Moderate hyperventilation during intravenous anesthesia increases net cerebral lactate efflux.

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Anesthesiology 2014; 120: 335–42

German Clinical Trials Register (DRKS00011535).
ABSTRACT

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

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

Results: Moderate hyperventilation significantly decreased CBF by 60%, blood flow velocity by 41%, cerebral oxygen delivery by 58%, and partial pressure of oxygen of the jugular-venous bulb by 45%. Cerebral metabolic rates for oxygen and glucose remained unchanged, however, net cerebral lactate efflux significantly increased from -0.38 (2.18) to -2.41 (2.43) µmol•min\(^{-1}\)•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 (cDO₂) and cerebral metabolism. 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.

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. 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]).

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. Similarly, investigations using magnetic resonance spectroscopy or the Kety-Schmidt-technique in awake volunteers undergoing hyperventilation showed an increase in net cerebral lactate efflux.

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. In humans induction of intravenous anesthesia even may reduce cerebral lactate efflux. But moderate hyperventilation during anesthesia also showed a trend to increase net cerebral lactate efflux though not reaching significance. 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 PaCO₂, CVR, CBF, global cDO₂, 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 cDO₂ 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 µg·kg$^{-1}$ fentanyl, 0.2 mg·kg$^{-1}$ midazolam, and 0.1 mg·kg$^{-1}$
pancuronium. Anesthesia was maintained with 10 µg·kg⁻¹·h⁻¹ fentanyl and 150 µg·kg⁻¹·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 VMCA 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 PaCO₂ 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, VMCA 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 PaCO₂ 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 VMCA envelope and arterial pressure curves. Over each 10-s period we first averaged diastolic, mean and systolic data of arterial blood pressure (ABP) and VMCA to obtain a pressure/flow velocity plot. Cerebral ZFP was then extrapolated by linear regression analysis of the ABP/VMCA 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·CBF⁻¹, respectively. Cerebrovascular CO₂-reactivity was calculated from the slope of the linear regression line of the relationship between CBF and PaCO₂ as well as VMCA and PaCO₂. Relative CO₂-reactivity was calculated as the percentage of change in CBF or VMCA per mmHg change in PaCO₂.²⁶
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. 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 $[\text{mmol·l}^{-1}] = \text{AJVDL}[\text{mmol·l}^{-1}] \cdot \text{AJVDO}_2^{-1}[\text{mmol·l}^{-1}]$. 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 into mmol·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.

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). 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 Bonferroni’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).

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>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Hyper-ventilation mean (SD)</th>
<th>Hypo-ventilation mean (SD)</th>
<th>Mean differences (CI 5%; 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO₂</td>
<td>[mmHg]</td>
<td>31 (3)</td>
<td>51 (3)</td>
<td>20 (19; 21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBF*§</td>
<td>[ml·min⁻¹·100g⁻¹]</td>
<td>27 (6)</td>
<td>68 (24)</td>
<td>41 (28; 53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VMCA mean*§</td>
<td>[cm·s⁻¹]</td>
<td>34 (12)</td>
<td>58 (17)</td>
<td>24 (19; 28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP</td>
<td>[mmHg]</td>
<td>76 (12)</td>
<td>71 (11)</td>
<td>-5 (-8; -2)</td>
<td>0.003</td>
</tr>
<tr>
<td>ZFP§</td>
<td>[mmHg]</td>
<td>24 (9)</td>
<td>11 (11)</td>
<td>-13 (-16; -9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPP eff</td>
<td>[mmHg]</td>
<td>51 (11)</td>
<td>59 (14)</td>
<td>8 (4; 12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVR§</td>
<td>[mmHg·ml⁻¹·min⁻¹·100g]</td>
<td>1.93 (0.52)</td>
<td>0.95 (0.32)</td>
<td>-0.95 (-1.11; -0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb</td>
<td>[mg·dl⁻¹]</td>
<td>12.7 (1.5)</td>
<td>12.4 (1.4)</td>
<td>-0.3 (-0.5; 1.0)</td>
<td>0.505</td>
</tr>
<tr>
<td>Temp_Blood</td>
<td>[°C]</td>
<td>35.3 (0.4)</td>
<td>35.3 (0.5)</td>
<td>-0.06 (-0.15; 0.03)</td>
<td>0.166</td>
</tr>
<tr>
<td>pH art</td>
<td>[-]</td>
<td>7.48 (0.03)</td>
<td>7.30 (0.03)</td>
<td>-0.18 (-0.19; -0.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO₂§</td>
<td>[%]</td>
<td>96 (1)</td>
<td>95 (2)</td>
<td>-1.6 (-2.4; -0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SjvO₂§</td>
<td>[%]</td>
<td>41 (8)</td>
<td>72 (5)</td>
<td>31 (28; 34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PaO₂</td>
<td>[mmHg]</td>
<td>121 (31)</td>
<td>109 (28)</td>
<td>-11 (-23; 0)</td>
<td>0.047</td>
</tr>
<tr>
<td>PjvO₂§</td>
<td>[mmHg]</td>
<td>30 (9)</td>
<td>46 (5)</td>
<td>16 (13; 19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AJVDG</td>
<td>[mg·dl⁻¹]</td>
<td>11.2 (2.7)</td>
<td>5.6 (2.3)</td>
<td>-5.6 (-4.4; -6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AJVDL§</td>
<td>[mmol·l⁻¹]</td>
<td>-0.080 (0.079)</td>
<td>-0.003 (0.033)</td>
<td>0.077 (0.047; 0.107)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cDO₂*§</td>
<td>[ml·min⁻¹·100g⁻¹]</td>
<td>4.61 (0.83)</td>
<td>11.08 (4.01)</td>
<td>6.49 (4.42; 8.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CMRO₂*</td>
<td>[ml·min⁻¹·100g⁻¹]</td>
<td>2.64 (0.68)</td>
<td>2.51 (0.77)</td>
<td>-0.14 (-0.20; 0.48)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>CMRG*</td>
<td>[mg·min⁻¹·100g⁻¹]</td>
<td>3.10 (1.23)</td>
<td>3.56 (1.49)</td>
<td>0.46 (1.43; 0.51)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>CMRL*</td>
<td>[µmol·min⁻¹·100g⁻¹]</td>
<td>-2.41 (2.43)</td>
<td>-0.38 (2.18)</td>
<td>2.03 (0.60; 3.48)</td>
<td>0.003</td>
</tr>
<tr>
<td>OEF</td>
<td>[-]</td>
<td>0.57 (0.09)</td>
<td>0.24 (0.05)</td>
<td>-0.34 (-0.36; -0.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOI</td>
<td>[-]</td>
<td>-0.014 (0.014)</td>
<td>-0.004 (0.016)</td>
<td>0.011 (0.004; 0.018)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGI</td>
<td>[-]</td>
<td>-0.13 (0.13)</td>
<td>-0.03 (0.15)</td>
<td>0.11 (0.04; -0.18)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

AJVDG = arterio-jugular venous difference in glucose, AJVDL = arterio-jugular venous difference in lactate, AJVDO₂ = arterio-jugular venous difference in oxygen, CBF = cerebral blood flow, cDO₂ = cerebral oxygen delivery, CI = 5%, 95% confidence interval, CMRG = cerebral metabolic rate of glucose, CMRL = cerebral metabolic rate of lactate, CMRO₂ = 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, PaCO₂ = arterial partial pressure of carbon dioxide, PaO₂ = arterial partial pressure of oxygen, pH art = negative logarithm of H⁺ concentration (molarity) of arterial blood, PjvO₂ = jugular venous partial pressure of oxygen, SD = standard deviation, SaO₂ = arterial blood saturation, SjvO₂ = venous blood saturation of the jugular bulb, Temp_Blood = blood temperature, VMCA 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 Bonferroni'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 PaCO₂ 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. Hyper- ventilation reduced CBF by 60%, and V̇_{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⁻¹·100g; 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.

![Graphs showing changes in 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.](image)

**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 (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 cDO2 (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 (PjvO2; MD, 21; 95% CI: 19, 22 mmHg; p<0.001; Fig. 1). The cDO2/CMRO2 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 µmol·min⁻¹·100g⁻¹, whereas mean CMRO2 and CMRG remained constant. LOI and LGI significantly decreased, that is, became more negative.

Cerebrovascular CO2 reactivity of CBF was 2.02 (1.18) ml·min⁻¹·100⁻¹·mmHg⁻¹, corresponding to a relative change of 2.79 (0.77) %-mmHg⁻¹. The cerebrovascular CO2 reactivity of mean VMCA was 1.18(0.48) cm·s⁻¹·mmHg⁻¹, corresponding to a relative change of 2.03 (0.50) %-mmHg⁻¹, which was significantly lower than the relative CO2-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, cDO2 and PjvO2. The mean cerebral efflux of lactate significantly increased, whereas mean CMRO2 and CMRG remained constant.

Hyperventilation reduces PaCO2 and decreases extracellular H⁺, leading to cerebral vasoconstriction and consecutively to reduced CBF and cDO2. An associated increase in net cerebral efflux of lactate at low PaCO2 levels in principle may be explained by different mechanisms:

- Dissociation of oxygen-bindings curve to the left as a result of the respiratory alkalo-
sis, (Bohr-effect)⁴⁰-⁴²
- 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. 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. Thus, partial metabolic compartmentalization appears to exist between astrocytes and neurons, with astrocytes feeding the neurons with lactate generated from glycolysis upon cerebral activation.

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. 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 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 (PₐO₂) gradient and the efficiency of oxygen transfer from the capillary bed. A definite ischemic threshold for brain tissue oxygenation has not yet been defined. Jones and colleagues demonstrated that CBF less than 18 ml-min⁻¹·100g⁻¹ in awake monkeys results in irreversible brain tissue infarction.

Most investigators have considered jugular-venous PO₂ below 20 mmHg and tissue PO₂ values below 10 mmHg as pathological. Clausen and colleagues 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 fell 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. Then, oxygen tension might play an essential role in mitochondrial cellular oxygen sensing and oxygen-regulated gene expression in clinical situations of low cDO₂.
Although net cerebral lactate efflux during hyperventilation increased in our patients, CMRO\textsubscript{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\textsubscript{2} could be demonstrated.\textsuperscript{8,10,15,52,53}

In contrast, other investigations could demonstrate that hyperventilation leads to a substantial decrease in CMRO\textsubscript{2}\textsuperscript{35,54} or tissue oxygen pressure.\textsuperscript{9} However, investigations of CBF and cerebral metabolism with variations of PaCO\textsubscript{2} in anesthetized patients or volunteers without cerebral disease are scarce and also showed an unchanged CMRO\textsubscript{2} at moderately low PaCO\textsubscript{2} levels.\textsuperscript{8,13,15,55} The Kety-Schmidt method measures only global CBF and metabolism. In case of regional hypoperfusion with increased CMRO\textsubscript{2} in other regions of the brain, global CMRO\textsubscript{2} may be unaffected. Only when global oxygen availability decreases below oxygen demand, CMRO\textsubscript{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\textsubscript{2}, AJVO\textsubscript{2}, CBF and thus cDO\textsubscript{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 \textit{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.\textsuperscript{12,14,56} The cerebrovascular CO\textsubscript{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 \textit{per se} may have affected the PCO\textsubscript{2}-induced changes in CMRL in our patients, the results of this study cannot \textit{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\textsubscript{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 VMCA. 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 PaCO2 levels of 30 and 50 mmHg. We chose these PaCO2 levels because they roughly reflect the range of unintended variations of PaCO2 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 PaCO2 of 40 mmHg gave a mean CBF under normocapnia of 48(10) ml·min⁻¹·100g⁻¹. The absolute and relative CO2-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 CO2-reactivity of CBF was significantly higher than cerebrovascular CO2-reactivity of VMCA. The most probable explanation is that changes of PaCO2 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, cDO2 and PjvO2 may partly impair cerebral aerobic metabolism at clinically relevant levels of hypocapnia.
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