

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. The authors 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. CBF velocity of the middle cerebral artery was recorded by transcranial Doppler sonography. Data were presented as mean (SD). 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) $\mu\text{mol min}^{-1} 100 \text{ g}^{-1}$.

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. ([ANESTHESIOLOGY 2014; 120:335-42](#))

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

What We Already Know about This Topic

- Hyperventilation decreases cerebral blood flow
- The threshold at which this reduction impairs cerebral metabolism in patients under intravenous anesthesia is unknown

What This Article Tells Us That Is New

- In 30 patients scheduled for coronary surgery with fentanyl or midazolam anesthesia, mild hyperventilation (PaCO_2 , 30 mmHg) reduced cerebral blood flow by 60%, did not alter cerebral metabolic rate for oxygen or glucose, but increased net cerebral lactate efflux, consistent with partial impairment of cerebral aerobic metabolism

However, until now there are only few studies describing the interrelation between hyperventilation and CMRL in animals and humans without cerebral diseases, and their results have not been consistent. A recent report about moderate and profound hyperventilation in anesthetized young pigs without cerebral disorder showed a reduction

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in 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 in net cerebral lactate efflux.^{8,10,11}

The anesthetized brain might be less vulnerable to ischemia than the nonanesthetized brain as the 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 P_{aCO_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.

Materials 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, CBF velocity (V), and the metabolic effects of hyper- versus 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 20, 1991 until May 10, 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, CMR of oxygen ($CMRO_2$), and CMR of glucose. 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 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 yr of age, female sex, 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 and 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 $\mu\text{g}/\text{kg}$ of fentanyl, 0.2 mg/kg of midazolam, and 0.1 mg/kg of pancuronium. Anesthesia was maintained with 10 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of fentanyl and 150 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of midazolam. The anesthesia procedure, the details of mechanical ventilation, and the methods of insertion of catheters have been described in detail in a previous report.¹⁴

Measurements

Cerebral blood flow was measured with the use of 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 0.5 ml/min by a high-precision aspiration pump with gas-tight Hamilton glass syringes. The withdrawal rate for probes of the argon end-concentration was 5 ml/20 s. 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 MCA 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 elder female patients, we included only male patients in this study.^{23,24}

Measurements were performed at two different P_{aCO_2} levels, approximately 50 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 kits; Boehringer, Mannheim, Germany). For comparisons with CBF measurements, V_{MCA} was averaged during 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 ZFP 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. During 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 $\text{CPP}_{\text{eff}} = \text{mean ABP} - \text{ZFP}$ and $\text{CVR} = \text{CPP}_{\text{eff}} \cdot \text{CBF}^{-1}$, 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 , CMR of glucose, and CMRL were calculated based on the reversed Fick principle, multiplying CBF by the difference in arterio-jugular venous 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 $\text{LOI} [\] = \text{AJVDL} [\text{mM}] \text{AJVDO}_2^{-1} [\text{mM}]$. The lactate–glucose index (LGI), that is, the fraction of glucose consumption that is metabolized and excreted from brain as lactate, was defined as the ratio between the arterio-jugular venous content differences of lactate and glucose. For these calculations, contents of oxygen and glucose concentrations have been converted in to mM. Because one molecule of glucose is metabolized to two molecules of lactate, an LGI of, for example, -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 (SD) unless otherwise stated. To provide an estimate of the effect of hypocapnia and its clinical meaningfulness, we calculated mean differences (MD) and their 95% CIs (MD; 95% CI, lower bound, upper bound; P value).²⁸ The difference between hyperventilation and hypoventilation was 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 Bonferroni multiple comparison tests. All statistical analyses

were performed two-sided, and a P value of less than 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, Department 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) yr (median, 58; range, 41–78 yr), 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.

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 increased 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 with hypoventilation. This reduction was predominantly caused by increased CVR (MD, 0.95; 95% CI, 0.75–1.11 $\text{mmHg} \cdot \text{m l}^{-1} \cdot \text{min}^{-1} \cdot 100 \text{g}^{-1}$; $P < 0.001$) and decreased CPP_{eff} (-14%). The decrease in CPP_{eff} during hyperventilation occurred because of a significant increase in the cerebral ZFP (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 $\text{cDO}_2/\text{CMRO}_2$ 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 with hypoventilation (table 1). The mean cerebral efflux of lactate significantly increased, by 2.0 $\mu\text{mol} \cdot \text{min}^{-1} \cdot 100 \text{g}^{-1}$, whereas mean CMRO_2 and CMR of glucose remained constant. LOI and LGI significantly decreased, that is, became more negative.

Cerebrovascular CO_2 reactivity of CBF was 2.02 (1.18) $\text{ml} \cdot \text{min}^{-1} \cdot 100^{-1} \cdot \text{mmHg}^{-1}$, corresponding to a relative change of 2.79 (0.77) $\% \cdot \text{mmHg}^{-1}$. The cerebrovascular CO_2 reactivity of mean V_{MCA} was 1.18 (0.48) $\text{cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$, corresponding to a relative change of 2.03 (0.50) $\% \cdot \text{mmHg}^{-1}$,

Table 1. Hemodynamic and Metabolic Data during Moderate Changes in P_{aCO_2} in Patients without Cerebral Disease with Intravenous Anesthesia

Parameters (n = 30)	Units	Hyperventilation, Mean (SD)	Hypoventilation, Mean (SD)	Mean Differences (CI, 5%; 95%)	P Value
P_{aCO_2}	mmHg	31 (3)	51 (3)	20 (19; 21)	<0.001
$CBF^{*\dagger}$	$ml \cdot min^{-1} \cdot 100 g^{-1}$	27 (6)	68 (24)	41 (28; 53)	<0.001
$V_{MCA} \text{ mean}^{*\dagger}$	cm/s	34 (12)	58 (17)	24 (19; 28)	<0.001
MAP	mmHg	76 (12)	71 (11)	-5 (-8; -2)	0.003
ZFP \dagger	mmHg	24 (9)	11 (11)	-13 (-16; -9)	<0.001
CPP $_{eff}$	mmHg	51 (11)	59 (14)	8 (4; 12)	<0.001
CVR \dagger	$mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100 g^{-1}$	1.93 (0.52)	0.95 (0.32)	-0.95 (-1.11; -0.75)	<0.001
Hb	mg/dl	12.7 (1.5)	12.4 (1.4)	-0.3 (-0.5; 1.0)	0.505
Temp $_{Blood}$	$^{\circ}C$	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
$SAO_2 \dagger$	%	96 (1)	95 (2)	-1.6 (-2.4; -0.7)	<0.001
$SjvO_2 \dagger$	%	41 (8)	72 (5)	31 (28; 34)	<0.001
P_{aO_2}	mmHg	121 (31)	109 (28)	-11 (-23; 0)	0.047
$P_{jvO_2} \dagger$	mmHg	30 (9)	46 (5)	16 (13; 19)	<0.001
AJVDO $_2 \dagger$	mg/dl	9.7 (1.6)	3.9 (0.9)	-5.8 (-6.3; -5.3)	<0.001
AJVDG	mg/dl	11.2 (2.7)	5.6 (2.3)	-5.6 (-4.4; -6.9)	<0.001
AJVDL \dagger	mm	-0.080 (0.079)	-0.003 (0.033)	0.077 (0.047; 0.107)	<0.001
$cDO_2^{*\dagger}$	$ml \cdot min^{-1} \cdot 100 g^{-1}$	4.61 (0.83)	11.08 (4.01)	6.49 (4.42; 8.51)	<0.001
CMRO $_2^*$	$ml \cdot min^{-1} \cdot 100 g^{-1}$	2.64 (0.68)	2.51 (0.77)	-0.14 (-0.20; 0.48)	>0.999
CMRG *	$mg \cdot min^{-1} \cdot 100 g^{-1}$	3.10 (1.23)	3.56 (1.49)	0.46 (1.43; 0.51)	>0.999
CMRL *	$\mu mol \cdot min^{-1} \cdot 100 g^{-1}$	-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

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 Bonferroni multiple comparison procedure (*n* = 29). † Because the variances of some outcome variables substantially differed between hyperventilation vs. hypoventilation, these parameters were additionally examined by Welch test and nonparametric Wilcoxon signed-rank tests, which showed that the differences persist.

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; 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; P_{aCO_2} = arterial partial pressure of carbon dioxide; P_{aO_2} = arterial partial pressure of oxygen; pH_{art} = negative logarithm of H^+ concentration (molarity) of arterial blood; P_{jvO_2} = jugular venous partial pressure of oxygen; SAO_2 = arterial blood saturation; $SjvO_2$ = venous blood saturation of the jugular bulb; Temp $_{Blood}$ = blood temperature; $V_{MCA} \text{ mean}$ = mean blood flow velocity of the middle cerebral artery; ZFP = zero-flow pressure.

which was significantly lower than the relative CO $_2$ reactivity of CBF (MD, -0.76; 95% CI, -0.96 to -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 or midazolam anesthesia. Compared with hypoventilation, moderate hyperventilation was associated with a significant reduction in CBF, cDO_2 , and P_{jvO_2} . The mean cerebral efflux of lactate significantly increased, whereas mean CMRO $_2$ and CMR of glucose remained constant.

Hyperventilation reduces P_{aCO_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 P_{aCO_2} levels in principle may be explained by different mechanisms:

- Dissociation of oxygen-binding 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 on 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 also 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 $\mu mol \cdot min^{-1} \cdot 100 g^{-1}$, 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

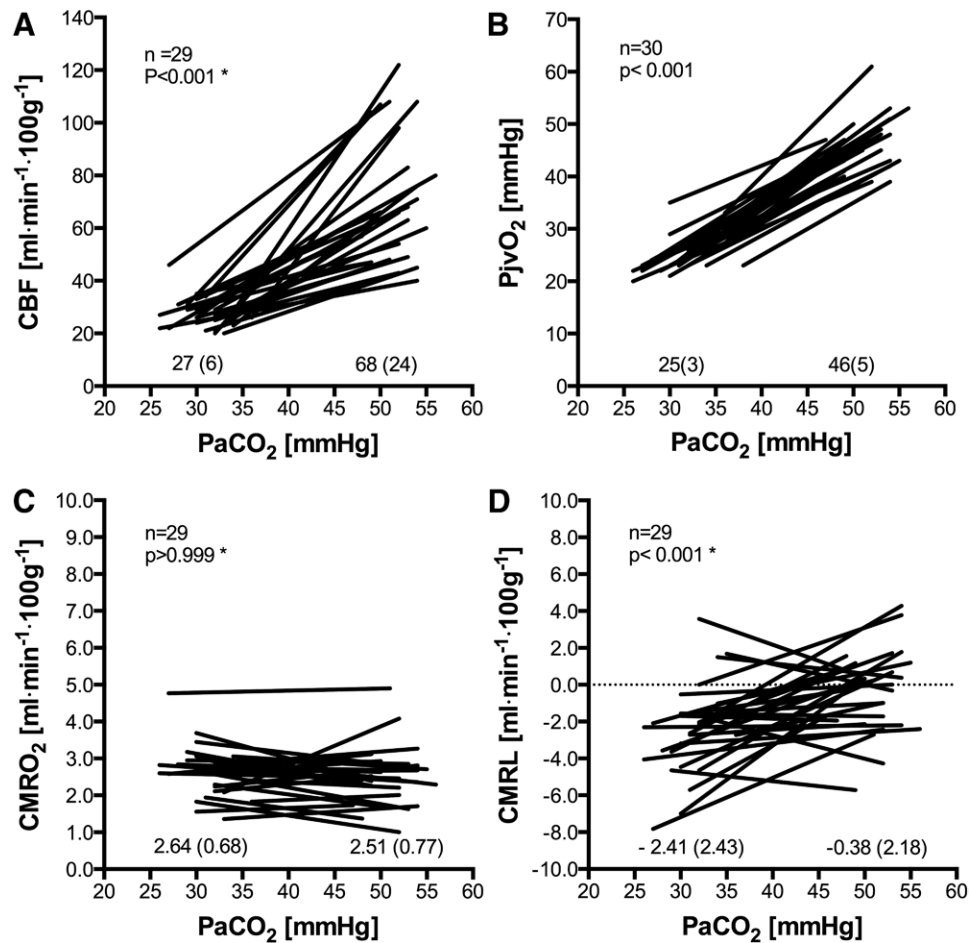


Fig. 1. (A–D) Values of cerebral blood flow (CBF), jugular venous partial pressure of oxygen (PjvO₂), cerebral metabolic rate of oxygen (CMRO₂), and lactate (CMRL) during moderate hyperventilation compared with moderate hypoventilation. *Straight lines* link individual values for each subject. Data are mean (SD) 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 multiple comparisons procedure (*). PaCO₂ = arterial partial pressure of carbon dioxide.

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 PaCO₂ levels might solely be caused by alkalosis-induced enzymatic effects. There are no oxygen stores in the brain in contrast to myoglobin which 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_{t,O₂}) 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 *et al.*⁴⁵ demonstrated that CBF less than 18 ml·min⁻¹·100g⁻¹ in awake monkeys results in irreversible brain tissue infarction. Michenfelder *et al.*⁴⁶ reported critical CBF values of approximately 10–20 ml·min⁻¹·100g⁻¹ in

patients with ischemic changes in electroencephalography during carotid endarterectomy. In awake humans under normocapnic conditions, the cDO₂/CMRO₂ 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 increased 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 cDO₂ while CMRO₂ remained unchanged.

Most investigators have considered jugular venous PO₂ below 20 mmHg and tissue PO₂ values below 10 mmHg as pathological. Clausen *et al.*⁹ showed that even moderate hyperventilation (PaCO₂ = 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 decreased below 10 mmHg in 30% of the animals undergoing moderate hyperventilation. 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 previous 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 on 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 decrease. The results of our report demonstrate that moderate hyperventilation, when compared with 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 in 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 measurements 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 ABP 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 CBF 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) $ml \cdot min^{-1} \cdot 100 g^{-1}$. 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 in $Paco_2$ do not only cause changes in vascular diameter at the arteriolar level but might also cause minor changes in diameter of the MCA, 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 with 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 P_{jvO_2} may partly impair cerebral aerobic metabolism at clinically relevant levels of hypocapnia.

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Competing Interests

The authors declare no competing interests.

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