

Controlled Hypercapnia Enhances Cerebral Blood Flow and Brain Tissue Oxygenation After Aneurysmal Subarachnoid Hemorrhage: Results of a Phase 1 Study

Thomas Westermaier¹ · Christian Stetter¹ · Ekkehard Kunze¹ · Nadine Willner¹ · Judith Holzmeier¹ · Judith Weiland¹ · Stefan Koehler¹ · Christopher Lotz² · Christian Kilgenstein² · Ralf-Ingo Ernestus¹ · Norbert Roewer² · Ralf Michael Muellenbach²

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Abstract

Background This study investigated if cerebral blood flow (CBF) regulation by changes of the arterial partial pressure of carbon dioxide (PaCO₂) can be used therapeutically to increase CBF and improve neurological outcome after subarachnoid hemorrhage (SAH).

Methods In 12 mechanically ventilated poor-grade SAH-patients, a daily trial intervention was performed between day 4 and 14. During this intervention, PaCO₂ was decreased to 30 mmHg and then gradually increased to 40, 50, and 60 mmHg in 15-min intervals by modifications of the respiratory minute volume. CBF and brain tissue oxygen saturation (StiO₂) were the primary and secondary endpoints. Intracranial pressure was controlled by an external ventricular drainage.

Results CBF reproducibly decreased during hyperventilation and increased to a maximum of 141 ± 53 % of baseline during hypercapnia (PaCO₂ 60 mmHg) on all days between day 4 and 14 after SAH. Similarly, StiO₂ increased during hypercapnia. CBF remained elevated within the first hour after resetting ventilation to baseline parameters and no rebound effect was observed within this time-span. PaCO₂-reactivities of CBF and StiO₂ were highest between 30 and 50 mmHg and slightly decreased at higher levels.

Conclusion CBF and StiO₂ reproducibly increased by controlled hypercapnia of up to 60 mmHg even during the period of the maximum expected vasospasm. The absence of a rebound effect within the first hour after hypercapnia indicates that an improvement of the protocol is possible. The intervention may yield a therapeutic potential to prevent ischemic deficits after aneurysmal SAH.

Keywords Subarachnoid hemorrhage · Vasospasm · Delayed cerebral infarction · Ischemia · DCI · Hypercapnia · CO₂-reactivity

Introduction

Under physiological conditions, cerebral blood flow (CBF) is determined by cerebral autoregulation, a self-regulating mechanism which adapts to changes of arterial wall tension and keeps CBF constant over a large mean arterial blood pressure (MABP) range, by an equilibrium of dilating and constricting local paracrine factors, and by the arterial partial pressure of carbon dioxide (PaCO₂). After aneurysmal subarachnoid hemorrhage (SAH), autoregulation is deranged and the equilibrium of local factors is shifted towards contraction. In contrast, the reactivity of CBF upon changes of PaCO₂ is still intact [1, 2]. There is experimental and clinical evidence that in cases of marginal CBF, such as during delayed vasospasm after SAH, hyperventilation induces ischemia and infarction due to an additional vessel constriction and is associated with poor outcome [3–6]. Recently, poor reactivity of CBF to changes of PaCO₂ has been identified as a prognosticator of delayed ischemia after aneurysmal SAH [7]. However, in spite of the observation that CBF can be enhanced by higher PaCO₂ in experimental studies and its clinical

✉ Thomas Westermaier
westermaier.t@nch.uni-wuerzburg.de

¹ Department of Neurosurgery, University Hospital Wuerzburg, Josef-Schneider-Str. 11, 97080 Würzburg, Germany

² Department of Anesthesia and Critical Care, University Hospital Wuerzburg, 97080 Würzburg, Germany

confirmation, it has not been investigated whether a manipulation of arterial carbon dioxide values in terms of hypercapnia may be used therapeutically to increase CBF and prevent ischemia after SAH. In a previous publication, we reported preliminary data of the first patients included in this study, indicating that an increase of CBF may in fact be achieved by transient hypercapnia [8]. The current article reports about a completed Phase 1 trial of hypercapnia for the treatment of poor-grade SAH patients focussing on changes of vessel reactivity and their relation to alterations of PaCO₂ during the course of the disease.

Materials and Methods

The study was approved by the ethics committee of the medical faculty of the University of Wuerzburg, Germany (Wue112/12). Based on experimental data of Diringer et al. (increase of CBF from baseline to 265 ± 50 % of baseline by a PaCO₂ increase of 20 mmHg) and clinical data of Schmieder et al. (increase of MFV in MCA of 30 cm/s by a PaCO₂ increase of 12.7 %), a desired test-power of 0.8 and a level of significance of $p < 0.05$ (one-way repeated measurement ANOVA with 5 points of measurements), a sample size of 6 and 10 patients, respectively, were calculated. The predefined primary endpoint was an increase of CBF upon an elevation of PaCO₂ from 40 to 60 mmHg for each individual day [1, 2]. For calculation of the sample size, G-Power 3.1 statistical software was used. Accordingly, the ethics vote covered 10 patients. Two further patients were included and treated for compassionate use according to the study protocol. Preliminary data of the first patients included in this trial have been reported previously [8]. This Phase 1 clinical trial was registered at ClinicalTrials.gov. (Trial-ID: NCT01799525, “Hypercapnia to Prevent Secondary Ischemia in SAH”).

Inclusion Criteria

Patients were eligible for inclusion if they had suffered aneurysmal SAH of a poor clinical (Hunt/Hess° 3–5) and radiological grade (Fisher° 3) within the last 96 h, had received an external ventricular drainage (EVD) and had undergone surgical or endovascular occlusion of the aneurysm within the first 72 h after SAH. In all patients, the EVD was placed into the right lateral ventricle via a burr hole at Kocher’s point. The written consent of a legal guardian was obtained before inclusion into the study.

Exclusion Criteria

Pregnancy, chronic obstructive lung disease, an intracranial pressure (ICP) of more than 20 mmHg on day 4 after SAH,

and age under 18 years were predefined exclusion criteria. An arterial pH under 7.25, an ICP over 25 mmHg for more than 2 min, and spontaneous breathing during the intervention were the predefined interruption criteria.

Standard Care

If patients met the inclusion criteria, had received an EVD, and the aneurysm was occluded, sedative and analgesic medications were reduced. If the patient did not wake up appropriately or ICP increased to continuous values above 20 mmHg, sedative and analgesic medication were readministered. A wake-up attempt was not conducted in patients who had developed pneumonia from aspiration after aneurysm rupture. For this purpose, Midazolam (10–30 mg/h) and Fentanyl (60–180 µg/h) were administered and the patients were mechanically ventilated. If further pharmacological therapy of elevated ICP was required, Thiopental was administered under continuous electroencephalographic surveillance (100–350 mg/h). EVDs were leveled at 15 cm above the external auditory canal and continuously drained CSF. Temperature was continuously measured via a probe included in the indwelling catheter. Aggressive temperature control was performed using external cooling, antiphlogistic medication, and targeted antibiotic therapy, if indicated. During the trial interventions, pharmacological therapy was continued and no other drugs or relaxants were administered.

Respirator Settings

Patient underwent one daily trial intervention between day 4 and 14. For the trial intervention, all patients were mechanically ventilated in a volume-controlled mode (pressure trigger –5 cm H₂O). After baseline measurements of arterial blood gases (PaCO₂, pH, PaO₂) and outcome parameters (see below), the respiratory minute volume (RMV) was, at first, increased from baseline values (PaCO₂ 36–44 mmHg) to reach a target PaCO₂ of 30 mmHg. Subsequently, the RMV was reduced in 15-min intervals to reach PaCO₂ values of 40, 50, and 60 mmHg. Thereafter, the respirator settings were reset to baseline values.

Primary Endpoint

CBF during the trial intervention was the primary endpoint. CBF was measured by an intracerebral thermodilution probe (Q-Flow 500®, Hemedex™, Cambridge, MA, USA). The probe was fixed in a bolt screw (BOLT KIT, Raumedic, Helmbrechts, Germany) which was tightly screwed into a burr hole in the right frontal bone 1.5 cm anterior to the entry point of the EVD (Kocher’s point). The probe was

inserted 5 cm from the surface of the bolt screw and fixed in the screw. CBF was monitored by a Bowman Perfusion Monitor[®] (Hemedex[™], Cambridge, MA, USA) and recorded throughout the 1-h trial intervention. After the end of the trial intervention, observation and CBF recording were continued for another hour to exclude a rebound effect.

Secondary Endpoints

StiO₂ was measured transcutaneously by near infrared spectroscopy (NIRS) (INVOS[®], Covidien, Neustadt/Donau, Germany) attached bilaterally on the forehead skin. Mean flow velocities (MFV) in both middle cerebral artery (MCA) trunks were determined by transcranial Doppler sonography (TCD) before and at each step of the trial intervention. TCD measurements were not continued after the end of the trial intervention. Heart rate (HR), MABP, and peripheral oxygen saturation were continuously monitored throughout the intervention. Cardiac Output (CO) was continuously measured using a FloTrac[®] sensor and monitored by a Vigileo[®] monitor (Edwards Life Science, Unterschleissheim, Germany).

Calculation of PaCO₂-Reactivity of CBF and StiO₂

The HEMEDEX[™] thermodilution probe displays absolute values of CBF in the right frontal cortex (in ml/100 mg brain tissue/min). In each patient, CBF values at baseline and at PaCO₂ target values of 30, 40, 50, and 60 mmHg were recorded. At the same time points, the actual PaCO₂ values were determined by arterial blood gas analysis. The differences of CBF- and the actual PaCO₂-values between the respective target points (40–30, 50–40, and 60–50) were calculated to determine the change of CBF and PaCO₂ in the respective interval. Thereafter, the change of CBF was divided by the change of PaCO₂ for each interval to calculate the PaCO₂ reactivity of CBF (ml/100 mg/min/mmHg). Mean values ± standard deviations for the intervals 30–40, 50–40, and 60–50 mmHg are presented in Fig. 3. In analogy, the PaCO₂-reactivity of StiO₂ was calculated over both hemispheres. StiO₂-values, displayed in % of maximum values, were recorded. The changes of StiO₂ in the above-mentioned intervals were divided by the changes of PaCO₂ in the respective intervals for each patient to obtain the PaCO₂-reactivity of StiO₂ (%/mmHg).

Computed tomography (CT) was obtained in 3-day intervals to monitor for newly appearing hypodensities [9] representing “delayed cerebral infarction.” In case of suspected vasospasm, angiography and, if possible, vasospasmolysis were performed. A final neurological

examination was conducted after 6 months to evaluate “neurological recovery” including the assessment of the Glasgow Outcome Scale (GOS) score.

Documentation and Statistical Analysis

Values were documented in written protocols and transferred to electronic datasheets. Testing for normal distribution was performed by a D’Agostino and Pearson normality test. If normality testing was passed for all measurement points, a one-way analysis of variance for repeated measurements (one-way RM ANOVA) was applied, followed by a Dunnett’s multiple comparisons test comparing measurements at the respective time-points to baseline values. Statistical analyses were performed using GraphPad Prism 4.0 Statistical Software.

Results

Following the inclusion criteria, all patients had suffered from SAH of poor clinical and radiological grades (Table 1). All aneurysms were occluded within the first 2 days after SAH by surgical clipping (5 patients) or endovascular coiling (7 patients).

Ventilation and Arterial Blood Gases

From a baseline of 7.5 ± 1.3 l/min, the RMV was changed to 11.8 ± 2.3 , 5.9 ± 1.4 , 4.1 ± 1.0 , and 2.9 ± 0.7 l/min to obtain a PaCO₂ of 38.7 ± 3.8 , 31.8 ± 2.5 , 41.0 ± 2.6 , 49.8 ± 2.5 , and 60.7 ± 4.0 mmHg, respectively. Changes of pH, PaO₂, and cardiocirculatory parameters are depicted in Table 2.

Cerebral Blood Flow

After reducing PaCO₂ to 30 mmHg, CBF declined to a mean of 83 ± 35 % of baseline. Increasing PaCO₂ to 40, 50, and 60 mmHg resulted in mean CBF values of 98 ± 41 , 123 ± 48 , and 141 ± 53 % of baseline, respectively. 15, 30, 45, and 60 min after resetting ventilation to baseline parameters, CBF gradually declined to 137 ± 39 , 134 ± 47 , 123 ± 35 , and 114 ± 23 % of baseline values, respectively (Fig. 1).

Brain Tissue Oxygenation Saturation (StiO₂)

StiO₂, measured by NIRS over the right forebrain, decreased to 94 ± 4 % of baseline values at a PaCO₂ of 30 mmHg and increased to 99.9 ± 4 , 105 ± 6 , and

Table 1 Patient characteristics and clinical appearance

Patient number	Clinical grade (hunt/hess)	CT grade (fisher)	Aneurysm (treatment)	Delayed cerebral infarction (CT)	GOS score (6 months)
1	Grade 3	Grade 3 + ICH	Right MCA (coil)	None	4
2	Grade 4	Grade 3 + ICH	Left ICA (clip)	None	5
3	Grade 4	Grade 3	Left ICA (coil)	None	5
4	Grade 5	Grade 3 + ICH	Acom (coil)	None	3
5	Grade 4	Grade 3	Acom (clip)	None	4
6	Grade 5	Grade 3 + ICH	Left MCA (clip)	None	4
7	Grade 3	Grade 3	Left ICA (coil)	None	5
8	Grade 3	Grade 3 + ICH	Right MCA (clip)	None	3
9	Grade 5	Grade 3 + IVH	Right ICA (coil)	None	5
10	Grade 4	Grade 3 + ICH	Right ICA (coil)	None	5
11	Grade 3	Grade 3	Left ICA (coil)	None	5
12	Grade 4	Grade 3	Acom (clip)	Partial left MCA infarction	4

All patients had suffered severe SAH with thick subarachnoid blood clots with or without additional intracerebral hemorrhage (ICH) or intraventricular hemorrhage (IVH) and predisposition to develop delayed vasospasm and secondary ischemia after SAH. One patient developed secondary partial MCA-territory infarction. All other patients had no signs of delayed ischemic infarction in serial CT-scans obtained during the course of therapy

MCA middle cerebral artery, *ACA* anterior cerebral artery, *ICA* internal carotid artery, *GOS* glasgow outcome scale

Table 2 Respiration parameters, arterial blood gases and cardiocirculatory parameters at baseline and during the trial intervention

	Baseline	30 mmHg	40 mmHg	50 mmHg	60 mmHg
RMV (l/min)	7.5 ± 1.3	11.8 ± 2.3	5.9 ± 1.4	4.1 ± 1.0	2.9 ± 0.7
FiO ₂ (%)	45.2 ± 6.6	45.2 ± 6.6	45.2 ± 6.6	45.6 ± 6.4	45.9 ± 6.6
PaCO ₂ (mmHg)	38.7 ± 3.8	31.8 ± 2.5**	41.0 ± 2.6	49.8 ± 2.5**	60.7 ± 4.0**
pH	7.44 ± 0.03	7.50 ± 0.03**	7.43 ± 0.03	7.37 ± 0.03**	7.30 ± 0.03**
PaO ₂ (mmHg)	105 ± 14	90 ± 16**	99 ± 13**	108 ± 13**	108 ± 15**
PaO ₂ /FiO ₂ (mmHg)	255 ± 52	228 ± 57**	244 ± 52**	251 ± 54	242 ± 51**
MABP (mmHg)	96.8 ± 8.6	97.7 ± 9.3	97.4 ± 8.5	97.5 ± 9.9	98.3 ± 12.2
HR (1/min)	64.5 ± 9.8	64.8 ± 9.6	63.8 ± 10.4	66.5 ± 11.4**	71.1 ± 13.5**
SV (ml)	92.7 ± 16.3	91.7 ± 15.1	93.3 ± 14.4	95.2 ± 17.0	94.4 ± 21.0
CO (l/min)	5.8 ± 1.0	5.7 ± 0.9	5.6 ± 0.8	6.0 ± 1.0*	6.4 ± 1.2*

RMV respiratory minute volume, FiO₂ inspiratory flow of oxygen, HR heart rate, SV stroke volume, CO cardiac output

* $p < 0.05$, ** $p < 0.01$ compared to baseline, one-way RM ANOVA, Dunnett's test for multiple comparisons

110 ± 7 % at PaCO₂ values of 40, 50, and 60 mmHg, respectively. 15, 30, 45, and 60 min after resetting ventilation to baseline parameters, StiO₂ gradually declined to 109 ± 7, 106 ± 6, 103 ± 6, and 101 ± 5 % of baseline. Over the left forebrain, StiO₂ decreased to 94 ± 5 % of baseline values at a PaCO₂ of 30 mmHg and increased to 101 ± 6, 107 ± 7, and 113 ± 9 % at PaCO₂ values of 40, 50, and 60 mmHg, respectively. 15, 30, 45, and 60 min after resetting ventilation to baseline parameters, StiO₂ gradually declined to 113 ± 10, 108 ± 8, 104 ± 7, and 102 ± 6 % of baseline values. On both sides, the increase of StiO₂ was statistically

significant at PaCO₂ values of 50 and 60 mmHg and 15, 30, 45, and 60 min after resetting the respirator to baseline values.

TCD

During the intervention, MFV in the left (right) MCA declined from a baseline of 81 ± 41 (81 ± 26)–68 ± 40 (63 ± 22) cm/s at a PaCO₂ of 30 mmHg and rose to 95 ± 45 (96 ± 33), 114 ± 47 (117 ± 35), and 131 ± 45 (127 ± 36) mmHg at PaCO₂ values of 40, 50, and 60 mmHg, respectively. All differences were significant compared to baseline values (Fig. 2).

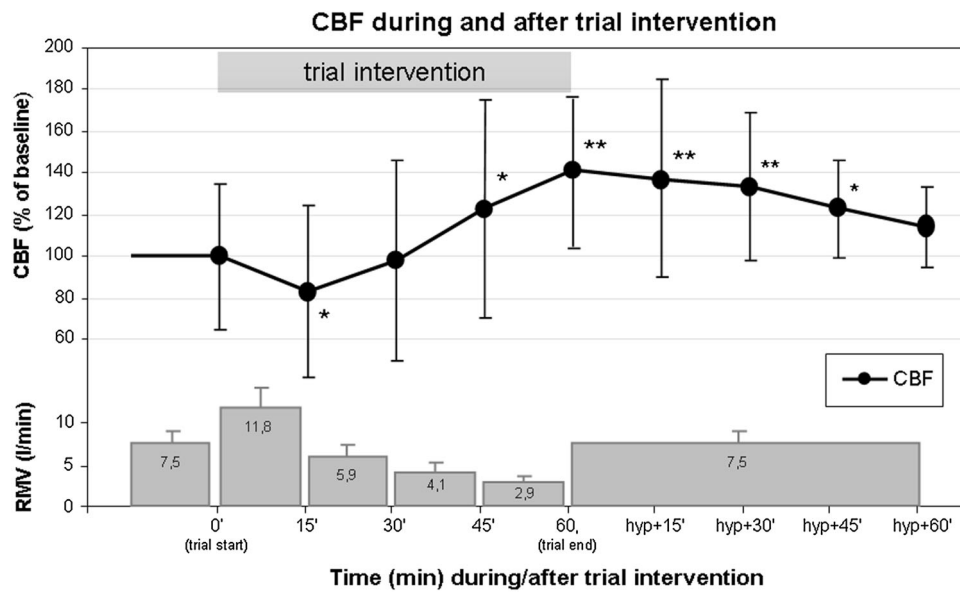
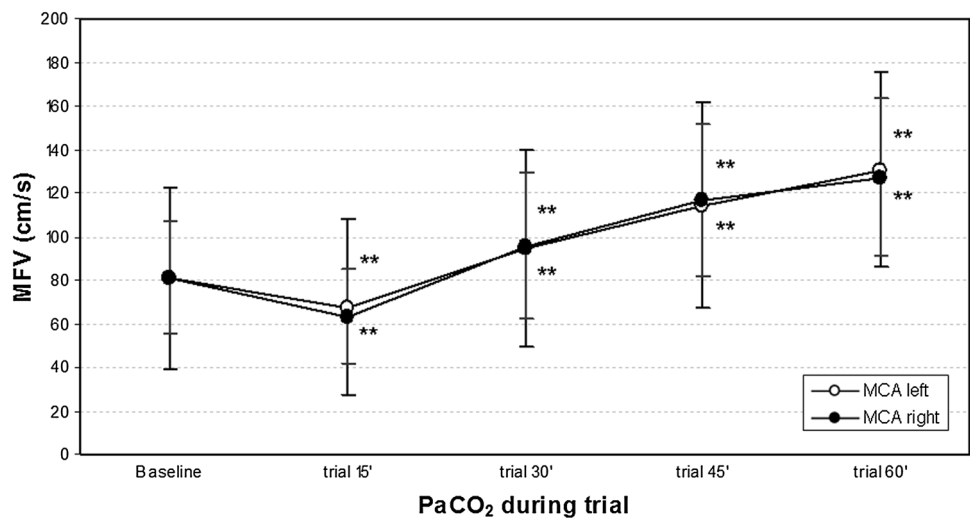


Fig. 1 Course of cerebral blood flow (CBF) during the hypercapnic trial intervention and 15, 30, 45, and 60 min after hypercapnia. CBF remained elevated after resetting the respirator to baseline parameters and slowly returned to pre-hypercapnia levels without a negative rebound effect. The gray columns indicate the respiratory minute volume (mean ± SD) before, at the different stages during, and after the trial intervention. Numbers within the columns represent the mean

respiratory minute volume during the respective time interval. After the end of the trial intervention, the respirator settings were returned to baseline, and pre-hypercapnia settings were maintained there during the following hour. (hyp + 15 = 15 min after resetting the ventilator to baseline, pre-hypercapnia, parameters, RMV respiratory minute volume, **p* < 0.05, ***p* < 0.01 compared to baseline values, one-way RM ANOVA, Dunnett’s test for multiple comparisons)

Fig. 2 Transcranial Doppler sonography during the trial intervention. The course of flow velocities in both middle cerebral arteries during the trial intervention is concordant with the course of CBF and $StiO_2$ and indicates that the increase of CBF is a global phenomenon. (MFV mean flow velocity, MCA middle cerebral artery, **p* < 0.05, ***p* < 0.01 compared to baseline values, one-way RM ANOVA, Dunnett’s test for multiple comparisons)

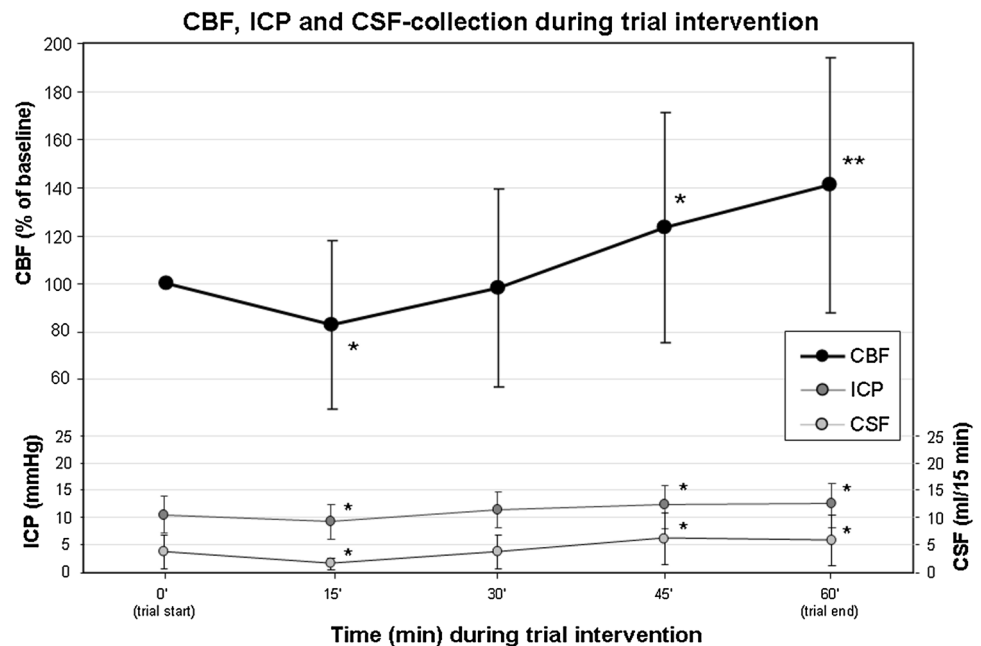


Side Effects

All patients had received an EVD prior to trial inclusion for continuous cerebrospinal fluid (CSF) drainage. Hence, only a mild decrease and increase of ICP from 11.2 ± 4.5 mmHg at baseline to 9.4 ± 4.3 , 12.3 ± 4.3 , 13.7 ± 4.9 , and 13.9 ± 4.8 mmHg at a $PaCO_2$ of 30, 40, 50, and

60 mmHg was observed during the trial intervention. The decrease and increase of ICP reached the level of significance. A potential further elevation of ICP under increasing $PaCO_2$ was reflected by a statistically significant surplus drainage of CSF from 4.3 ± 4.5 ml over 15 min at baseline to 1.7 ± 1.3 , 4.6 ± 4.0 , 7.9 ± 6.3 , and 7.4 ± 6.2 ml over 15 min at a $PaCO_2$ of 30, 40, 50, and 60 mmHg. ICP

Fig. 3 CBF, ICP, and CSF collection during the trial intervention. The course of CBF, ICP, and the volume of CSF drained within the 15 min of each trial step are presented. During the increase of CBF, a minor but statistically significant increase of ICP occurred. More excessive elevations of ICP have obviously been prevented by a surplus drainage of CSF during the trial intervention. (* $p < 0.05$ vs. baseline, one-way RM ANOVA, Dunnett's test for multiple comparisons)



and the amount of CSF drained during the trial intervention are depicted in Fig. 3.

Reactivity of CBF and StiO_2 by PaCO_2 Interval

PaCO_2 -reactivities of CBF and StiO_2 were calculated for the intervals between PaCO_2 -steps during the intervention (between 30–40, 40–50, and 50–60 mmHg, respectively). PaCO_2 -reactivity of CBF was 0.45 ± 0.74 , 0.56 ± 0.83 ,

and 0.28 ± 0.44 ml/100 g/min/mmHg between a PaCO_2 of 30–40, 40–50, and 50–60 mmHg, respectively (Fig. 4). PaCO_2 -reactivity of StiO_2 measured over the left forebrain was 0.52 ± 0.43 , 0.60 ± 0.73 , and 0.46 ± 0.51 %/mmHg between a PaCO_2 of 30–40, 40–50, and 50–60 mmHg, respectively. PaCO_2 -reactivity of StiO_2 measured over the right forebrain was 0.54 ± 0.36 , 0.48 ± 0.81 , and 0.41 ± 0.47 %/mmHg between a PaCO_2 of 30–40, 40–50, and 50–60 mmHg, respectively.

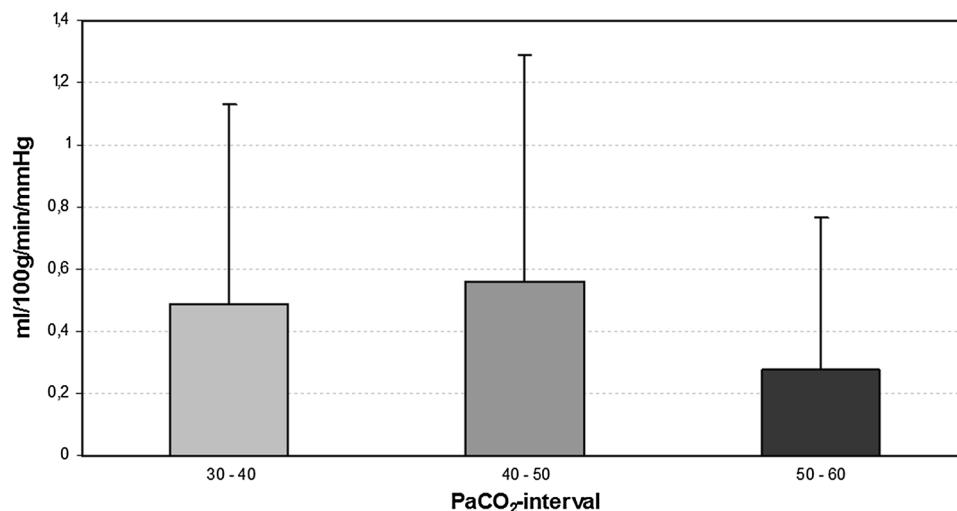


Fig. 4 PaCO_2 -reactivity of CBF in different CO_2 -intervals. The reactivity of CBF is highest between 40 and 50 mmHg, slightly decreases at higher PaCO_2 -values. The differences of CBF- and actual PaCO_2 -values between the respective target points (40–30, 50–40, and 60–50 mmHg) were calculated to determine the change of CBF

and PaCO_2 in the respective interval. Thereafter, the change of CBF was divided by the change of PaCO_2 for each interval to calculate the PaCO_2 reactivity of CBF (ml/100 mg/min/mmHg). Mean values \pm standard deviations for each interval are presented

Reactivity of CBF and St*i*O₂ by Days After SAH

The increase of CBF by elevating PaCO₂ to 60 mmHg was significant on days 4, 5, 7, 8, and 10–14, the increase of St*i*O₂ on the left side on days 4–14, on the right side on days 4–6 and days 8–14 (Fig. 5). The increase of CBF by elevating PaCO₂ to 50 mmHg was not on any day. The increase of St*i*O₂ on the left side was significant on days 6–12 and day 14, and the increase of St*i*O₂ on the right side on days 8, 12 and 13. There was a trend to a higher PaCO₂-reactivity of CBF before day 5 and after day 9 after SAH which did not reach the level of significance.

Clinical and Radiological Outcome

10 of 12 patients were forwarded to re-angiography because of suspected severe vasospasm by TCD and/or Perfusion-CT. Nine received balloon dilatation of spasms and/or pharmacological vasospasmolysis. One patient developed delayed cerebral infarction in the watershed zone between the left ACA and MCA territories in spite of vasospasmolysis of the left internal carotid artery. Patient characteristics and neurological outcome after 6 months are depicted in Table 1.

Discussion

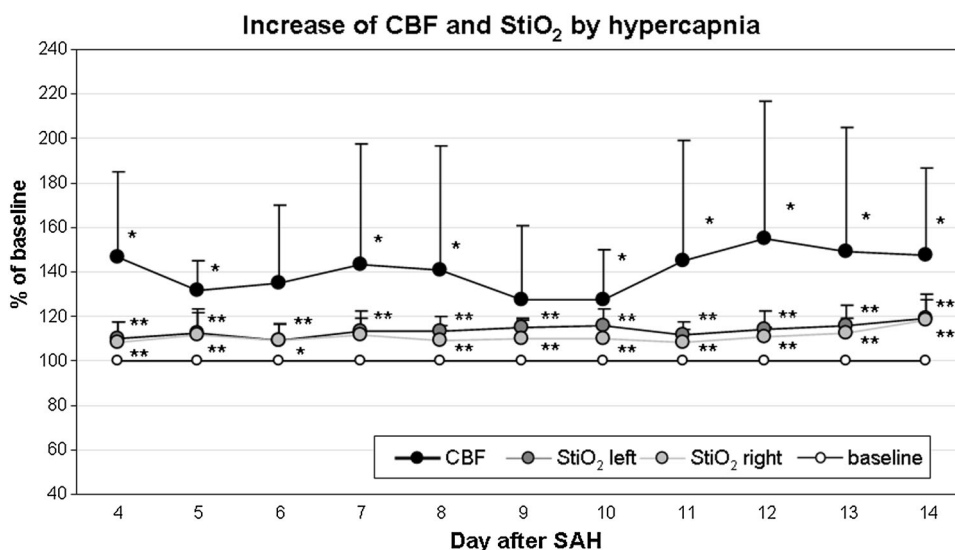
In this Phase 1 study, we investigated the feasibility and safety of therapeutic hypercapnia in patients with poor-grade SAH. We found a reliable and reproducible improvement of the primary and secondary endpoints—CBF and St*i*O₂—by a stepwise increase of PaCO₂ without relevant harmful side effects. Considering that the patients

included in this study have a particularly high risk for delayed cerebral ischemia and poor outcome, the incidence of secondary infarctions was low and the neurological outcome is comparatively good [10–12].

Side Effects

Known side effects of hypercapnia include ICP elevation and blood acidification. According to the Monro-Kellie doctrine, the intracranial volume is the sum of brain tissue, intracranial CSF, and intracranial blood-volume. As such, an increase of ICP is an inevitable side effect of all CBF enhancing therapies. Hence, the presence of an EVD for continuous CSF drainage was a prerequisite for inclusion into the present study. During the interventions, it was closed for approximately 30 s every 5 min in order to measure ICP. Furthermore, predefined exclusion and interruption criteria were an ICP above 20 mmHg at the time of proposed trial inclusion and an ICP above 25 mmHg for more than 2 min during the intervention. Although ICP increased by a mean of 2.7 mmHg under hypercapnia, neither of the predefined interruption criteria occurred in this series of twelve consecutive poor-grade SAH patients, who met the inclusion criteria and underwent a total of 107 interventions. During the interventions, a surplus drainage of CSF was noted and may have prevented an excessive rise in ICP. The increase of ICP by 2.7 mmHg may be caused by the stepwise PaCO₂ change and the 15-min time scale and of the study protocol including a reduction of PaCO₂ to 30 mmHg prior to the induction of hypercapnia. During this period, almost no CSF was drained. In the following period of hypercapnia, the drainage of CSF occurred slower than the increase of CBF and resulted in a transient increase of ICP. This is

Fig. 5 Increase of CBF upon hypercapnia through the course of therapy. The elevation of PaCO₂ to 60 mmHg resulted in a marked increase of CBF and St*i*O₂ between days 4 and 14. While the increase of St*i*O₂ was largely constant throughout the observation period, the increase of CBF tended to be lower between days 5 and 10. (**p* < 0.05, ***p* < 0.01 compared to baseline values, one-way RM ANOVA, Dunnett’s test for multiple comparisons)



supported by the observation that even during the first step of PaCO₂ increase from 30 mmHg back to a target value of 40 mmHg, ICP was slightly higher than baseline values. However, no intervention had to be interrupted with respect to the predefined interruption criteria. This is in accordance with the findings of Petridis and coworkers who reported about the effects of lung-protective ventilation and permissive hypercapnia (PaCO₂ 50–60 mmHg) in SAH-patients who had developed early ARDS. All of these patients had an EVD for continuous CSF drainage and an intracerebral ICP probe for continuous ICP-measurement. In analogy to our results, the authors did not find a relevant increase of ICP in this setting during hypercapnia [13]. Some patients in this series had moderate early brain swelling as defined by Claassen et al. [14], but none had decompensated brain edema. In patients with even more pronounced brain edema, the surplus drainage of CSF may not be sufficient to prevent ICP elevations during hypercapnia. These patients will not be candidates for a hypercapnic therapy. If decompressive craniectomy is indicated, their eligibility may be reevaluated thereafter.

A pH below 7.25 during the intervention was a further potential interruption criterion in our study in order to exclude a possible cardiocirculatory effect by profound acidosis [15]. However, no intervention in this series had to be interrupted because pH fell below this predefined value. The reduction of PaO₂ during hyperventilation and slight increase during hypercapnia might be explained by pulmonary vessel contraction during a lack of CO₂ causing a decreased uptake of O₂ [16]. On the other hand, hyperventilation has been reported to increase systemic vascular resistance and to reduce perfusion in most tissues while peripheral oxygen extraction may increase [17].

Increase of CBF

Secondary ischemic events are a major cause of in-hospital mortality and morbidity after aneurysmal SAH. Most likely, the cause of delayed ischemic neurological deficit (DIND) is multifactorial [18]. Delayed vasospasm (DV) probably contributes, but cortical electrical hyperactivity, hypermetabolism, a disturbance of local vasorelaxing and vasoconstricting factors, and inflammation may also be of importance. Our therapeutic approach does not focus on a single pathophysiological factor but rather targets the common denominator—the mismatch of oxygen demand and supply. While cerebral autoregulation is disturbed after SAH, there is evidence in animals [1, 19, 20] and humans that the PaCO₂-reactivity remains intact after SAH [2, 21, 22].

Recently, the loss of cerebrovascular reactivity on changes of PaCO₂ was identified as a predictor of DCI and poor outcome [7]. A large number of experimental and

clinical studies investigated the principle mechanisms of CBF reactivity on changes of PaCO₂ and the harmful effects of prolonged hyperventilation. Nevertheless, prior to this present Phase 1 trial, no study has investigated the therapeutic potential of hypercapnia in SAH patients. In the current study, the elevations of PaCO₂ to a target of 60 mmHg led to reproducible increases of CBF and St_iO₂ in all patients. As previously reported, CO slightly increases under moderate hypercapnia [23, 24] whereas it decreases under pronounced hypercapnia and acidity [23]. In this study, cardiac output moderately increased by approximately 10 %, partly by an increase of HR, partly by an increase of stroke volume. Assuming that the surplus cardiac output is approximately evenly distributed in the systemic circulation, it cannot account for the increase of CBF. Therefore, an immediate vasodilating effect is likely to occur under hypercapnia. The measurement of CBF in this study was only punctual in the right frontal cortex. Rabinstein and coworkers observed a correlation of secondary ischemia with the site of the aneurysm [25]. Due to ethical aspects, however, a non-eloquent area was chosen for this single-point CBF measurement. Hence, the issue of a possible “steal-effect” may be raised with a shift of blood from areas with no reserve capacity into better perfused areas. To account for this, we added bilateral frontal St_iO₂ measurements and bilateral TCD as secondary endpoints. By this way, four of six supratentorial vascular territories were covered and a “steal-effect” was not observed during the trial interventions. The bilateral symmetric increase of TCD values indicates that the increase of CBF and St_iO₂ is a global rather than a local phenomenon.

The increase of CBF tended to be slightly less pronounced in case of higher baseline flow velocities in TCD in the major cerebral arteries. This indicates that the increase of CBF upon hypercapnia may be somewhat lower in case of cerebral vasospasm, an observation which is in accordance with the findings of Carrera et al. [7]. However, this correlation was not statistically significant in this present series. In general, the PaCO₂ reactivity was preserved in all patients and CBF could reliably be increased by hypercapnia of over 50 mmHg even in patients with signs of severe vasospasm as determined by high baseline TCD values.

The fact that 10 of 12 patients were transferred to reangiography due to suspected vasospasm indicates that temporary hypercapnia does not prevent or treat vasospasm in large vessel trunks but rather affect the cerebral vasculature at the level of small conductive vessel or microcirculation. We based the decision for reangiography and endovascular vasospasm therapy on clinical, ultrasonographic and CT-criteria as described previously resulting in a relatively high number of endovascular spasm therapies [26]. The parallel course of TCD in the

MCA trunks and CBF also indicates that there is no relevant dilatory effect of hypercapnia in large vessels. If there was such an effect, the increase of MFV in TCD would be expected to be less pronounced than the increase of CBF during hypercapnia. The high rate of patients transferred to reangiography and angioplasty results from the above-mentioned criteria and may be center-specific and might have helped to protect from DCI. Although the development of DCI was rare and outcome was comparatively good considering the very poor starting condition, this may limit the power of this series to generalize the beneficial effect regarding the secondary endpoints “delayed cerebral infarction” and “neurological recovery.”

Improvement of Study-Protocol

The next step to this phase 1 trial will be a randomized controlled trial comparing patients treated by intermittent hypercapnia to a control group. Prior to starting an RCT, the optimum trial protocol needs to be found. The present data suggests that the current protocol can be optimized in two ways. First, our results indicate that the maximum reactivity of both CBF and StiO_2 lies between a PaCO_2 of 30–50 mmHg and already decreases between 50 and 60 mmHg. Considering the accompanying changes of pH, we hypothesize that a PaCO_2 of 55–60 mmHg may be an effective target to reliably increase CBF while maintaining patient safety over a longer period.

Second, the absence of a rebound effect after resetting the respirator to baseline values suggests that longer periods of hypercapnia may safely be possible and might actually increase CBF for a longer period of time. The study was designed as a Phase 1 trial with the primary target to determine the changes of CBF during temporary iatrogenic induction of hypercapnia in order to evaluate its potential capability for a therapeutic use in SAH patients. The primary observation time was during the 60 min of the trial intervention. Unfortunately, TCD and arterial blood gases were not measured at the end of the trial intervention. In contrast, CBF and StiO_2 were further recorded, mainly because a rebound effect had to be excluded after returning to normoventilation. Regarding the dynamics of PaCO_2 changes during the trial intervention, it seems likely that PaCO_2 values returned to baseline within several minutes after resetting the respirator to baseline parameters. In contrast, CBF and StiO_2 had not returned to baseline even 60 min after restoring normoventilation. However, since arterial blood gases were not available after the end of the hypercapnic period, the course of PaCO_2 and its correlation with the sustained elevation of CBF and StiO_2 cannot be drawn from the present data.

The optimal duration cannot be concluded from the present data. While the presented PaCO_2 values were measured at the end of a 15-min interval and constitute steady state values, dependent parameters like the pH or target parameters like CBF or StiO_2 may not have reached an equilibrium after 15 min. In addition, there may be significant interindividual variations. It has to be considered that CSF quickly acidifies during respiratory acidosis. The decline of pH in the CSF and the interstitial fluid has been shown to be the immediate factor governing the vasodilatory response of hypercapnia, subsequently increasing CBF [27–29]. However, buffer systems in the blood and CSF start to counteract the acidosis, leading to a decline of CBF after its maximum. At that time, a deleterious rebound effect below ischemic thresholds must be expected if the respirator is reset to baseline parameters [30]. Hence, therapeutic hypercapnia should ideally be terminated shortly before CBF leaves its maximum under constant hypercapnia. During hyperventilation in healthy humans, Raichle et al., for example, found a near-complete recovery of CBF after 4 h of constant *hypocapnia* [31]. Taking our own data into account and assuming that the adaptation to hyper- and hypocapnia occurs in a similar fashion, the ideal time point to terminate therapeutic hypercapnia will probably be after 30–180 min. This issue will be investigated in a further trial.

Conclusion

Graded temporary hypercapnia was easily applicable and could be safely performed under the prerequisite that a continuous CSF drainage buffered excessive increases of ICP. Therapeutic hypercapnia up to 60 mmHg resulted in a reproducible increase of CBF and StiO_2 . The present data suggest that the therapeutic approach may be further enhanced via a longer duration of hypercapnia which will be investigated in a further trial. The results of this Phase 1 trial are promising. However, the therapeutic potential of this non-pharmacological treatment to prevent secondary ischemic deficits after poor-grade aneurysmal SAH and improve neurological recovery finally has to be evaluated in a randomized trial.

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Compliance with Ethical Standards

Conflict of Interest None of the authors has a conflict of interest to declare.

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