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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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, $p<0.05$)

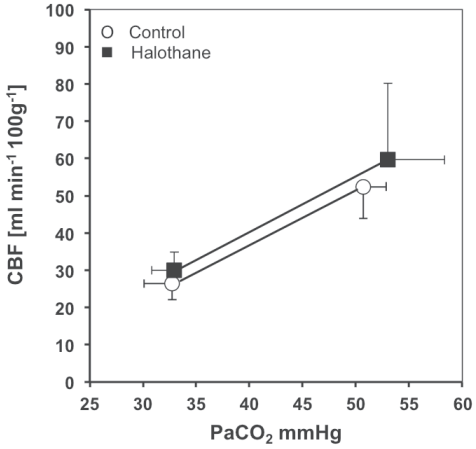

Figure 1: Cerebral blood flow (CBF) as a function of arterial $PaCO_2$.
Administration of 1 MAC halothane does not significantly alter cerebral blood flow. The cerebrovascular CO_2 reactivity of CBF remains unchanged.

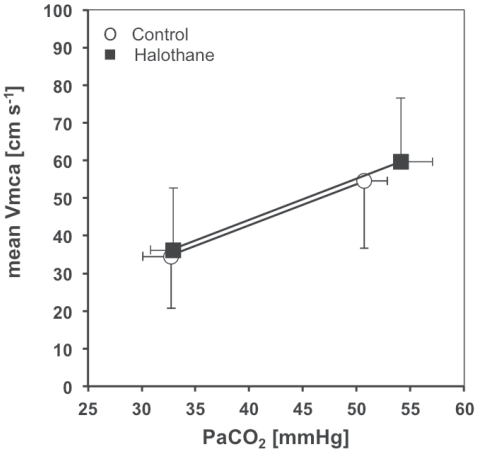

Figure 2: Mean cerebral blood flow velocity of the mean cerebral artery (V_{MCA}) as a function of arterial $PaCO_2$.
The administration of 1 MAC halothane does not result in any significant change in mean V_{MCA} measured by transcranial Doppler sonography. The cerebrovascular CO_2 reactivity of V_{MCA}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

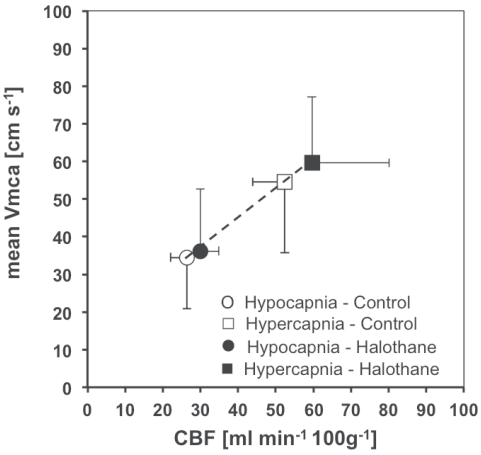

Figure 3: Relationship between cerebral blood flow (CBF) and mean blood flow velocity in the mean cerebral artery (Vmca) with variation of $PaCO_2$.
The application of 1 MAC halothane does not shift the relationship of flow and flow velocity, so that defined CBF values correspond to the same V_{MCA}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

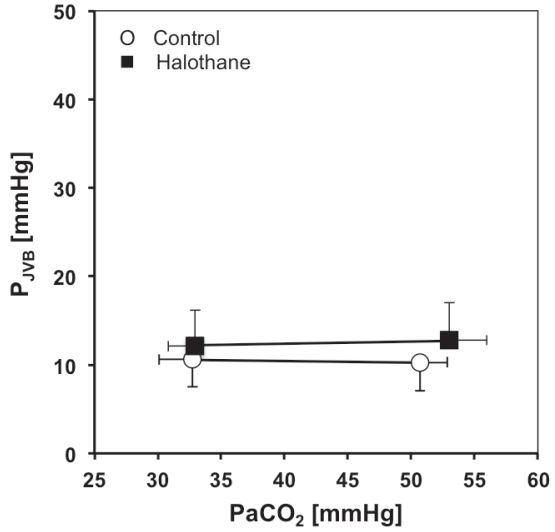
The RAP also showed a reduction after halothane administration. Under hypocapnia RAP was reduced by 27 %, (MD 0.53 (0.39), 95%CI 0.13 to 0,90, P 0.01) and under hypercapnia by 37% (MD 0.53 (0.31), 95%CI 0.19 to 1.80, P 0.03). When changing from hypercapnia to hypocapnia under halothane RAP increased 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

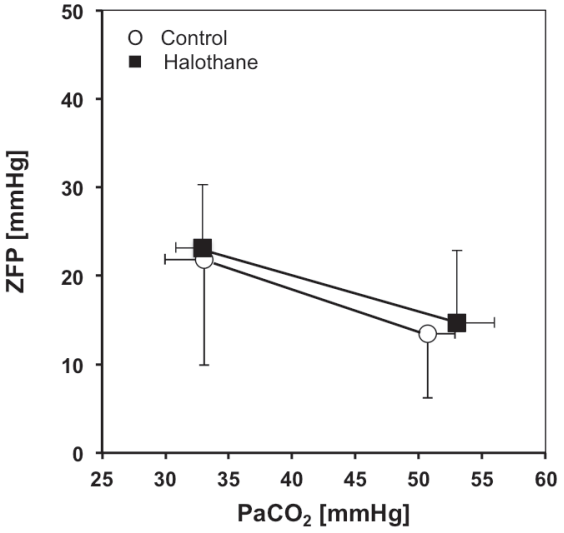
Table A2: Cerebrovascular effects of 1 MAC halothane (0.8 vol%) and moderate changes in $PaCO_2$ in 10 patients without cerebral disease with intravenous anesthesia.

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}.



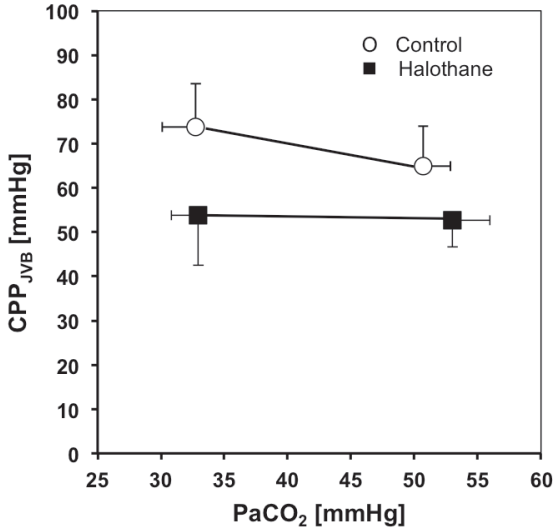
A



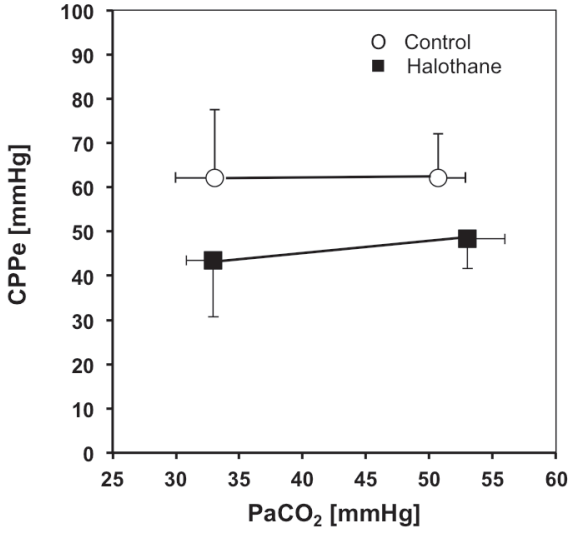
B

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.



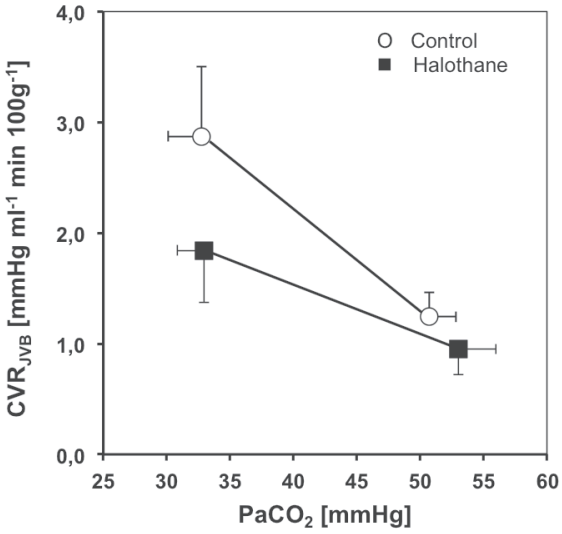
A



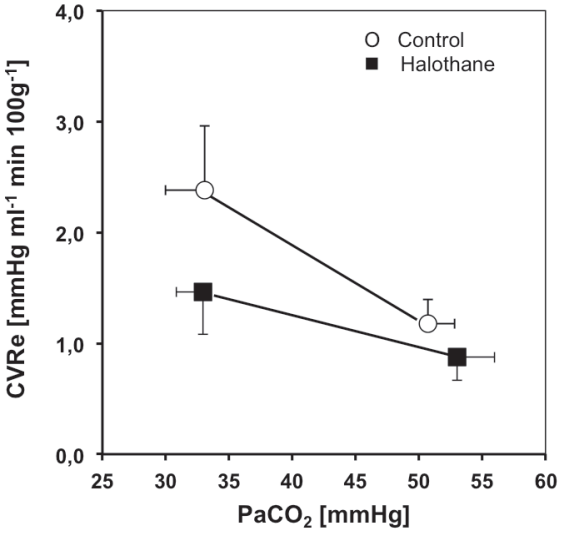
B

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.

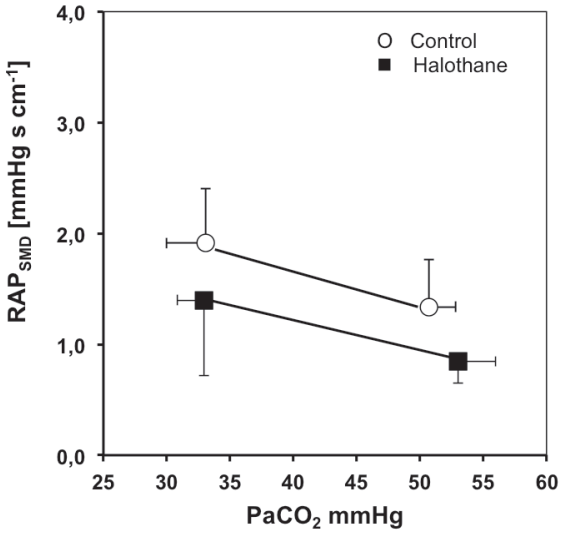


Figure A4: Resistance area product as a function of arterial $PaCO_2$ and 1 MAC Halothane.
Analog to the effects on CVRe induced halothane administration also a strong reduction in RAP. The reactivity to changes in $PaCO_2$ was unchanged.

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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