonography. ZFP and RAP were estimated by linear regression analysis of pressure-flow velocity relationships of the middle cerebral artery. CPPe was calculated as the difference between mean arterial pressure and ZFP. $AJVDO_2$, AJVDG and AJVDL were calculated as the differences in contents between arterial and jugular-venous blood of oxygen, glucose, and lactate. Statistical analysis was done by t-tests and ANOVA.

**Results:** Mechanical ventilation with 70% Ar did not cause any significant changes in mean arterial pressure, Vmca, FI, ZFP, CPPe, RAP, $AJVDO_2$, AJVDG, and AJVDL.

**Discussion:** Short-term inhalation of 70% Ar does not affect global cerebral circulation or metabolism in male humans under general anaesthesia.


**Keywords:** Noble gases, Argon, cerebral circulation, transcranial Doppler, neurophysiology, energy metabolism, neuroprotection.

## INTRODUCTION

Argon is the longest known rare gas of the group of noble gases. Compared to xenon, it has a higher natural abundance in the atmosphere (gas fraction of dry air at sea level: 20.9% oxygen, 78.1% nitrogen, 0.9% argon, 0.03 % carbon dioxide, helium 0.000005% and 0.00000009% xenon) [1]. It can be obtained as a pure gas of pharmaceutical quality at low costs. Stable argon gas is known to be inert. It does not change vital parameters and has no anaesthetic properties at sea level [2,3]. When argon is administered by inhalation it does not require complex ventilator settings. Inhalation of argon/oxygen mixtures is used in humans to measure coronary [4] and cerebral blood flow [5,6]. Argons beneficial neuroprotective and organoprotective properties have been observed in animal experiments *in vitro* and *in vivo*, but rarely in human studies [7,8].

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, which in part has been recently published [9]. In the same group of patients we also investigated the short-term effects of argon inhalation. We hypothesized that argon has no effects on parameters of cerebral blood flow velocity, cerebrovascular perfusion pressure, blood gas analysis, and global cerebral metabolism.

The original rationale for this substudy was a methodological question, as we wanted to rule out the possibility, that our method of CBF measurement (which required argon inhalation) *per se* might have any influence on the cerebrovascular and cerebrometabolic variables. Because of the recent interest in potential organoprotective properties of argon, we believe that these data should be made accessible to the scientific community.



## MATERIAL AND METHODS

### Design

In this prospective controlled study we investigated the cerebrovascular $CO_2$-reactivity of CBF, cerebral blood flow velocity of the middle cerebral artery (Vmca), and cerebral metabolic rate of oxygen, glucose and lactate ($CMRO_2$, CMRG, CMRL) in 30 patients before cardiovascular surgery at the University of Göttingen Medical Centre, Germany. CBF was measured using the modified Kety-Schmidt inert gas saturation technique with stable argon gas as an indicator (70% Ar / 30% $O_2$ gas mixture). Vmca was simultaneously

measured by transcranial Doppler sonography (TCD) [9]. Subsequently, after this investigation of hypoventilation versus hyperventilation on CBF, Vmca and CMR, we divided the 30 patients into 3 subgroups (10 patients per group) for further examinations in the same setting. With additional measurements in these patients we studied the cerebrovascular effects (i) of nitroglycerine [10], (ii) of halothane [11], and (iii) of more extensive variations of $PaCO_2$ [12].

For quality control purposes, we also studied in these patients the cerebrovascular and metabolic effects of argon itself at the beginning of each series of CBF measurements. The primary rationale for this analysis was to investigate if our method of CBF measurement (argon saturation method) *per se* has any influence on cerebrovascular circulation or metabolism. Thus haemodynamic and laboratory data, which have been used to calculate variables of the first point of measurement in previous publications, are partly used in this analysis [9-12].

Cerebral flow index (FI), effective cerebral perfusion pressure (CPPe), cerebral zero flow pressure (ZFP), and the inverse slope of pressure-flow velocity relationships (resistance area product, RAP) were calculated in addition to standard variables from transcranial Doppler and haemodynamic recordings.

The study project followed the recommendations of the Declarations of Helsinki and the European Union Commission and European Medicines Agency (Council Directive 91/507/EEC and 75/318/EEC). Ethical approval for this study was provided by the Medical Ethical Committee of the Georg-August-University of Göttingen, Göttingen, Niedersachsen, Germany (Trial: Validation of transcranial Dopplersonography as a monitoring technique of the cerebral circulation during general anaesthesia (Validierung der transkraniellen Dopplersonographie als Überwachungsverfahren der zerebralen Hämodynamik unter anästhesiologischen Bedingungen), Ethical Committee N° 07/09/90). The trial has been retrospectively registered at the German Clinical Trials Registry (No.: DRKS00011535).

## Endpoints

The endpoints of the study were changes in the mean Vmca, FI, CPPe, ZFP, RAP, and the arterio-jugularvenous content differences of oxygen ($AJVDO_2$), glucose (AJVDG), and lactate, (AJVDL). We hypothesized that in patients under intravenous anaesthesia short-term inhalation of 70% argon does not alter cerebral haemodynamics or metabolism.

## Inclusion

Due to logistical reasons and funding we could perform only 1-2 measurements per month. Thus, standard-screening procedures could not be applied in this cross-over trial. Patients were eligible for inclusion if scheduled for elective coronary surgery. Exclusion criteria were: age older than 80 years, active neurological disease, and a history of cerebrovascular disease, brain injury, or intracranial surgery.

Transcranial Doppler measurements of Vmca from the transtemporal window fail with above average incidence in elderly female patients due to less mineral bone density and subsequently reduced ultrasound penetration [13]. Therefore, we included only male patients in this study. All patients were informed about the purpose of the study and provided written informed consent before being enrolled. None of the eligible patients refused inclusion in the trial.

**Anaesthesia procedure**

Individual medications were continued until surgery. Intravenous anaesthesia was induced and maintained by continuous intravenous administration of fentanyl, midazolam and pancuronium. All patients received two peripheral intravenous lines, an endotracheal tube, a nasogastric tube, and a urine catheter. After arterial, central venous and pulmonary artery catheterization a jugular bulb catheter was inserted by retrograde puncture of the right internal jugular vein. The correct position of the jugular bulb catheter tip was verified by fluoroscopy to prevent inadvertent extracerebral contamination of blood samples. The withdrawal rate of blood samples used for blood gas analysis, metabolic tests and for gas chromatographic determination of the argon concentration at the end of the saturation period was 5 mL / 20 s [14]. The anaesthesia procedure, the details of mechanical ventilation and the methods of catheter insertion have been described in previous reports in detail [5,9].

**Measurements and calculations**

Measurements were performed in 30 patients after induction of general anaesthesia and before surgery during haemodynamic and respiratory steady-state conditions.

First measurements were performed under 70%$N_2$/30%$O_2$, then ventilation was switched to 70% argon/30%$O_2$ mixture for 15 minutes. The ventilator settings have been adjusted following to our study protocol. All patients have been ventilated by two identical anaesthesia machines. When starting the argon-wash-in-period we changed the ventilators, which had been prefilled with the respective gas mixture, using identical respiratory settings and identical inspired oxygen fraction. End-expiratory $CO_2$ concentrations were continuously recorded to ensure a stable $PaCO_2$ during argon ventilation.

Blood samples were drawn twice, at the beginning (baseline) and end of the argon wash-in period (argon), to measure variables of blood gas analysis (ABL; Radiometer, Copenhagen, Denmark), glucose and lactate.

Blood flow velocity in the proximal (M1) segment of the middle cerebral artery (Vmca) was measured by TCD. To ensure a constant position of the ultrasound probe during the investigation period, we used a probe holder (IMP2 monitoring probe holder, EME, Überlingen, Germany). During measurements the patients' heads were fixed in midline

position. Arterial blood pressure was measured invasively in the radial artery, ipsilateral to the TCD probe.

The analyses of the ZFP, CPPe and RAP have been performed after the study period. Cerebral ZFP was calculated from data at baseline and at the end of each argon gas saturation phase from two simultaneous 10 s recordings (two breathing cycles) of the Vmca curves and arterial pressure curves. Over each 10 s period we first averaged consecutive pairs of diastolic, mean and systolic data of ABP and Vmca. These data were used to generate a pressure/flow velocity plot. ZFP was then extrapolated by linear regression analysis of the ABP-Vmca relationship. The ABP axis intercept of the regression line determines the ZFP [15,16]. The cerebral ZFP was used as a measure of the effective downstream pressure of the cerebral circulation. Consequently, CPPe was calculated as CPPe = mean ABP-ZFP. In the relationship between ABP and Vmca, the RAP is defined as the inverse slope of their linear regression line [17,18].

Inside the spectral envelope each velocity has an intensity (usually color-coded on the display), which is proportional to the volume of blood at this velocity. The flow related to that volume of blood is therefore proportional to the product of its velocity and acoustic intensity. Summing these different flows gives a flow index (FI), which is proportional to total flow. The FI was thus computed as the sum of each acoustic intensity within the TCD spectrum multiplied by the corresponding velocity. We averaged all signals over the entire waveform, which yields the mean FI for that particular 10 s interval [19-21].

The arterial-to-jugular venous concentration difference of a substance *x*, was calculated as AJVD(x) = Ca(x) - Cjv(x). We calculated the difference in arterio-jugular venous content of oxygen ($AJVDO_2$), glucose (AJVDG), and lactate (AJVDL) [22]. By definition, positive AJVD values indicate consumption or net influx, and negative values indicate production or net efflux. For AJVDL, in case of cerebral lactate production, we thus expected negative values.

## Statistical analysis

In this secondary analysis study setting a prior sample size calculation was not performed. Each patient served as his own control. The results presented are expressed as mean (standard deviation) unless otherwise stated. Normal distribution of data was assessed both visually with inspection of histograms and with the D'Agostino-Pearson omnibus K2 method. The differences between baseline and argon gas inhalation were calculated using t-tests for paired data or Welch-test and non-parametric Wilcoxon signed-rank test, if indicated [23]. To provide an estimate of the effect of argon gas and its clinical meaningfulness, we calculated mean differences (MD) and their 95 per cent confidence intervals (MD; 95% CI upper bound, lower bound; *P*-value) [24]. In case of significant differences between the baseline and the argon period, all primary endpoints were ad-

ditionally tested by one-way ANOVA for repeated measurements followed by Bonferoni multiple comparison tests in order to prevent type I error [25].

All statistical analyses were performed two-sided and a p-value of $p< 0.05$ was considered to be significant. Database sheets were done by MS Excel® for Mac 2011 (Microsoft, Redmond, Washington, USA). Statistical procedures and graphs were made using Prism 6.0 (GraphPad Software, La Jolla, California, USA).

## RESULTS

The study period was 27 months (February 20, 1991 until May 10, 1993). A total of 30 male patients were examined. In one patient an unexpected sudden increase in heart rate and blood pressure occurred after an unintended surgical stretcher movement during the recordings. This was interpreted as a short phase of insufficient depth of anaesthesia, which ceased following an additional bolus of fentanyl and midazolam. The patient was thereafter completely excluded from further analysis because we assumed insufficient steady state conditions.

The mean TCD-insonation depth of the MCA was 51 (3) mm. TCD signals were of high quality in all patients except for two patients during the baseline measurement (patient 1 and 5). These data have been excluded from respective analysis.

Mean age of the included 29 patients was 56 (6) yrs. (median 57, range 41-65 yrs.), mean height 174 (6) cm, and mean body weight 78 (8) kg. One of our patients had diabetes mellitus type 2, treated with biguanides. None of the patients showed increased levels of blood glucose. A minimal, but significant decrease of mean blood temperature between the two periods of measurements was observed (Temp baseline 35.6 (0.5)°C, argon 35.5 (0.5)°C, MD 0.1, 95% CI 0.07 to 0.2, $P< 0.01$). There was a minimal decrease in heart rate (HR) baseline 58 (8) bpm and argon 56 (8) bpm, MD 2; 95% CI 1 to 2, $P < 0.01$), arterial oxygen saturation ($SaO_2$ baseline 97 (1)% and argon 96 (2)%, MD 1, 95% CI 1 to 1, $P < 0.01$), and arterial partial pressure of oxygen ($PaO_2$ baseline 139 (42) mmHg and argon 109 (26) mmHg, MD 29, 95% CI 17 to 41, $P < 0.01$). Arterial lactate concentration showed a very small but significant increase ($Lac_{ART}$ baseline 0.59 (0.16) $mmol{\cdot}L^{-1}$ and argon 0.63 (0.17) $mmol{\cdot}L^{-1}$, MD -0.04, 95% CI −0.08 to -0.01, P 0.04). Levels of haemoglobin were unchanged before and after argon exposure (Hb baseline 12.7 (1.4) $mg{\cdot}dL^{-1}$ and argon 12.7 (1.4) $mg{\cdot}dL^{-1}$, MD 0.01, 95% CI −0.06 to 0.08, P 0.84) as well as levels of jugular venous oxygen saturation ($SjvO_2$ baseline 50 (10)% and argon 50 (11)%, MD 0.44, 95% CI −0.78 to 1.67, P 0.46).

When comparing inhalation of 70% $N_2$ / 30% $O_2$ with 70% Ar / 30% $O_2$ there were no significant and clinically relevant changes in mean arterial pressure (MAP), mean Vmca, FI, ZFP, CPPe, RAP $AJVDO_2$, AJVDG and AJVDL.

The most important haemodynamic and metabolic data are presented in Table 1 and Fig 1. There were no relevant changes in other basic haemodynamic and blood gas variables between the baseline and argon inhalation period (see S1 Table in the supplemental data content).

Ventilation parameters and $PaCO_2$ levels of the patients were effectively kept constant (mean $PaCO_2$ baseline = 36 (5) mmHg, (median 34, range 28 to 45), mean $PaCO_2$ argon = 37 (7) mmHg (median 34, range 26 to 50). The mean difference of $PaCO_2$ between the baseline and the argon measurements was minimal MD = −0.6 (2.4), CI −1.5 to 0.36 mmHg, P 0.22 (median differences 0.0, P 0.46).

**Table 1 - Haemodynamic and metabolic data**

| | Baseline | | Argon | | | | n= 29 | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **mean** | **SD** | **mean** | **SD** | **Dimension** | **MD** | **CI limits** | **P** |
| mean$V_{MCA}$ | 36 | 11 | 36 | 11 | [cm·s$^{-1}$] | 0 | (-0.5; 0.4) | 0.87* |
| FI #$ | 154 | 84 | 147 | 74 | [ ] | 7 | (-4; 17) | 0.20* |
| MAP | 74 | 12 | 73 | 13 | [mmHg] | 1 | (-1; 3) | 0.33§ |
| ZFP #$ | 20 | 8 | 20 | 8 | [mmHg] | 0 | (-2; 2) | 0.91* |
| CPPe | 54 | 14 | 53 | 13 | [mmHg] | 1 | (-2; 4) | 0.60* |
| RAP #$ | 1.65 | 0.56 | 1.59 | 0.48 | [mmHg·s·cm$^{-1}$] | 0.06 | (-0.03; 0.15) | 0.18* |
| $AJVDO_2$ | 8.5 | 2.0 | 8.3 | 2.4 | [ml dL$^{-1}$] | 0.2 | (-0.1; 0.4) | 0.12 |
| AJVDG# | 10.1 | 4.6 | 9.1 | 4.1 | [mg dL$^{-1}$] | 1.1 | (-0.5; 2.6) | 0.18 |
| AJVDL#$ | -0.06 | 0.07 | -0.04 | 0.11 | [mmol L$^{-1}$] | 0.02 | (-0.07; 0.02) | 0.26 |

Baseline = inhalation of 70% $N_2$ / 30% $O_2$. Argon = inhalation with 70% Ar / 30% $O_2$. The P values, which refer to the difference between two measurement points, were calculated using two-sided t-test for paired data. Because the variances of some outcome variables differed between two measurement points, these parameters were additionally examined by Welch test (#) and nonparametric Wilcoxon signed-rank test ($) (P<0.05). Due to artefacts during TCD or blood pressure recording, data of patient 1 and 5 have been excluded from respective analysis § n= 28, * n= 27.

AJVDG = arterio-jugular venous difference in glucose; AJVDL = arterio-jugular venous difference in lactate; $AJVDO_2$ = arterio-jugular venous difference in oxygen, CI = confidence interval (5%; 95%), CPPe = effective cerebral perfusion pressure defined as MAP-ZFP, FI = Flow index, MAP = mean arterial pressure, MD = mean differences, RAP = resistance area product, SD = standard deviation, mean Vmca = mean blood flow velocity of the middle cerebral artery, ZFP = zero flow pressure.

**S1 Table. Effect of argon on parameters of blood gas analysis and hemodynamics.**

| | Baseline | | Argon | | | | n= 29 | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | **mean** | **SD** | **mean** | **SD** | **Dimension** | **MD** | **CI limits** | **P** |
| HR* | 58 | 9 | 56 | 9 | [bpm] | 2 | (1; 2) | <0.01§ |
| MAP | 74 | 12 | 73 | 13 | [mmHg] | 1 | (-1; 3) | 0.33§ |
| Hb | 12.7 | 1.4 | 12.7 | 1.4 | [ml $dL^{-1}$] | 0.01 | (-0.1; 0.1) | 0.84 |
| Hct | 38 | 4 | 38 | 4 | [%] | 0.1 | (-0.1; 0.4) | 0.33 |
| Na | 143 | 2 | 143 | 2 | [mmol $L^{-1}$] | 0 | (0; 0) | 0.57 |
| K | 4.3 | 0.4 | 4.3 | 0.3 | [mmol $L^{-1}$] | -0.01 | (-0.13; 0.11) | 0.82 |
| $Gluc_{ART}$ | 77 | 9 | 77 | 9 | [ml $dL^{-1}$] | 1 | (-1; 2) | 0.56 |
| $Gluc_{JV}$ | 67 | 8 | 67 | 8 | [ml $dL^{-1}$] | -1 | (-2; 1) | 0.51 |
| $Lac_{ART}$* | 0.59 | 0.16 | 0.63 | 0.18 | [mmol $L^{-1}$] | -0.04 | (-0.08; -0.01) | 0.04 |
| $Lac_{JV}$ | 0.65 | 0.15 | 0.67 | 0.20 | [mmol $L^{-1}$] | -0.02 | (-0.04; 0.01) | 0.21 |
| $PaO_2$* | 139 | 42 | 109 | 29 | [mmHg] | 29 | (17; 41) | <0.01 |
| $PjvO_2$ | 30 | 6 | 30 | 7 | [mmHg] | 0 | (-1; 1) | 0.45 |
| $SaO_2$* | 97 | 1 | 96 | 2 | [%] | 1 | (1; 1) | <0.01 |
| $SjvO_2$ | 50 | 10 | 49 | 11 | [%] | 0 | (-1; 2) | 0.48 |
| $PaCO_2$ | 36 | 5 | 37 | 7 | [mmHg] | -1 | (-1; 0) | 0.24 |
| $PjvCO_2$ | 47 | 5 | 47 | 6 | [mmHg] | 0 | (-1; 1) | 0.68 |
| $pH_{ART}$ | 7.43 | 0.06 | 7.43 | 0.07 | [ ] | 0.01 | (-0.01; 0.01) | 0.94 |
| $pH_{JV}$ | 7.36 | 0.04 | 7.36 | 0.05 | [ ] | 0.01 | (-0.01; 0.01) | 0.43 |
| $SBC_{ART}$ | 25.4 | 1.1 | 25.5 | 1.4 | [mmol $L^{-1}$] | -0.1 | (-0.5; 0.2) | 0.50 |
| $SBC_{JV}$ | 25.1 | 1.2 | 25.0 | 1.0 | [mmol $L^{-1}$] | 0.1 | (-0.2; 0.4) | 0.60 |

Baseline = inhalation of 70% $N_2$ / 30% $O_2$. Argon = inhalation with 70% Ar / 30% $O_2$. The P values, which refer to the difference between two measurement points, were calculated using two-sided t-test for paired data (* $P<0.05$). Due to artefacts during blood pressure recording, data of patient 1 has been excluded from respective analysis § n= 28.

CI = confidence interval (5%; 95%), $Gluc_{ART}$ = arterial blood glucose concentration, $Gluc_{JV}$ = jugular bulb blood glucose concentration, Hb = haemoglobin concentration, Hct = haematocrit, HR = heart rate in beats per minute, K = serum potassium concentration, $Lac_{ART}$ = arterial blood lactate concentration, $Lac_{JV}$ = jugular bulb blood lactate concentration, MD = mean differences, MAP = mean arterial blood pressure, Na = serum sodium concentration, $pH_{ART}$ = pH of arterial blood, $pH_{JV}$ = pH of jugular bulb blood, $PaCO_2$ = arterial partial pressure of $CO_2$, $PjvCO_2$ = jugular bulb partial pressure of $CO_2$, $PaO_2$ = arterial partial pressure of $O_2$, $PjvO_2$ = jugular bulb partial pressure of $O_2$, $SaO_2$ = arterial blood oxygen saturation, $SjvO_2$ = jugular bulb blood oxygen saturation, SBC = standard bicarbonate concentration, SD = standard deviation.

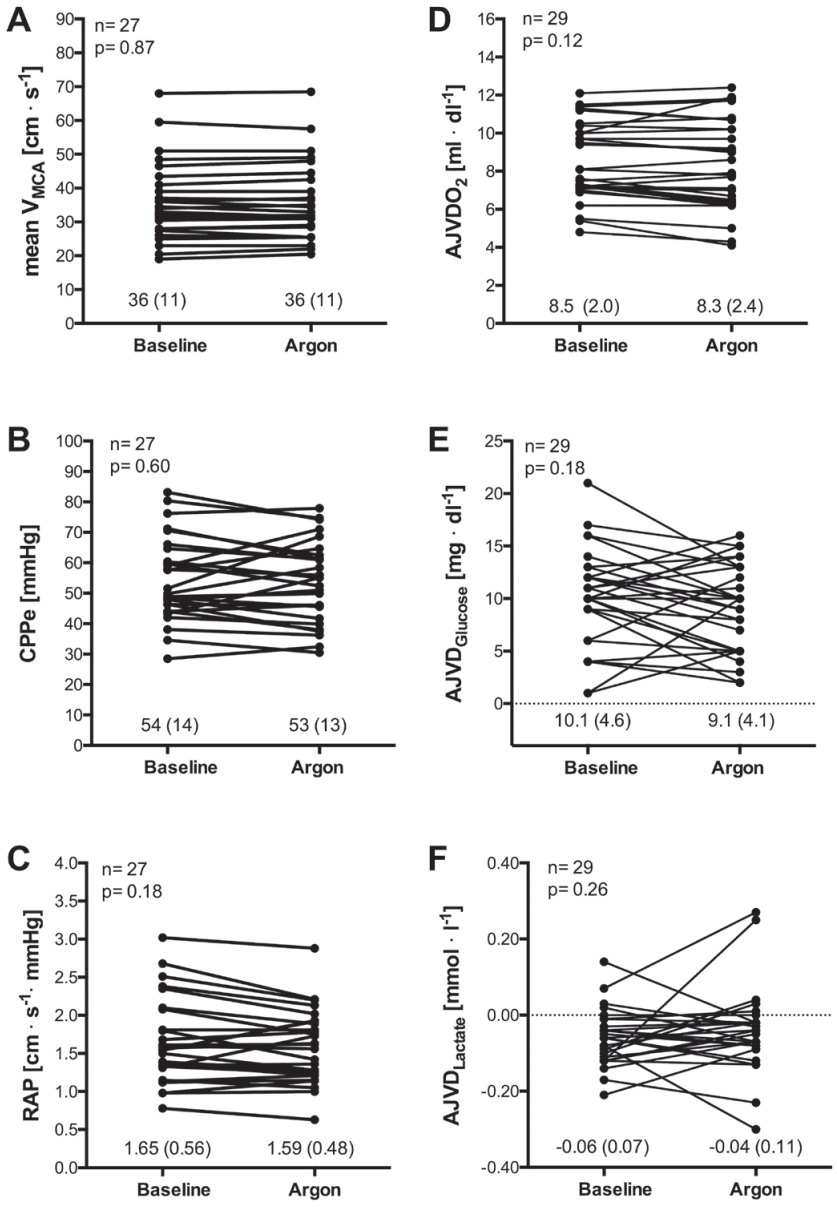


**Figure 1 (A-F)**

Values of mean blood flow velocity of the middle cerebral artery (Vmca), effective cerebral perfusion pressure (CPPe), resistance area product (RAP), arterio-jugular venous differences in oxygen ($AJVDO_2$) glucose (AJVDG), and lactate (AJVDL) during baseline (70%$N_2$/30%$O_2$) compared with argon inhalation (70%Ar/30%$O_2$). *Straight lines* link individual values for each subject. Data are mean (SD) for each measurement. The P values, which refer to the difference between two measurement points, were calculated using two-sided t-test for paired data. Due to artefacts during TCD recording, data of patient 1 and 5 have been excluded from respective analysis § n= 28, * n= 27.

## DISCUSSION

We investigated the effects of an argon-oxygen gas mixture on cerebral circulation and metabolism in cardiovascular patients under fentanyl-midazolam anaesthesia. The most prominent result of our study is that no significant and clinically relevant changes were found in Vmca, FI, CPPe, ZFP, RAP, $AJVDO_2$, AJVDG and AJVDL when comparing inhalation of 70% Ar / 30% $O_2$ with 70% $N_2$ / 30% $O_2$.

To the best of our knowledge, this study is the first report about cerebrovascular and cerebrometabolic effect of argon in humans. Most of the data on biological effects of argon has been accomplished by *in vitro* and *in vivo* animal studies, but rarely in humans. Medical research in the 1930s among military divers was one of the earliest observations of the biological effects of argon. Argon is well known to be inert at standard gas conditions. Mental impairment at high pressures had been observed [26, 27]. One trial in humans examined the long-term effects (up to 9 days) under hyperbaric argon atmosphere, which showed no negative influence on work performance [28]. These data suggested a shift in lipid metabolism and an increased resistance to hypoxic hypoxia under argon atmosphere. Other studies observed an increase of oxygen consumption under argon, which was interpreted as a catalytic activity of argon on oxygen kinetics [25]. Recently, Alderliesen et al. explored the potential effect of argon ventilation on important physiological parameters in newborn piglets. Argon exposure up to 80% did not change heart rate, arterial blood pressure, rectal temperature, arterial oxygen saturation, amplitude-integrated electro-encephalogram and regional cerebral oxygen saturation measured by near infrared spectrometry [3]. Our data in humans support these former observations that argon inhalation did not cause relevant changes in basic vital parameters.

Transcranial Doppler sonography measures flow velocity in the basal cerebral arteries. Today, 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, except for specific situations, which may affect MCA diameter such as vasospasm, hypercapnia, migraine attacks, nitroglycerine, or other vasoactive agents [30-32]. In our study we additionally monitored the sonographic flow index, which showed consistent results when compared with Vmca. We thus have no reason to assume that a possible change in CBF during argon exposure has not been detected by our TCD measurements because of methodological limitations.

The noble gas xenon has excellent narcotic properties and may affect cerebral circulation [33, 34]. Trials about the effect of xenon on CBF showed inconsistent results in animals and humans [35-39]. The dose of xenon inhalation, however, seems to play an important role. In monkeys, subanaesthetic xenon (35%) caused a global reduction in CBF [37], whereas anaesthetic concentration (80%) increased CBF by 53% [40]. Using

the 133-xenon clearance method, subanaesthetic (35%) xenon was shown to increase human rCBF by approximately 12% [41]. A recent investigation under steady conditions showed that anaesthetic concentration of xenon (65%) decreased regional CBF in several brain regions in animals and in humans. The greatest decreases were detected in the cerebellum (-35%), the thalamus (-23%) and the parietal cortex (-11%) [42]. However, xenon anaesthesia increases flow velocity of basal cerebral arteries by about 30% [43,44]. The inconsistency of these results may partly be explained by methodological reasons such as inconstant carbon dioxide levels, different anaesthetic agents and by interspecies differences in anaesthetic concentrations for xenon in animals and in humans [42]. Argon has, in contrast to xenon, no anaesthetic properties at sea level [45]. Up to now there are no reports about the effects of argon on cerebral circulation obtained by TCD. Our data demonstrate that inhalation of 70% argon in humans did not affect Vmca or cerebral FI.

Cerebral ZFP, CPPe and RAP are supplemental determinants of cerebral blood flow. Using the CPPe as the driving pressure of the cerebral circulation does not require invasive measurements of intracranial pressure (ICP) and offers advantages in understanding pathophysiology, because changes of the effective downstream pressure irrespective of ICP will also be reflected by this kind of calculation [12,15]. The inverse of the slope of the arterial blood pressure-Vmca plot, the RAP, has been used as index of cerebrovascular resistance [12]. These less invasive methods of assessing cerebral perfusion are well established and have improving accuracy [46]. In our study, inhalation of argon showed no clinically relevant changes in ZFP, CPPe, and RAP.

Reports on the effect of argon on CBF and parameters of cerebral metabolism are not available up to now. Global cerebral hypoperfusion often is defined as a $SjvO_2$ less than 50% whereas cerebral ischemia is assumed when $SjvO_2$ is less than 40% and $AJVDO_2$ is greater than 9 $ml \cdot dL^{-1}$ [47]. Total intravenous anaesthesia with fentanyl/midazolam in humans causes a moderate proportional reduction in CBF due to a decrease in both cerebrovascular resistance and $CMRO_2$ [5, 48]. Thus, a constant $SjvO_2$ and unchanged arterio-jugular venous content differences of oxygen, glucose, and lactate ($AJVDO_2$, AJVDG, AJVDL) suggest intact flow-metabolic coupling of the brain [22, 49]. In contrast to intravenous anaesthesia, volatile anaesthetics cause a partial uncoupling of CBF and metabolism because of a direct cerebral vasodilatatory effect [50, 51]. In our patients inhalation of 70% argon showed no clinically relevant changes in $SjvO_2$ 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.

Despite the increasing comprehension of neuroplasticity and neuroprotection, the exact mechanisms by which argon improves outcome remain far from being understood [52]. Besides an interference with neuronal ion-gated channels and cellular signalling

pathways as well as anti-apoptotic effects, the modulation of neuroinflammation seems to play a crucial role [53]. Neuroprotective effects of argon were observed at different concentrations (25%, 50% and 74%) in both *in vitro* models of cerebral ischemia and traumatic brain injury [54]. Brücken and colleagues demonstrated in rats that one hour of 70% argon inhalation after cardiac arrest provided a significant reduction in histopathological damage of the neocortex and hippocampus, and was associated with a marked improvement in functional neurological recovery. At baseline, as well as after 4 hours after cardiac arrest, no significant differences were observed with regard to hemodynamics, variables of gas exchange, or lactate and glucose concentrations between groups [55]. In a postresuscitation treatment study in pigs, 70% argon inhalation lead to a fast and complete neurological recovery 72 hours after cardiopulmonary resuscitation. In perinatal asphyxia animal models with piglets, ventilation with up to 80% argon during normoxia, and 50% argon after hypoxia did not affect heart rate, blood pressure, cerebral saturation and electrocortical brain activity [3].

Our study was not designed to assess the neuroprotective effect of argon ventilation. Based on our observations and the previous, safe use of argon in adults in the past, as well as the efficacy studies described above, further safety studies in humans (e.g. after cardiac arrest, cerebral ischemia, traumatic brain injury, or even in neonates with perinatal asphyxia) appear warranted.

Some methodological aspects of our study have to be considered. The type of anaesthesia may have potential influence on the results of our study. We have no reason to assume that intravenous anaesthesia with fentanyl and midazolam *per se* may have confounded our results. However, the results of this study cannot *a priori* be extrapolated to other types of anaesthesia. Similarly, the external validity of our data could be limited by the fact that some of our patients with coronary artery disease might be suffering from concomitant asymptomatic cerebrovascular disease.

Unexpectedly, there was a very slight reduction in $SaO_2$ and $PaO_2$. All patients have been ventilated by two identical anaesthesia machines. When starting the argon-wash-in-period we changed the ventilators, using identical respiratory settings and identical inspired oxygen fraction. The mild decrease in $SaO_2$ and $PaO_2$ might be related to the short discontinuation of PEEP during this manoeuvre. Fortunately, our measurements did not affect general conditions in our patients. All surgical procedures were without complications. All patients had been discharged from ICU within 2 days. There were no suspected unexpected serious adverse reactions (SUSARS) or serious adverse events (SAE).

## CONCLUSIONS

In male cardiac surgical patients under fentanyl-midazolam anaesthesia, short-term ventilation with argon (70%Ar / 30% $O_2$) did not show any effects on the cerebral circulation or on global oxygen and glucose metabolism. 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.

**Acknowledgements relating to this article:**

We gratefully thank Hans Sonntag (MD. Ph.D.) for his work as member of the research team, teacher, colleague, and friend. Prof. Hans Sonntag was former chair of the Dept. of Anaesthesiology IV, University Hospital of Göttingen, Germany. He was responsible for study project conceptualization, supervision, validation, and resources. Unfortunately he died in 2011.

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# Chapter 8

## Cerebral perfusion pressure in pre-eclamptic patients is elevated even after treatment of elevated blood pressure.

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Acta Obstet Gynecol Scand 2014;93:508–11

## ABSTRACT

**Background:** Cerebral perfusion pressure (CPPe) is elevated in pre-eclampsia, and may predispose to cerebrovascular complications and progression to eclampsia.
**Methods:** We estimated zero flow pressure (ZFP) and CPPe using simultaneously obtained arterial blood pressure and middle cerebral artery blood flow velocity in 10 pre-eclamptic women, all treated with methyldopa, and 18 healthy pregnant controls.
**Results:** Mean (SD) ZFP was lower in patients than in controls (16.8 (10.9) versus 31.7 (15.0) mmHg, p=0.01) whereas CPPe was considerably higher (82.3 (17.7) versus 55.0 (11.7) mmHg, p<0.001), as was the cerebral flow index (41.9 (18.0) versus 25.6 (11.2), p=0.02). There was a significant correlation between blood pressure and CPPe in patients with pre-eclampsia, but not in controls.
**Discussion:** 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.


**Key Words:** Pre-eclampsia, transcranial Doppler, zero flow pressure, cerebral perfusion, autoregulation

**Abbreviations:** CPPe, effective cerebral perfusion pressure; ZFP, zero flow pressure; ABP, arterial blood pressure; CFI, cerebral flow index; ISSHP, International Society for the Study of Hypertension in Pregnancy; CRF, case record form.

## INTRODUCTION

Pre-eclampsia complicates 3% of pregnancies and is a major cause of maternal and foetal morbidity and mortality.(1) Cerebral infarction and haemorrhage account for the majority of maternal deaths from preeclampsia. The pathophysiology of cerebral damage in pre-eclampsia is unclear, but recent studies conducted with MRI have shown an increased cerebral blood flow in pre-eclamptic patients,(2) and Belfort *et al.* reported patients with severe pre-eclampsia have an increased effective cerebral perfusion pressure (CPPe).(3) High CPPe was also shown to be associated with pre-eclampsia related symptoms such as headache, and has also been reported in patients who subsequently developed eclamptic seizures.

Currently used drugs in patients with pre-eclampsia, such as labetalol and $MgSO_4$, tend to lower CPPe, while nimodipine is associated with a mild increase. Furthermore, a randomized study in pre-eclamptic patients reported that therapy with nimodipine is associated with more frequent eclamptic seizures in comparison with $MgSO_4$.(4) These findings may be explained by the different effects of these drugs on CPPe.

We aimed to investigate whether CPPe, as estimated using simultaneously measured arterial blood pressure (ABP) and middle cerebral artery blood flow velocity ($V_{mca}$), is elevated in pre-eclamptic patients, in whom blood pressure is adequately treated with antihypertensive medication.

## MATERIAL AND METHODS

After obtaining informed consent, 10 pre-eclamptic patients and 18 healthy pregnant controls, admitted to the department of obstetrics of the Erasmus Medical Center, University Medical Center Rotterdam, were consecutively enrolled in this study. Preeclampsia was diagnosed according to the definition of the International Society for the Study of Hypertension in Pregnancy (ISSHP).(5) Pre-eclampsia was diagnosed as: hypertension in the presence of de novo proteinuria.(5) Severe preeclampsia was diagnosed if one or more of the following criteria were present: blood pressure of 160 mmHg systolic or higher than 110 mmHg diastolic or higher on two occasions at least 6 hours apart; proteinuria of 5 gram or more in a 24-hour urine specimen or dipstick urinalysis of 3+ or greater in two random urine samples collected at least 4 hours apart; oliguria of less than 500 mL in 24 hours; cerebral or visual disturbances; pulmonary edema or cyanosis; epigastric or right upper-quadrant pain; impaired liver function; thrombocytopenia; fetal growth restriction.(5) Exclusion criteria for this study were cerebral vascular disorders, diabetes mellitus, pre-existing hypertension and inadequate language skills. The study protocol was approved by the Institutional Review Board of the Erasmus MC University Medical Centre Rotterdam.

Transcranial Doppler measurements of the middle cerebral artery flow velocity ($V_{MCA}$) were conducted using a Digi-Lite monitoring system (RIMED, Jerusalem, Israel) using a 2 MHz probe after identification using imaging. Mean $V_{MCA}$ was estimated as a weighted mean velocity. ABP was continuously measured non-invasively using a Finometer Midi (Finapres Medical Systems, Amsterdam, the Netherlands). The Finometer Midi allows for easy, non-invasive measurement of ABP using a finger cuff with a mounted infrared plethysmograph.(6) Expired $CO_2$ was measured using the Capnomac Ultima.

The zero-flow pressure (ZFP) in the circulation is the arterial pressure at which flow ceases. Dynamic pressure-flow-plots of the ABP and $V_{MCA}$ have been used to extrapolate the ZFP of the cerebral circulation.(7, 8) During measurement sessions, a 2 to 5 minute time interval with stable measurements was specified on the CRF. For our analysis we used systolic, diastolic and mean values from up to 10 pulse waves (two respiratory cycles) to minimize the effect of breathing. ZFP was subsequently extrapolated by linear regression analysis through the individual measurements (figure 1). The CPPe was calculated as the difference between weighted mean ABP (MAP) and ZFP. CPP was also calculated using a formula proposed by Belfort et al.(3): CPPe = (mean$V_{mca}$/(mean $V_{mca}$ – diastolic $V_{mca}$)) x(mean ABP-diastolic ABP). Resistance area product (RAP) is an index of cerebrovascular resistance is obtained by dividing MAP by the mean $V_{MCA}$ . Cerebral Flow Index (CFI), and index of total cerebral blood flow (CBF), was calculated as CFI = CPPe / RAP. (3)

SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Results of continuous variables are presented as mean (standard deviation, SD) and results between groups were compared using t tests and chi square tests. All statistical tests were two-sided and were evaluated at 0.05 level of significance. The study protocol (MEC-2008-035) was approved by the Institutional Review Board of the Erasmus MC University Medical Center on April 29th 2008.

## RESULTS

Age, parity and gestational age at inclusion were similar between patients and controls (table 1). Five patients had severe pre-eclampsia, and all patients were receiving methyldopa. One of the patients smoked during pregnancy, including the day that the measurements were performed, compared to none of the controls. Three patients were treated with a combination of methyldopa with nifedipine. None of the patients developed complications during follow-up. Gestational age at delivery for cases and controls was 32 (4.9) versus 37.4 (3.4) weeks (p = 0.012). Patients with pre-eclampsia had higher ABP and $V_{MCA}$ than controls (table 1). End-tidal $CO_2$ did not differ between cases and controls (41.15 (2.52) versus 41.63 (2.97) mmHg, p=0.699). Pulsatility indices of the MCA were 0.47 and 0.40 in cases and controls (p=0.23).

Extrapolated ZFP was 16.8 (10.9) mmHg in pre-eclamptic women, compared to 31.7 (15.0) mmHg in controls (p = 0.01). Estimated CPPe was 82.3 (17.7) mmHg in patients compared to 55.0 (11.7) mmHg in controls (p< 0.001). Consequently, pre-eclamptic patients had a higher CFI than controls (41.9 (18.0) versus 25.6 (11.2), p = 0.02). We have also calculated CPPe using the method as proposed by Belfort et al. (3): the two measures of CPP are highly correlated (r = 0.659, p= 0.001). Patients also had higher CPPe than controls when estimated using the Belfort method: 87.1 (26.3) vs 70.7 (22.1) mmHg (p = 0.09).

In a multivariate regression model adjusting for parity, gestational age at time of measurement and age at enrolment, patients with pre-eclampsia had higher CPP both when calculated using the regression method (adjusted CPPe 83.2 versus 54.5 mmHg, p<0.001) and the Belfort method (adjusted CPP 86.1 versus 69.6 mmHg, p=0.036).

In controls, there was no correlation between mean ABP and CPPe (r =- 0.004, p= 0.99), but in patients a distinct correlation was found between these parameters (r = 0.859, p = 0.001).

**Table 1: A comparison of characteristics and measurements between cases and controls.**

| Patient characteristics | Patients (n=10) | Controls (n=18) | P-value |
|---|---|---|---|
| **Demographics** | | | |
| Age | 29.9 (2.3) | 32.4 (6.4) | 0.14 |
| Nulliparous | 7 (70%) | 10 (56%) | 0.51 |
| Severe pre-eclampsia | 5 (50%) | - | |
| Gestational age | 30.4 (3.2) | 32.1 (3.2) | 0.18 |
| **Blood pressure (mmHg)** | | | |
| Systolic | 123.8 (12.7) | 101.5 (12.3) | <0.001 |
| Mean | 99.1 (9.1) | 86.7 (9.3) | 0.002 |
| Diastolic | 84.2 (7.7) | 78.2 (10.3) | 0.12 |
| **MCA flow velocity (cm/s)** | | | |
| Systolic | 65.4 (25.0) | 49.2 (17.2) | 0.05 |
| Mean | 50.7 (19.6) | 38.8 (13.5) | 0.07 |
| Diastolic | 41.5 (15.8) | 33.8 (12.3) | 0.16 |
| **Cerebral Perfusion** | | | |
| Zero Flow Pressure | 16.8 (10.9) | 31.7 (15.0) | 0.01 |
| Cerebral Perfusion Pressure | 82.3 (17.7) | 55.0 (11.7) | <0.001 |
| Cerebral Flow Index | 41.9 (18.0) | 25.6 (11.2) | 0.02 |
| **Resistance are product** | 2.3 (1.21) | 2.54 (1.04) | 0.583 |

Mean levels of blood pressure, middle cerebral artery flow velocity, zero flow pressure, effective cerebral perfusion pressure and cerebral flow index. MCA, middle cerebral artery. Standard deviations are shown in brackets.

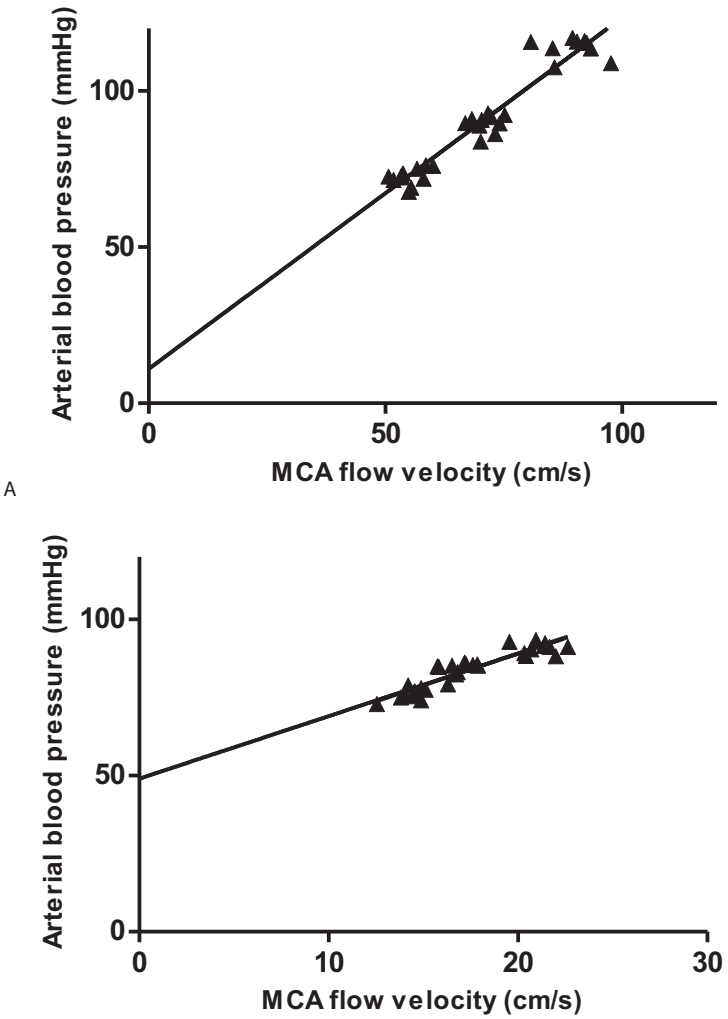


**Figure 1. Estimation of the zero flow pressure**

by extrapolation of simultaneously measured beat-by-beat data on arterial blood pressure (systole and diastole) and middle cerebral artery blood flow velocity in a woman with preeclampsia (a) and a control woman (b). MCA, middle cerebral artery.

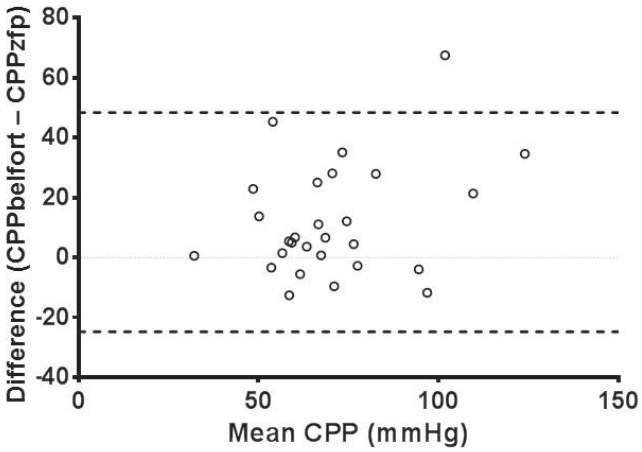


**Figure 2. Bland–Altman comparison of the two methods for cerebral perfusion pressure estimation.** Bold dashed lines represent the 95% confidence limits for the difference. CPPe, cerebral perfusion pressure.

## DISCUSSION

The Dutch Maternal Mortality Committee reported cerebrovascular complications to be the major cause of death in hypertensive pregnant women.(9) Increased CPPe has been implicated as a possible mechanism to induce a cerebral hyperperfusion syndrome and subsequent cerebrovascular complications in pre-eclamptic patients.(2, 3) The CPPe in our healthily pregnant control group compares well with those from other reports, including large study by Belfort et al.(10) In the current study, we found that CPPe was elevated in pre-eclamptic patients after adequate treatment with antihypertensive therapy. Interestingly, this increase seems to be dependent upon a decrease in ZFP, as opposed to being merely an effect of the difference in blood pressure between patients and controls. The ZFP we found for healthy pregnant controls is compatible with earlier reports,(11) but whereas Sherman *et al.* found an increased ZFP in their population of untreated pre-eclamptics, we found a thoroughly decreased level in our study. A possible explanation for this discrepancy is the effect of medication on the ZFP: while the antihypertensive agents lowered blood pressure, other cerebrovascular mechanisms may have been induced that lowered ZFP, thereby maintaining an elevated cerebral perfusion pressure.(11) In our study we used methyldopa and nifedipine to lower blood pressure.

CPPe in patients with pre-eclampsia strongly correlates with ABP whereas this correlation is absent in healthy pregnant controls. The elevated CPPe was also accompanied by an increase in $V_{mca}$ and CFI. Under normal circumstances, cerebrovascular autoregulation would maintain a stable cerebral blood flow, using cerebral vasoconstriction and a

subsequent change in ZFP, in the face of changes in the systemic circulation. Our findings therefore allude to a possible loss of cerebral autoregulation in pre-eclamptic patients.

A limitation of our study is that we used non-invasive methods for estimation of ZFP and CPPe. These methods have not been validated in vivo in humans. Given these limitations, we have chosen to use the two most often applied methods for estimation of CPPe and show that our findings are consistent irrespective of the method used, despite varying estimates observed across the methods (figure 2). The reason for the variation is currently unclear, and requires further investigation. Also, pre-eclamptics had a higher ABP than did the controls, despite antihypertensive therapy. This is in line with current treatment guidelines and therefore reflects clinical practice.(12)

In conclusion, the current study shows that in pre-eclamptic patients treated with antihypertensive therapy to reduce systolic ABP to <140 mmHg, in line with international and Dutch guidelines, CPPe and consequently cerebral perfusion are elevated. Possibly, more rigorous antihypertensive therapy, aimed at reducing CPPe, could therefore result in a decrease in cerebral complications in these patients although further studies are required to confirm this hypothesis. Future studies on elevated blood pressure control in pre-eclampsia should investigate the effect of reducing CPPe on the risk of cerebral complications in pre-eclampsia.

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# II

# General Discussion, Conclusions, and Future Perspectives

Grüne F.

## 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).

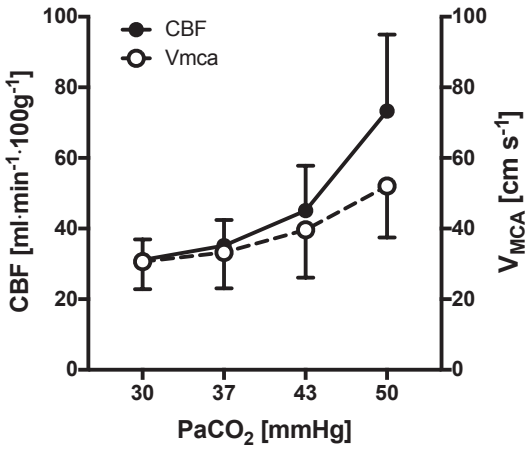


**Figure 1: CBF versus Vmca at four different levels of $PaCO_2$ (Chapter 3)**

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

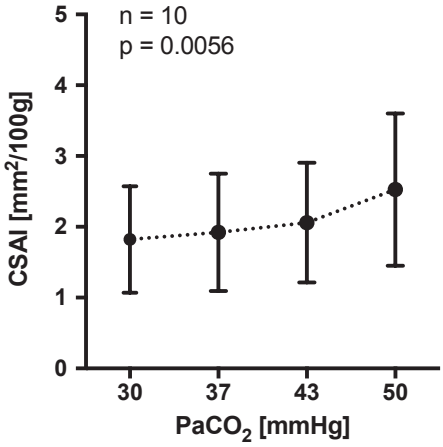


**Figure 2: Cerebral cross-sectional area index (CSAI) at four different levels of $PaCO_2$ (Chapter 3)**

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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# III

# Summary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

# IV

## Nederlandstalige samenvatting

Om patiënten in de perioperatieve periode adequaat te kunnen behandelen is het belangrijk om kennis te hebben van de cerebrale perfusiedruk (CPP) en de componenten hiervan. Helaas zijn traditionele methoden van intracraniale drukmeting invasief; zij vereisen plaatsing van een intracraniale katheter. De mogelijkheid de cerebrale perfusiedruk minder invasief te kunnen bepalen heeft dus een enorm potentieel voor gebruik bij de behandeling van patiënten met bijvoorbeeld een gestoorde (auto)regulatie van de cerebrale bloedstroom, schedeltrauma, intracraniële hypertensie of ischemie.

Het doel van dit proefschrift was om determinanten van de cerebrale perfusiedruk regulatie te onderzoeken en vervolgens aanbevelingen te doen voor het behouden van adequate cerebrale perfusie in de perioperatieve periode.

De Inleiding beschrijft het doel van het proefschrift, de huidige wetenschappelijke stand van zaken en de praktische relevantie van het onderzoek. Gewoonlijk wordt de cerebrale perfusiedruk beschreven als het verschil tussen de gemiddelde arteriële druk (MAP = mean arterial pressure) en de intracraniale druk (ICP = intracranial pressure). Dit 'klassieke model' (CPP = MAP - ICP) heeft echter beperkingen. Als de perfusiedruk wordt verminderd, zal er een moment zijn waarop de transmurale druk niet voldoende zal zijn om de actieve spanning, die wordt opgelegd door de gladde spieren in de vaatwand, op te heffen. Het vat zal dan collaberen en bloedstroom stopt. De bijbehorende arteriële druk wordt de kritieke sluitdruk of nulstroomdruk (ZFP = *zero flow pressure*) genoemd. De *effectieve cerebrale perfusiedruk* (CPPe) kan beter worden bepaald door het verschil tussen de gemiddelde arteriële druk (MAP) en de cerebrale ZFP, het 'alternatieve' model (CPPe = MAP – ZFP). De inverse helling van de drukstromingsgrafiek geeft de weerstand van het vaatbed weer en wordt *resistance area product* (RAP) genoemd. De ZFP van de cerebrale circulatie kan echter niet direct worden gemeten. Transcraniële Dopplerechografie (TCD) maakt non-invasieve, continue metingen van de stroomsnelheid van de arteria cerebri media (Vmca) mogelijk, die 80% van de totale cerebrale bloedstroom voor haar rekening neemt. Er is aangetoond dat in vivo druk-stroomsnelheidsrelaties lineair zijn voor veel vaatbedden, waaronder de cerebrale vaten. De ZFP die wordt geëxtrapoleerd door regressieanalyse van de drukstroomsnelheidscurves die zijn afgeleid van volledige druk- en stroomsnelheids-metingen, wordt verondersteld de meest nauwkeurige methode te zijn. Dit vergt gedetailleerde berekeningen en perfecte synchronisatie van de druk- en stroomsnelheidscurves.

**Hoofdstuk 1** geeft een update over de invloed van intra-operatieve hypotensie, vaak beschreven als gemiddelde arteriële druk onder de 65 mmHg, op de cerebrovasculaire, coronaire en renale pathofysiologie en de klinische consequenties daarvan. Verschillende retrospectieve studies bij zeer grote patiëntenpopulaties suggereren een verband tussen het optreden van intra-operatieve hypotensie en cerebrale, cardiale en renale complicaties, en postoperatieve sterfte na één jaar.

**Hoofdstuk 2** bespreekt de resultaten van een methode-vergelijkingsonderzoek met betrekking tot CPPe metingen. De resultaten tonen aan dat het mogelijk en betrouwbaar genoeg is om de CPPe, ZFP en het RAP te bepalen met minder complexe formulebenaderingen, die gebaseerd zijn op de lineaire vergelijking formule.

Koolstofdioxide is een sterke vasodilatator in de cerebrale circulatie. In **Hoofdstuk 3** wordt aangetoond dat variatie van $PaCO_2$, binnen een bereik van 30-50 mmHg, exponentiële veranderingen in cerebrale bloedstroom en MCA-snelheid induceerde. De hypocapnie-geïnduceerde verlaging van de cerebrale bloedstroom en MCA-snelheid beïnvloedde beide componenten van de druk-flowplot: een toename in ZFP en RAP. De verhogingen van effectieve cerebrovasculaire weerstand en RAP, geassocieerd met hypocapnie, waren gelijkaardig. Desondanks, vertoonde de correlatieanalyse slechts een zwakke lineaire relatie.

Hypocapnie geïnduceerd door hyperventilatie en geassocieerde alkalose hebben een breed bereik van fysiologische effecten, waaronder verhoogde cerebrovasculaire weerstand, verminderde cerebrale bloedstroom en cerebrale zuurstofafgifte. **Hoofdstuk 4** bespreekt de drempel waarop deze vermindering het cerebrale metabolisme schaadt. In deze studie wordt aangetoond dat matige hyperventilatie ($PaCO_2$ 30 mmHg), in vergelijking met matige hypoventilatie, de cerebrale bloedstroom en de partiële zuurstofdruk van de bulbus venae jugularis aanzienlijk vermindert. De verhoging van het cerebraal lactaat ,is een aanwijzing voor een stoornis van hersenmetabolisme op klinisch relevante niveaus van hypocapnie.

**Hoofdstuk 5** onderstreept dat er geen bewijs is voor het therapeutisch gebruik van geïnduceerde hypocapnie . De voordelen van normocapnie voor het in stand houden van cardiale output, weefseloxygenatie en perfusie en voor het behoud van een CPPe, cerebrale bloedstroom en cerebrovasculaire reactiviteit, zijn goed gedefinieerd. Ondanks routinematige end-tidal koolstofdioxidemonitoring, komen perioden van onopzettelijke hyperventilatie vaak voor tijdens mechanische beademing onder algemene anesthesie. Dit gaat gepaard met bijwerkingen, zoals cognitieve stoornissen en een langere opnameduur.

**Hoofdstuk 6** bespreekt de effecten van het dampvormige anestheticum halothaan op de cerebrale bloedstroom en -snelheid en hun componenten. Halothaan (0,8 vol%, 1 MAC) leidt tot een vermindering van de CPPe, RAP en effectieve cerebrovasculaire weerstand, terwijl ZFP, cerebrale bloedstroom en MCA-snelheid vrijwel onveranderd blijven. De cerebrovasculaire $CO_2$-reactiviteit blijft onveranderd. De afname in cerebrovasculaire weerstand is voornamelijk gerelateerd aan vermindering van de gemiddelde arteriële druk. Het lijkt erop dat halothaan als een “perifere” vasodilatator eerder de helling van de drukstroomgrafiek beïnvloedt dan de vasomotorische tonus.

Argon behoort tot de edelgassen en heeft gunstige neuro-protectieve en orgaanprotectieve eigenschappen, die zijn waargenomen in dierproeven, maar zelden in

studies bij mensen. **Hoofdstuk 7** bespreekt de vasculaire en cerebrometabole effecten van argon in de hersenen van de mens. Ventilatie met een gasmengsel van 70% Argon en 30% zuurstof vertoont geen klinisch relevante veranderingen van de CPPe en zijn componenten. De koppeling van cerebrale stroming en metabolisme lijkt dus ongewijzigd te blijven tijdens blootstelling aan argon. Onze bevindingen wijzen op een constante cerebrale metabole activiteit van zuurstof, glucose en lactaat. Deze resultaten bevestigen de veiligheid van argon-inhalatie, die essentieel kan zijn voor een mogelijke toekomstige klinische toepassing van argon als een orgaan-protectief middel.

Pre-eclampsie (hypertensie, proteïnurie en oedeem), een complicatie bij 3-5% van de zwangerschappen, is een belangrijke oorzaak van maternale en foetale morbiditeit en mortaliteit. **Hoofdstuk 8** beschrijft dat vrouwen met pre-eclampsie, ondanks op richtlijnen gebaseerde antihypertensieve behandeling met methyldopa of methyldopa in combinatie nifedipine, een verhoogde cerebrale perfusie hebben als gevolg van een verminderde ZFP en een verhoogde CPPe. Toekomstige onderzoeken naar bloeddrukcontrole bij pre-eclampsie zouden het effect moeten onderzoeken van het verminderen van CPPe op het risico van hersencomplicaties bij pre-eclampsie.

In de afrondende **algemene discussie** worden de bevindingen van het gepresenteerde onderzoek beoordeeld en gewogen. Onze studies hebben aangetoond dat het mogelijk en betrouwbaar is om de CPPe, de ZFP en het RAP te meten, zelfs met eenvoudiger formules en minder invasief. Bovendien konden we aantonen dat de monitoring en normalisatie van de CPPe van onze patiënten een belangrijke rol speelt in de perioperatieve periode.

De WHO voorspelt dat door toename van vergrijzing tegen 2030 chronische ziekten het leven van ongeveer 52 miljoen mensen in de Europese regio zullen beïnvloeden. Meer dan 80% van de mensen, ouder dan 65 jaar, zal dus lijden aan chronische ziekten, met name van het cardiovasculaire en neurovasculaire systeem. Veel van onze patiënten in de toekomst zullen een gestoorde cerebrale autoregulatie hebben. In de perioperatieve periode dient elke fase van arteriële hypotensie en daaropvolgende afname van de CPPe te worden vermeden en direct te worden behandeld. Behandeling van intra-operatieve hypotensie dient niet te worden uitgevoerd door middel van "automatisch" gebruik van vasoconstrictoren. Interventies moeten primair gericht zijn op de onderliggende oorzaken, waaronder vasoplegie, hypovolemie en een verminderde cardiale pompfunctie. Elke hyperventilatie tijdens de intraoperatieve fase moet worden vermeden. De drempel van duidelijk verminderde cerebrale bloedstroom en CPPe in overeenstemming met gedeeltelijke verslechtering van het cerebrale metabolisme ligt al bij een $PaCO_2$ 30 mmHg (4 kPa). Het effect van elk vasoconstrictief medicijn wordt door hyperventilatie meer dan teniet gedaan.

# V

## Deutschsprachige Zusammenfassung

Die Kenntnis des zerebralen Perfusionsdrucks (CPP) und seiner Komponenten ist wichtig für das Verständnis und die Behandlung von Patienten in der perioperativen Phase. Leider sind traditionelle Verfahren zur Messung des intrakranialen Drucks invasiv und erfordern die Platzierung eines intrakraniellen Katheters. Die Fähigkeit, den zerebralen Perfusionsdruck weniger invasiv messen zu können, hat somit ein enormes Potenzial für die Behandlung von Patienten mit einer gestörten (Auto-) Regulation des zerebralen Blutflusses, Schädelhirntrauma, intrakranialer Hypertonie, intrakranieller Blutung oder Ischämie.

Das Ziel dieser Arbeit war es, wichtige Determinanten der Regulation des zerebralen Perfusionsdrucks zu untersuchen und anschließend Empfehlungen zu geben, wie eine adäquate Durchblutung des Gehirns in der perioperativen Phase aufrechterhalten werden kann.

Das **Einführungskapitel** erläutert den Zweck der Arbeit und beschreibt die aktuelle wissenschaftliche Situation und die praktische Relevanz der Untersuchung. Im Allgemeinen wird der zerebrale Perfusionsdruck (CPP) als Differenz zwischen dem durchschnittlichen arteriellen Blutdruck (MAP) und dem intrakraniellen Druck (ICP) beschrieben („klassisches Modell" CPP = MAP - ICP). Dieses „klassische Modell" hat jedoch Einschränkungen. Wenn der Perfusionsdruck verringert wird, gibt es einen Punkt, an dem der transmurale Druck nicht ausreicht, um der aktiven Spannung entgegenzuwirken, die durch die glatte Muskelschicht ausgeübt wird. Dann wird das Blutgefäß kollabieren. An diesem Punkt sistiert der Blutfluss und der entsprechende arterielle Druck repräsentiert den kritischen Verschlussdruck oder den *Nullflussdruck* (*Zero Flow Pressure* = ZFP). Der *effektive zerebrale Perfusionsdruck* (CPPe) wird daher besser durch die Differenz zwischen dem mittleren arteriellen Druck (MAP) und dem zerebralen Nullflussdruck definiert (CPPe = MAP – ZFP). Die inverse Steigung der Druckfluss-Beziehung stellt den Gefäßwiderstand dar und wird als *„Resistance Area Product"* (*RAP*) bezeichnet. Der ZFP der zerebralen Perfusion kann jedoch nicht direkt gemessen werden. Die transkranielle Doppler-Sonographie (TCD) ermöglicht nicht-invasive, kontinuierliche Messungen der Flußgeschwindigkeit der Arteria cerebri media (Vmca), die 80% des globalen zerebralen Blutflusses ausmacht. Die Beziehung von Druck und Flussgeschwindigkeit ist „in-vivo" für viele Gefäßsysteme, einschließlich der Gehirngefäße, linear. Die parallele Aufzeichnung des arteriellen Blutdrucks einer peripheren Arterie und der Blutflussgeschwindigkeit in der A. cerebri media ermöglicht eine graphische Darstellung der Druck- Fluss- Beziehung. Die Extrapolation des Blutdruckes bei null Blutfluss mittels linearer Regressionsanalyse ist vermutlich die genaueste Methode zur Ermittlung des kritisches Verschlussdrucks oder Nullflussdrucks. Sie erfordert jedoch aufwändige Berechnungen und eine perfekte Synchronisation der Druck- und Strömungsgeschwindigkeitskurven.

**Kapitel 1** behandelt die Bedeutung der intraoperativen Hypotonie, die meistens als mittlerer arterieller Blutdruck unter 65 mmHg definiert wird. Wichtige Aspekte bezüglich

der zerebrovaskulären, koronaren und renalen Physiologie und Pathophysiologie und ihren klinischen Auswirkungen werden besprochen. Mehrere retrospektive Studien mit sehr großen Patientenpopulationen deuten auf eine Korrelation zwischen dem Auftreten einer intraoperativen Hypotonie und kardialen, renalen, zerebralen Komplikationen sowie der postoperativen einjährigen Mortalität hin.

**Kapitel 2** behandelt die Ergebnisse einer Methodenvergleichsstudie zur Bestimmung des effektiven zerebralen Perfusionsdruckes. Die Studienergebnisse zeigen, dass es möglich und sicher ist, den CPPe, den ZFP und das RAP mit einfacheren Formeln, die auf der linearen Extrapolation basieren, zu bestimmen.

Kohlendioxid ist ein starker Vasodilatator im zerebralen Kreislauf. In **Kapitel 3** konnte gezeigt werden, dass bei Variation des arteriellen Kohlendioxidpartialdruckes, innerhalb eines Bereichs von 30-50 mmHg, sich der zerebrale Blutflusses und die MCA-Geschwindigkeit exponentiell veränderten. Die Hypokapnie-induzierte Reduktion des zerebralen Blutflusses und der MCA-Geschwindigkeit führte zu Veränderungen beider Komponenten der Druckflusskurve: einem Anstieg des Nullflussdrucks und des RAP. Die Korrelationsanalyse zwischen effektivem zerebrovaskulären Widerstand und RAP zeigte jedoch nur eine schwache lineare Beziehung.

Die durch Hyperventilation und assoziierte Hypokapnie induzierte Alkalose hat eine Vielzahl physiologischer Wirkungen, einschließlich eines erhöhten zerebrovaskulären Widerstands, einer verminderten zerebralen Durchblutung und einer verminderten zerebralen Sauerstoffzufuhr. In **Kapitel 4** wird die Schwelle diskutiert, bei der diese Reduktion den zerebralen Stoffwechsel beeinträchtigt. In der vorliegenden Studie konnte gezeigt werden, dass eine moderate Hyperventilation ($PaCO_2$ 30 mmHg) im Vergleich zu einer moderaten Hypoventilation den Netto-Laktatausfluss erhöht und den zerebralen Blutfluss und die hirnvenöse Sauerstoffsättigung deutlich verringert. Das bedeutet, dass schon eine milde Hypokapnie, zu einer partiellen Beeinträchtigung des zerebralen Metabolismus führen kann.

**Kapitel 5** unterstreicht, dass es keine Evidenz für die therapeutische oder prophylaktische Anwendung von induzierter Hypokapnie gibt. Die Vorteile der Erhaltung der Normokapnie für die Aufrechterhaltung von Herzzeitvolumen, effektiven Perfusionsdruck und Gewebeoxygenierung sind gut untersucht. Während einer mechanischen Beatmung im Rahmen einer allgemeinen Anästhesie treten trotz routinemäßiger Überwachung des Kohlendioxidsgehaltes häufig Phasen von ungewollter Hyperventilation auf. Dies ist mit ungünstigen Nebenwirkungen wie kognitiver Dysfunktion und längeren Krankenhausaufenthalten verbunden.

In **Kapitel 6** werden die Auswirkungen des Anästhetikums Halothan auf die Durchblutung und Flussgeschwindigkeit des Gehirns und dessen Determinanten beschrieben. Halothan (0,8 Vol-%, 1 MAC) führt zu einer Verringerung des CPPe, RAP und des zerebrovaskulären Widerstands, während ZFP, zerebraler Blutfluss und MCA-

Flussgeschwindigkeit unverändert waren. Die zerebrovaskuläre $CO_2$-Reaktivität blieb unverändert. Die Abnahme des zerebrovaskulären Widerstandes war hauptsächlich auf die Abnahme des mittleren arteriellen Drucks zurückzuführen. Es scheint, dass Halothan als „peripherer" Vasodilatator die Steigung der Druckflusskurve eher beeinflusst als den Vasomotorentonus.

Argon gehört zu den Edelgasen und hat neuroprotektive und organoprotektive Eigenschaften, die im Tierversuch beobachtet wurden. Bislang existieren jedoch nur sehr wenige Untersuchungen über den Einfluss von Argon auf den menschlichen Organismus. **Kapitel 7** behandelt die zerebrovaskulären und zerebrometabolischen Wirkungen von Argon beim Menschen. Die Beatmung mit einem Gasgemisch aus 70% Argon und 30% Sauerstoff zeigte keine klinisch relevanten Veränderungen des CPPe und seiner Komponenten. Die Kopplung von Hirnfluss und Stoffwechsel scheint während der Exposition mit Argon unverändert zu sein, und unsere Ergebnisse deuten auf eine konstante zerebrale Stoffwechselrate von Sauerstoff, Glukose und Laktat hin. Diese Ergebnisse bestätigen die Sicherheit der Argon-Inhalation, die für eine mögliche zukünftige klinische Anwendung von Argon als Organoprotektivum wesentlich sein kann.

Das Auftreten einer Präeklampsie (Hypertonie, Proteinurie und Ödem) kommt bei ca. 3-5% aller Schwangerschaften vor und ist eine der Hauptursachen für Morbidität und Mortalität von Mutter und Kind. Eine Behandlung mit blutdrucksenkenden Medikamenten (Methyldopa oder Methyldopa / Nifedepin) wird, entsprechend niederländischer und europäischer Therapie-Empfehlungen, durchgeführt. **Kapitel 8** beschreibt, dass auch behandelte Frauen mit einer Präeklampsie eine erhöhte zerebrale Perfusion aufgrund eines verringerten ZFP und eines erhöhten CPPe aufweisen. Zukünftige Studien zur Blutdruckkontrolle bei Präeklampsie sollten die Auswirkungen einer Verringerung des CPPe auf das Risiko von zerebralen Komplikationen bei Präeklampsie untersuchen.

Im **Diskussionskapitel** werden die Ergebnisse der vorgestellten Studien zusammengefasst und gewichtet. Unsere Studien konnten zeigen, dass es möglich ist den CPPe, den ZFP und den RAP auch mit einfacheren Formelansätzen und weniger invasiv messen zu können. Weiterhin konnten wir zeigen, dass die Überwachung und Normalisierung des CPPe unserer Patienten eine wichtige Bedeutung in der perioperativen Phase hat.

Die WHO geht davon aus, dass im Jahre 2030 das Leben von rund 52 Millionen Menschen in der europäischen Region durch chronische Krankheiten beeinträchtigt sein wird. So werden vorrausichtlich mehr als 80% der Menschen über 65 Jahre an chronischen Erkrankungen, insbesondere am kardiovaskulären und neurovaskulären System leiden. Viele unserer Patienten werden in der Zukunft somit eine gestörte zerebrale Autoregulation aufweisen. In der perioperativen Periode sollte daher jede Phase einer arteriellen Hypotonie und nachfolgender Abnahme des CPPe vermieden und bei Auftreten umgehend behandelt werden. Die Behandlung der intraoperativen Hypotonie sollte nicht durch unreflektierte Anwendung von Vasokonstriktoren erfolgen. Interventionen

sollten in erster Linie auf die zugrunde liegenden Ursachen abzielen, zu denen Vasoplegie, Hypovolämie sowie eine Beeinträchtigung der Herzpumpfunktion gehören können. Jede Hyperventilation während der perioperativen Phase sollte vermieden werden. Die Schwelle eines deutlich reduzierten zerebralen Blutflusses und CPPe, die mit einer teilweisen Beeinträchtigung des zerebralen Metabolismus einhergehen, liegt bereits bei $PaCO_2$ 30 mmHg (4 kPa). Darüberhinaus verstärkt eine Hyperventilation alle anderen vasokonstriktiven Arzneimittelwirkungen.

# VI

## Acknowledgements


"Sensei ni rei" position – At the end of the lesson.

*A true friend is someone who lets you have total freedom to be yourself. That's what real love amounts to – letting a person be what he really is.*
*Jim Morrison*

*I am indebted to my mother and father for living,*
*but to my teacher for living well.*
*Alexander the Great*

The combination of writing a dissertation, working daily as an anesthesiologist, being a husband to my lovely wife Nicole, being a good father of my two beautiful girls Frieda and Jona, was a very complex balancing act. But challenges and have been always a stimulating drugs to me.

When I started this scientific project, I completely underestimated the workload to receive a Ph.D. degree. My wife Nicole knows everything about this. For me personally, such a Ph.D. project has many parallels with the sports I like to do (Kendo, open water swimming, road cycling, hiking and running). To perform a series of competitions I was aware that I need to train hard and effectively, that I need to follow a good teacher or coach (Sensei) and that I have to join a good team or club (Dojo). Furthermore, I learned that using doping with liters of espresso and EPO (= endless positive optimism) isn't a bad thing. But more than that, you a need a family, which understands your personality, supports your motivation to preserve your goals, gives positive and negative feedback, catches counterstrikes, and loves you and vice versa.

The most important person I have to thank first, is my wife Nicole.

*Liebe Nicole, Du hast zweifellos am meisten zu dieser Dissertation beigetragen. Jeden Tag kümmerst Du Dich am meisten um unser Familienleben und dass jeder zufrieden und froh den Tag beenden kann. Das unsere Tochter Frieda, trotz schwerer körperlich und geistig Behinderung, ein so liebes, aktives und fröhliches Kind ist, ist in sehr großen Maße Deiner Verlässlichkeit, Nähe, Vertrauen und Liebe zu verdanken. Diese Aufgabe stellt jeden uns immer wieder vor große Herausforderungen. Das bedeutet ein großes Maß an Aufmerksamkeit, Flexibilität, Geduld und Dankbarkeit was sicherlich nicht selbstverständlich ist. Ich bin sehr froh, dass wir diesen Weg gemeinsam gehen können. Du gabst mir viel Freiraum, Energie, Inspiration aber auch Kritik, um einen meiner Lebensträume, das Ph.D. Projekt, zu verwirklichen. Vielen Dank für die wundervollen Jahre und ich hoffe, dass noch viele weitere folgen werden.*

*Liebe Frieda und liebe Jona, Ihr seid das Schönste, was mir passiert ist.*
*Wenn sich Papa morgens von Euch verabschiedend und zur Arbeit geht, komme ich nachmittags mit noch viel mehr Freude nach Hause, um mit Euch zu toben und spielen. Eure Lebensfreude erfüllt mich sehr. Dieses kleine Buch hat vielleicht etwas zu viel unserer gemeinsamen Zeit gestohlen, aber ich verspreche Euch, dass ich diese aufholen werden!*

I am deeply thankful to my mother Irmgard and my father Daniel (who unfortunately died too early) for their constant love and support throughout my life. Many thanks to the love of my sister Daniela and brother Oliver and their families who have been at my side.

There have been so many people who have helped me and I owe my thanks to so many people that it is impossible to name everyone. Thanks to all my friends and colleagues. I feel very fortunate to have worked with so many wonderfull people with bright minds during the creation of this thesis.

Further, I wish to express my honest gratitude to my promotors and friends Andreas Weyland, Robert Jan Stolker, as well as my copromotor Gerhard Visser for their great support, trust, motivation, and patience they had shown during my Ph.D. study and research. They knew my great interest in applied physiology, focused my enthusiasm and sharpened my mind. They played a great role in making me a scientist.

I am very grateful to my very valuable friends Felix van Lier and Koos van Hattum in supporting me as paranymphs.

Twenty years ago I started a journey to my own personality – Kendo (Japanese fencing) – , which has become a very important part of my life. Simplified, Kendo still teaches me to perform today better than yesterday, which could be translated to many parts of our lives. I deeply appreciate all the efforts of my teachers in getting me better (Senseis Koos van Hattum, Gerard Barbier, Hein Odinot, Yukio Shimizu, Rene Führen and Roland Niewert). I am very thankful to all my kendo friends especially at Dojo Fumetsu Rotterdam and other Dojo where I could join their lessons. I will never give up in learning, how to hit the perfect Men (strike to the head).

# VII

## Curriculum vitae

**Frank Grüne** was born on October 12th, 1964 in Bremen, Germany. As a pupil he attended school education at Gymnasium an der Herman-Böse-Strasse in Bremen and finished in 1984. During military education from 1984 to 1986 he joined a nursing educational program the Airforce Medical School in Giebelstadt near Würzburg, Germany.

From 1985 until 1987 he studied Chemistry at University of Hannover, Germany. From 1987 until 1994 he studied Medicine at Georg-August University of Göttingen. Next to his study he worked as a male nurse on different wards and later at the Departments of Transfusion medicine and Anatomy. In 1990 he joined the research team of the Department of Anesthesiology at University Medical Center of Göttingen (Prof. Dr. med. Andreas Weyland and Prof. Dr. med Heidrun Stephan †). In 1996 he finished and defended his doctoral thesis with the title "Influence of cerebral vasodilatators on cerebral blood flow and blood flow-velocity" and graded with "magna cum laude" (Promotor: Prof. Dr. med. Hans Sontag †).

From 1994 until 1999 Frank worked as a resident at the Department of Anesthesiology, Intensive Care, Emergency and Pain Medicine, University of Cologne, Germany (Chairman: Prof. Dr. med. Walter Buzello). In 1999 he became certified as anesthesiologist. After an Intensive Care medicine fellowship from 2000 until 2002 at the same Department, Frank was certified as Intensivist. During his training he developed and deepened his interest in physiology and teaching at Anesthesia and ICU Nursing School.

From 1990 until 2000 Frank joined a Fellowship Quality Control & Public Health at the Institute of Health Economics and Clinical Epidemiology, University Medical Center of Cologne (Prof. Dr. Mathias Schrappe). Frank managed several projects regarding infection control, operation room management, internal guidelines and transfusion protocols.

After working as senior anesthesiologist and intensivist at University Medical Center of Cologne, Frank started in 2004 working as staff anesthesiologist at Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands (Chairmen: Prof. Dr. med Jan Klein and later Prof. Dr. med Robert Jan Stolker. In Rotterdam Frank focuses clinically on major abdominal and vascular surgery. He is member of the Liver transplantation team and the OR-Management team. Frank joined two research teams focusing on cerebral perfusion in the perioperative setting (Dr. Visser, clinical neurologist and neurophysiologist, Prof. Weyland and Prof. Stolker) and on perioperative myocardial ischemia (Dr. Felix van Lier, Dr. Sanne E Hoeks, and Prof. Stolker).

Frank, his wife Nicole and their two children Frieda and Jona are living in Rotterdam. They enjoy outdoor activities like hiking, skiing, swiming and cycling and spending time together with friends and families. Frank is performing Kendo with great pleasure for more than 20 years, (Japanese fencing) at Fumetsu Dojo Rotterdam (Sensei. Koos van Hattum 7th Dan).

# VIII

## Portfolio

Frank Grüne, MD, senior anesthesiologist
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| | |
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| Erasmus MC | f.grune@erasmusmc.nl |
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| | Prof. dr. Andreas Weyland (UMC Oldenburg, D) |
| Copromotor | Dr. Gerhard H. Visser (SEIN, Heemstede NL) |


## ACTIVITIES

| | |
|---|---|
| *Languages* | Dutch, English, German |
| *Scientific Memberships* | • Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI) https://www.dgai.de<br>• Dutch Association for Regional Anesthesia (DARA) https://www.dara-esra.nl<br>• European Society of Anaesthesiology (ESA) https://www.esahq.org<br>• European Society of Regional Anaesthesia and Pain Therapy (ESRA) https://esraeurope.org/about/<br>• Gesellschaft für Qualitätsmanagement in der Gesundheitsversorgung (GQMG) https://www.gqmg.de<br>• Nederlandse Vereniging voor Anesthesiologie (NVA) https://www.anesthesiologie.nl<br>• Nederlandse Vereniging voor Medisch Onderwijs (NVMO) http://www.nvmo.nl |
| *Reviewer for Scientific Journals* | British Journal for Surgery, British Journal for Anaesthesia, Digestive Surgery, Transplantation International. |
| *Interests* | Kendo, open water swimming, skiing, hiking, cycling |

## PUBLICATIONS 2010 – 2018 (OTHER THAN PHD. THESIS)

### Journal Publications (other than PhD. Thesis)

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| • MC Kortekaas, MHN van Velzen, F Grüne, SP Niehof, RJ Stolker, FJPM Huygen: Small intra-individual variability of the pre-ejection period justifies the use of pulse transit time as approximation of the vascular transit. PLoS ONE 10/2018; 13(10): e0204105, DOI:10.1371/journal.pone.0204105 | 1 |
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*Oral presentations*

| | **ETCS** |
|---|---|
| • F Grüne: Stollingsstoornissen bij patiënten met leverchirurgie en levertransplantatie<br>Conference: A & I Nascholing<br>At: Thiel, NL, 12/2018 | 1 |
| • F Grüne: Argon - From doping to neuroprotection.<br>Conference: Wetenschapsdag Anesthesiologie -<br>At: Erasmus MC, Rotterdam, NL, 01/2017 | 1 |
| • F Grüne: Anesthesia and Electroconvulsive therapy.<br>Conference: Netherlands Society for Psychiatry (NVvP) Congres, At: MECC, Maastricht, NL, 03/2016 | 1 |
| • F Grüne: Centraal veneuze druk en leverchirurgie.<br>Conference: Symposium "Anesthesie bij leverchirurgie",<br>At: Amphia Ziekenhuis, Breda, NL, 02/2014 | 1 |
| • F. Grüne: De ondergrens van de cerebrale perfusie.<br>Conference: Wetenschapsdag Anesthesiologie<br>At: Erasmus MC, Rotterdam, NL, 02/2014 | 1 |
| • F Grüne: Anesthesiologische zorg voor de buismaag - patiënt.<br>Conference: Refereeravond "Ketenzorg", Anesthesiologie -<br>At: Erasmus MC Rotterdam, NL, 05/2012 | 1 |
| • F Grüne: Perioperatief hemodynamisch monitoring en een algoritme voor vocht en inotropie / vasopressie.<br>Conference: Mini-symposium "Top klinische perioperatieve zorg voor oesophagus cardiaresectie met buismaag reconstructie", Anesthesiologie, AMC<br>At: AMC Amsterdam, NL, 11/2011 | 1 |

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|---|---|
| • F Grüne: Perioperatief hemodynamisch beleid. Goal directed therapy bewaking tijdens slokdarmresectie.<br>Conference: Refereeravond, Anesthesiologie, UMC Leiden<br>At: UMC Leiden, NL, 09/2011 | 1 |
| • F Grüne: Goal directed therapy<br>Conference: Refereeravond, Anesthesiologie,<br>At: Catharina Ziekenhuis, Eindhoven, NL, 05/2011 | 1 |
| • F Grüne: Tussen walvis en Darth Vader: de fysiologisch – filosofische insteek.<br>Conference: Erasmus Edwards<br>Conference: Anesthesiology Master Class " Cardiac Output "<br>At: SS Rotterdam, Rotterdam, NL, 09/2010 | 1 |
| • F Grüne: Hemodynamische bewaking tijdens hoog risico ingrepen.<br>Conference: Pulsion Anesthesiology Master Class " PiCCO"<br>At: St. Elisabeth Ziekenhuis, Tilburg, NL, 05/2010 | 1 |
| • F Grüne. Preoperative risk assessment and peri-operative management<br>Conference: DOCG Symposium: Current and future management of oesophageal cancer<br>At: De Doelen Center, Rotterdam 04/2010 | 1 |
| • F Grüne: Hemodynamische bewaking tijdens slokdarmresectie.<br>Conference: Pulsion Anesthesiology Master Class " PiCCO"<br>At: MC Leeuwarden, NL, 02/2010 | 1 |
| | **12** |

*Poster presentations*

| | **ETCS** |
|---|---|
| • F Grüne, S Kazmaier, A Weyland: Hemodynamic effects of Argon in humans. Deutscher Anästhesie Congress 2013, Nürnberg Convention Center Ost; 04/2013 | 1 |
| • F Grüne, S Kazmaier, H Sonntag, RJ Stolker, A Weyland: Moderate hyperventilation during intravenous anaesthesia increases cerebral lactate production. Euroanaesthesia 2012, Paris; 06/2012 | 1 |
| | **2** |

## COURSES

| | **ETCS** |
|---|---|
| • Biomedical English Writing and Communication (self taught) | 1 |
| • Adult Life support (ERC), Erasmus MC, Rotterdam, NL, 11/2013 | 1 |
| • Advanced Trauma Critical Care (ATACC), Cheshire, UK, 09/2016 | 1 |

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|---|---|
| • Bijscholing moderisering medische vervolgopleiding (NVA), Rotterdam, 11/2011 | 0.3 |
| • Cannot intubate, cannot oxygenate (CICO), Erasmus MC, 02/2017 | 0.3 |
| • Master Class: Presentation training: "Onderwijs en de techniek van het theater". Erasmus Universiteit, Rotterdam, NL, 04/2010 | 1 |
| • Echocardiography (DEGUM), Oldenburg, Germany 2012 | 1 |
| • Sono-anatomy (ESRA) Längenfeld, Austria 2017 and 2018 | 2 |
| • Strahlingsbeschermimg Erasmus MC 01/2016 | 0.3 |
| • Time management "Battling your Brain" Erasmus MC, 2016 | 0.3 |
| • Teach the teacher, Erasmus MC, 2010 | 1 |
| | **9.2** |

## CONGRESS / CONFERENCE

| | **ETCS** |
|---|---|
| • Anesthesiologendagen (NVA), Maastricht, 2010 | 1 |
| • Congress of the Dutch Oesophageal Cancer Group (DOCG), Rotterdam, 2010 | 0.3 |
| • Euroanaesthesia (ESA), Paris 2012, Stockholm 2014 | 2 |
| • Erasmus Master Class Obese Patients (EMCOP), Rotterdam, 2010 | 0.6 |
| • International Symposium of Intensive Care Medicine, Bremen, 2013, 2015 | 2 |
| • International Symposium AINS – St. Anton 2010, 2011, 2012, 2015, 2016 | 5 |
| • Deutscher Anästhesie Congress (DGAI, BDA) 2010, 2013 | 2 |
| • Congress of the European Society of Regional Anaesthesia (ESRA), Dublin, 2018 | 1 |
| • Congress of the Liver Intensive Care Group of Europe (LICAGE), Essen, 2013 | 0.6 |
| | **14.5** |

## TEACHING

| | ETCS |
|---|---|
| Lectures for medical students, Erasmus MC<br>• Minor Course Transplantation medicine 2010-2016<br>• Bedside teaching Anesthesia 2010-2018<br>• Minor Course Anesthesia 2012-2018<br>• Master Course Surgery 2017-2018 | 20 |
| Lectures for Intensive Care Nurses, Erasmus MC<br>• Bijscholing hemodyamisch monitoren 2011- 2014<br>• Bijscholing Vochtbeleid en Infuustherapie 2015-2016 | 6 |
| Lectures for residents Anesthesiology, Erasmus MC<br>• Major surgery, risk evaluation, liver surgery, LTX, hemodynamic monitoring, coagulation disorders, cerebral perfusion | 10 |
| Research Tutorship, Medical students; Erasmus MC, NL<br>• S. Sewdin 2010, B. Broeders 2013, R. van der Graaf 2014, T. Kerver 2018 | 8 |
| Research Tutorship Master of Science Students; NIHES, NL<br>• M Sonneveld 2010, HJ Mijderwijk 2012 | 6 |
| | **50** |
| **Total =** | **106** |

# IX

## Propositions

1. It has to be considered that flow, pressure and resistance are not independent variables but are linked through various physiological regulatory circuits. (this thesis)
2. Mild hyperventilation ($PaCO_2$ 30 mmHg) reduced cerebral blood flow by 60%, did not alter cerebral metabolic rate for oxygen or glucose, but increased net cerebral lactate efflux, consistent with partial impairment of cerebral aerobic metabolism. (this thesis)
3. Changes of the arterial partial pressure of carbon dioxide do not only cause changes in vascular diameter at the arteriolar level but may also cause minor changes in main trunk diameter of the middle cerebra artery resulting in a slight systematic difference between relative changes in flow and flow velocity. (this thesis)
4. International and Dutch guidelines should advise more rigorous antihypertensive therapy in women with preeclampsia in order to decrease cerebral perfusion pressure and subsequently reduce cerebral complications. (this thesis)
5. Short-term ventilation with argon (70%Ar / 30% $O_2$) did not show any effects on the cerebral circulation or on global oxygen, glucose and lactate metabolism. (this thesis)
6. Normal average value of cerebral blood flow in younger adults is 50 ml/ 100 g/ min.
   Niels A. Lassen (1926 – 1997), 1985, JCBFM
7. If a job has to be done the nature knows more than one way.
   Julius Hiram Comroe (1911 – 1984)
8. In a structure as complex as the human brain a multitude of things can go wrong. The wonder is that for most people the brain functions effectively and unceasingly for more than 60 years.
   Seymour S. Kety (1915 – 2000), Scientific American 1979
9. Humor is by far the most significant activity of the human brain.
   Edward de Bono (1933 – today), Daily Mail 1990
10. 勝って兜の緒を締めよ
    Katte kabuto no o o shimeyo.
    Tighten the string of the kabuto after winning the war. Japanese proverb
11. There is a crack in everything. That's how the light gets in.
    Leonard Cohen (1934 – 2016) – Song Anthem

IX