Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux.

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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) $\mu mol \cdot min^{-1} \cdot 100g^{-1}$.

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

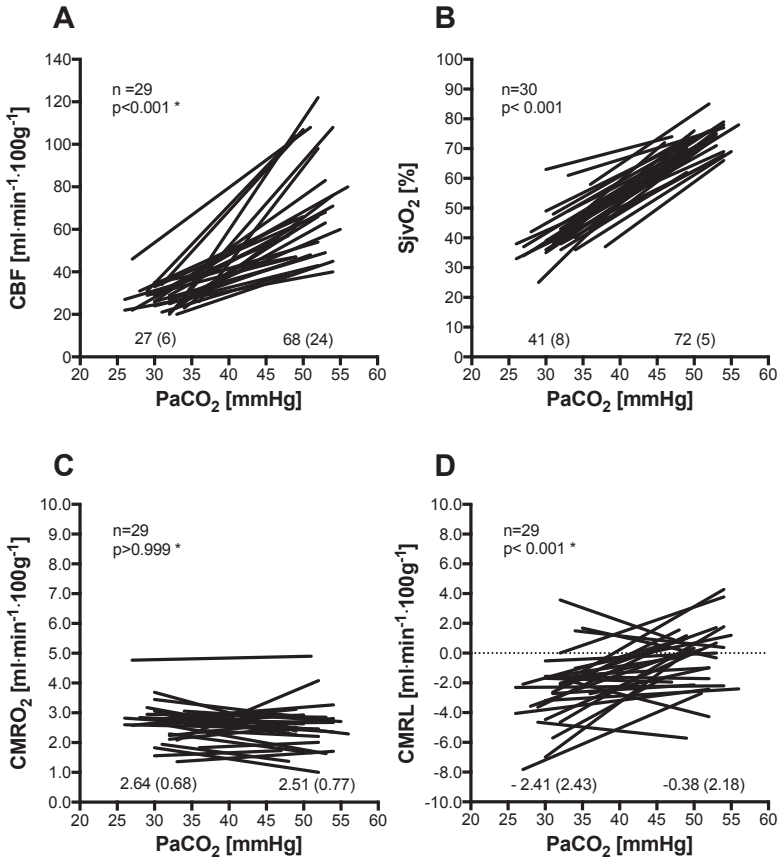

Fig. 1. A-D. Values of cerebral blood flow (CBF), jugular-venous partial pressure of oxygen ($PjvO_2$), cerebral metabolic rate of oxygen ($CMRO_2$), and lactate (CMRL) during moderate hyperventilation compared with moderate hypoventilation.

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.

REFERENCES

1. Brian JE: Carbon dioxide and the cerebral circulation. Anesthesiology 1998; 88:1365–86
2. Wax DB, Lin H-M, Hossain S, Porter SB: Intraoperative carbon dioxide management and outcomes. Eur J Anaesthesiol 2010; 27:819–23
3. Nagata K, Buchan R, Yokoyama E, Kondoh Y, Sato M, Terashi H, Satoh Y, Watahiki Y, Senova M, Hirata Y, Hatazawa J: Misery perfusion with preserved vascular reactivity in Alzheimer's disease. Ann NY Acad Sci 1997; 826:272–81
4. Meyer JS, Sawada T, Kitamura A, Toyoda M: Cerebral oxygen, glucose, lactate, and pyruvate metabolism in stroke: Therapeutic considerations. Circulation 1968; 37:1036–48
5. Robertson CS, Narayan RK, Gokaslan ZL, Pahwa R, Grossman RG, Caram P, Allen E: Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. J Neurosurg 1989; 70:222–30
6. Thees C, Scholz M, Schaller M D C, Gass A, Pavlidis C, Weyland A, Hoeft A: Relationship between intracranial pressure and critical closing pressure in patients with neurotrauma. Anesthesiology 2002; 96:595–9
7. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, Downey SPMJ, Williams G, Chatfield D, Matthews JC, Gupta AK, Carpenter TA, Clark JC, Pickard JD, Menon DK: Effect of hyperventilation on cerebral blood flow in traumatic head injury: Clinical relevance and monitoring correlates. Crit Care Med 2002; 30:1950–9
8. Møller K, Strauss GI, Thomsen G, Larsen FS, Holm S, Sperling BK, Skinhøj P, Knudsen GM: Cerebral blood flow, oxidative metabolism and cerebrovascular carbon dioxide reactivity in patients with acute bacterial meningitis. Acta Anaesthesiol Scand 2002; 46:567–78
9. Clausen T, Scharf A, Menzel M, Soukup J, Holz C, Rieger A, Hanisch F, Brath E, Nemeth N, Miko I, Vajkoczy P, Radke J, Henze D: Influence of moderate and profound hyperventilation on cerebral blood flow, oxygenation and metabolism. Brain Res 2004; 1019:113–23
10. van Rijen PC, Luyten PR, van der Sprenkel JW, Kraaier V, van Huffelen AC, Tulleken CA, Hollander den JA: 1H and 31P NMR measurement of cerebral lactate, high-energy phosphate levels, and pH in humans during voluntary hyperventilation: Associated EEG, capnographic, and Doppler findings. Magn Reson Med 1989; 10:182–93
11. Friedman SD, Jensen JE, Frederick BB, Artru AA, Renshaw PF, Dager SR: Brain changes to hypocapnia using rapidly interleaved phosphorus-proton magnetic resonance spectroscopy at 4 T. J Cereb Blood Flow Metabol 2007; 27:646–53
12. Stephan H, Sonntag H, Lange H, Rieke H: Cerebral effects of anaesthesia and hypothermia. Anaesthesia 1989; 44:310–6
13. Stephan H, Gröger P, Weyland A, Hoeft A, Sonntag H: [The effect of sufentanil on cerebral blood flow, cerebral metabolism and the CO_2-reactivity of the cerebral vessels in man]. Anaesthesist 1991; 40:153–60
14. Weyland A, Stephan H, Kazmaier S, Weyland W, Schorn B, Grüne DF, Sonntag H: Flow velocity measurements as an index of cerebral blood flow. Anesthesiology 1994; 81:1401–10
15. Cohen PJ, Wollman H, Alexander SC, Chase PE, Behar MG: Cerebral carbohydrate metabolism in man during halothane anesthesia: Effects of $PaCO_2$ on some aspects of carbohydrate utilization. Anesthesiology 1964; 25:185–91
16. Alexander SC, Smith TC, Strobel G, Stephen G, Wollman H: Cerebral carbohydrate metabolism of man during respiratory and metabolic alkalosis. J Appl Physiol 1968; 24:66–72

17. Mielck F, Stephan H, Buhre W, Weyland A, Sonntag H: Effects of 1 MAC desflurane on cerebral metabolism, blood flow and carbon dioxide reactivity in humans. Br J Anaesth 1998; 81:155–60
18. Mielck F, Stephan H, Weyland A, Sonntag H: Effects of one minimum alveolar anesthetic concentration sevoflurane on cerebral metabolism, blood flow, and CO_2-reactivity in cardiac patients. Anesth Analg 1999; 89:364–9
19. Rau G: [Measurement of the coronary blood flow with argon-foreign gas method in the patient]. Basic Res Cardiol 1969; 58:322–98
20. Ohta Y, Ar A, Farhi LE: Solubility and partition coefficients for gases in rabbit brain and blood. J Appl Physiol 1979; 46:1169–70
21. Weyland A, Stephan H, Grüne DF, Weyland W, Sonntag H: Effect of ketanserin on global cerebral blood flow and middle cerebral artery flow velocity. Anesth Analg 1995; 80:64–70
22. Weyland A, Buhre W, Grund S, Ludwig H, Kazmaier S, Weyland W, Sonntag H: Cerebrovascular tone rather than intracranial pressure determines the effective downstream pressure of the cerebral circulation in the absence of intracranial hypertension. J Neurosurg Anesthesiol 2000; 12:210–6
23. Widder B: Transkranielle Doppler-Sonographie bei zerebrovaskulären Erkrankungen, 1st edition. Berlin Heidelberg, Springer-Verlag, 1987
24. Halsey JHH: Effect of emitted power on waveform intensity in transcranial Doppler. Stroke 1990; 21:1573–8
25. Dewey RC, Pieper HP, Hunt WE: Experimental cerebral hemodynamics. Vasomotor tone, critical closing pressure, and vascular bed resistance. J Neurosurg 1974; 41:597–606
26. Strauss GI, Møller K, Holm S, Sperling B, Knudsen GM, Larsen FS: Transcranial Doppler sonography and internal jugular bulb saturation during hyperventilation in patients with fulminant hepatic failure. Liver Transpl 2001; 7:352–8
27. McKennia MC, Dienel GA, Sonnewald U: Energy metabolism of the brain, Basic Neurochemistry, 8th edition. Edited by Bradly ST, Siegel GJ, Albers RW, Price DL. Elsevier, 2011, pp 200–34
28. Cummings P: Arguments for and against standardized mean differences (effect sizes). Arch Pediatr Adolesc Med 2011; 165:592–6
29. Faul F, Erdfelder E, Buchner A, Lang A-G: Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009; 41:1149–60
30. MacMillan V, Siesjö BK: The influence of hypocapnia upon intracellular pH and upon some carbohydrate substrates, amino acids and organic phosphates in the brain. J Neurochem 1973; 21: 1283–99
31. Weyne J, Demeester G, Leusen I: Effects of carbon dioxide, bicarbonate and pH on lactate and pyruvate in the brain of rats. Pflugers Arch 1970; 314:292–311
32. Druml W, Grimm G, Laggner AN, Lenz K, Schneeweiss B: Lactic acid kinetics in respiratory alkalosis. Crit Care Med 1991; 19:1120–4
33. Hirsch H, Grote G, Schlosser V: [On the effects of hexobarbituric acid on oxygen consumption and vulnerability of the brain]. Pflugers Arch 1961; 272:247–53
34. Granholm L: Cerebral effects of hyperventilation. Acta Anaesthesiol Scand 1971; 45:114–22
35. Grote J, Zimmer K, Schubert R: Effects of severe arterial hypocapnia on regional blood flow regulation, tissue PO_2 and metabolism in the brain cortex of cats. Pflugers Arch 1981; 391:195–9
36. Kennealy JA, McLennan JE, Loudon RG, McLaurin RL: Hyperventilation-induced cerebral hypoxia. Am Rev Respir Dis 1980; 122:407–12
37. Duong TQ, Iadecola C, Kim SG: Effect of hyperoxia, hypercapnia, and hypoxia on cerebral interstitial oxygen tension and cerebral blood flow. Magn Reson Med 2001; 45:61–70

38. van Hall G, Strømstad M, Rasmussen P, Jans O, Zaar M, Gam C, Quistorff B, Secher NH, Nielsen HB: Blood lactate is an important energy source for the human brain. J Cereb Blood Flow Metab 2009; 29:1121–9
39. Figley CR: Lactate transport and metabolism in the human brain: Implications for the astrocyte-neuron lactate shuttle hypothesis. J Neurosci 2011; 31:4768–70
40. Seifert T, Secher NH: Sympathetic influence on cerebral blood flow and metabolism during exercise in humans. Prog Neurobiol 2011; 95:406–26
41. Gibbs EL, Lennox WG, Nims LF, Gibbs FA: Arterial and cerebral venous blood: Arterial-venous differences in man. J Biol Chem 1942; 144:325–32
42. Gam CMB, Rasmussen P, Secher NH, Seifert T, Larsen FS, Nielsen HB: Maintained cerebral metabolic ratio during exercise in patients with beta-adrenergic blockade. Clin Physiol Funct Imaging 2009; 29:420–6
43. Hyder F, Shulman RG, Rothman DL: A model for the regulation of cerebral oxygen delivery. J Appl Physiol 1998; 85:554–64
44. Hyder F, Kennan RP, Kida I, Mason GF, Behar KL, Rothman D: Dependence of oxygen delivery on blood flow in rat brain: A 7 tesla nuclear magnetic resonance study. J Cereb Blood Flow Metab 2000; 20:485–98
45. Jones MD, Traystman RJ, Simmons MA, Molteni RA: Effects of changes in arterial O_2 content on cerebral blood flow in the lamb. Am J Physiol 1981; 240:H209–15
46. Michenfelder JD, Sundt TM, Fode N, Sharbrough FW: Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. Anesthesiology 1987; 67:336–40
47. Wolff CB: Normal cardiac output, oxygen delivery and oxygen extraction. Adv Exp Med Biol 2007; 599:169–82
48. Hutchinson PJ, Gupta AK, Fryer TF, Al-Rawi PG, Chatfield DA, Coles JP, O'Connell MT, Kett-White R, Minhas PS, Aigbirhio FI, Clark JC, Kirkpatrick PJ, Menon DK, Pickard JD: Correlation between cerebral blood flow, substrate delivery, and metabolism in head injury: A combined microdialysis and triple oxygen positron emission tomography study. J Cereb Blood Flow Metabol 2002; 22: 735–45
49. Mik EG, Johannes T, Zuurbier CJ, Heinen A, Houben-Weerts JHPM, Balestra GM, Stap J, Beek JF, Ince C: In vivo mitochondrial oxygen tension measured by a delayed fluorescence lifetime technique. Biophys J 2008; 95:3977–90
50. Wilson DF: Quantifying the role of oxygen pressure in tissue function. Am J Physiol Heart Circ Physiol 2008; 294:H11–3
51. Mik EG: Hyperbaric oxygen preconditioning: What remains between hypoxia and hyperoxia? Clin Exp Pharmacol Physiol 2011; 38:656–7
52. Alberti E, Hoyer S, Hamer J, Stoeckel H, Packschiess P, Weinhardt F: The effect of carbon dioxide on cerebral blood flow and cerebral metabolism in dogs. Br J Anaesth 1975; 47:941–7
53. Mielck F, Wietasch G, Weyland A, Buhre W, Meier-Theile C, Hoeft A, Sonntag H: Reliability of cerebral blood flow measurements by transcerebral double-indicator dilution technique. Eur J Anaesthesiol 2001; 18:653–61
54. Albrecht RF, Miletich DJ, Ruttle M: Cerebral effects of extended hyperventilation in unanesthetized goats. Stroke 1987; 18:649–55
55. Wietasch GJ, Mielck F, Scholz M, Spiegel von T, Stephan H, Hoeft A: Bedside assessment of cerebral blood flow by double-indicator dilution technique. Anesthesiology 2000; 92:367–75

56. Baughman VL, Hoffman WE, Albrecht RF, Miletich DJ: Cerebral vascular and metabolic effects of fentanyl and midazolam in young and aged rats. Anesthesiology 1987; 67:314–9
57. Hancock SM, Mahajan RP, Athanassiou L: Noninvasive estimation of cerebral perfusion pressure and zero flow pressure in healthy volunteers: The effects of changes in end-tidal carbon dioxide. Anesth Analg 2003; 96:847–51
58. McCulloch TJ, Turner MJ: The effects of hypocapnia and the cerebral autoregulatory response on cerebrovascular resistance and apparent zero flow pressure during isoflurane anesthesia. Anesth Analg 2009; 108:1284–90
59. Tauchert M, Kochsiek K, Heiss HW, Rau G, Bretschneider HJ: [Methods of measuring the blood supply of an organ using argon]. Z Kreislaufforsch 1971; 60:871–80
60. Lassen NA: Normal average value of cerebral blood flow in younger adults is 50 ml/100 g/min. J Cereb Blood Flow Metabol 1985; 5:347–9
61. Madsen PL, Sperling BK, Warming T, Schmidt J, Secher NH, Wildschiødtz G, Holm S, Lassen NA: Middle cerebral artery blood velocity and cerebral blood flow and O_2 uptake during dynamic exercise. J Appl Physiol 1993; 74:245–50
62. Nuttall GA, Cook DJ, Fulgham JR, Oliver WC, Proper JA: The relationship between cerebral blood flow and transcranial Doppler blood flow velocity during hypothermic cardiopulmonary bypass in adults. Anesth Analg 1996; 82:1146–51