Secondary ischemic events are a much-feared complication and the most important cause of in-hospital mortality and morbidity after aneurysmal subarachnoid hemorrhage (aSAH). A variety of drugs have been tested to enhance cerebral blood flow (CBF) after SAH, but none has shown a marked benefit with respect to the prevention of delayed cerebral ischemia (DCI) or secondary infarction and the improvement of neurological outcome. The arterial partial pressure of carbon dioxide (PaCO₂) is one of the major determinants of CBF regulation under physiological conditions. Experimental data suggest that this regulatory mechanism may be altered but still working after SAH. During delayed vasospasm of proximal intracranial vessel trunks, hyperventilation induces ischemia and infarction due to an additional constriction of small distal blood vessels and is associated with poor outcome after SAH. Hypercapnia, however, has not yet been tested for its ability to enhance CBF and prevent DCI after aSAH. This article reports on a study of controlled gradual hypercapnia and its potential to enhance CBF in a subset of patients with a particularly high risk of developing secondary cerebral ischemia after aSAH.

Controlled transient hypercapnia: a novel approach for the treatment of delayed cerebral ischemia after subarachnoid hemorrhage?

Clinical article

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Object. The authors undertook this study to investigate whether the physiological mechanism of cerebral blood flow (CBF) regulation by alteration of the arterial partial pressure of carbon dioxide (PaCO₂) can be used to increase CBF after aneurysmal subarachnoid hemorrhage (aSAH).

Methods. In 6 mechanically ventilated patients with poor-grade aSAH, the PaCO₂ was first decreased to 30 mm Hg by modification of the respiratory rate, then gradually increased to 40, 50 and 60 mm Hg for 15 minutes each setting. Thereafter, the respirator settings were returned to baseline parameters. Intracerebral CBF measurement and brain tissue oxygen saturation (S₉O₂), measured by near-infrared spectroscopy (NIRS), were the primary and secondary end points. Intracranial pressure (ICP) was controlled by external ventricular drainage.

Results. A total of 60 interventions were performed in 6 patients. CBF decreased to 77% of baseline at a PaCO₂ of 30 mm Hg and increased to 98%, 124%, and 143% at PaCO₂ values of 40, 50, and 60 mm Hg, respectively. Simultaneously, S₉O₂ decreased to 94%, then increased to 99%, 105%, and 111% of baseline. A slightly elevated delivery rate of cerebrospinal fluid was noticed under continuous drainage. ICP remained constant. After returning to baseline respirator settings, both CBF and S₉O₂ remained elevated and only gradually returned to pre-hypercapnia values without a rebound effect. None of the patients developed secondary cerebral infarction.

Conclusions. Gradual hypercapnia was well tolerated by poor-grade SAH patients. Both CBF and S₉O₂ reacted with a sustained elevation upon hypercapnia; this elevation outlasted the period of hypercapnia and only slowly returned to normal without a rebound effect. Elevations of ICP were well compensated by continuous CSF drainage. Hypercapnia may yield a therapeutic potential in this state of critical brain perfusion. Clinical trial registration no.: NCT01799525 (ClinicalTrials.gov).

Key Words • subarachnoid hemorrhage • hypercapnia • CBF • vasospasm • delayed cerebral ischemia • neuroprotection • vascular disorders

Abbreviations used in this paper: aSAH = aneurysmal SAH; CBF = cerebral blood flow; DCI = delayed cerebral ischemia; ICP = intracranial pressure; NIRS = near-infrared spectroscopy; PaCO₂ = arterial partial pressure of carbon dioxide; PaO₂ = arterial partial pressure of oxygen; SAH = subarachnoid hemorrhage; S₉O₂ = brain tissue oxygen saturation; TCD = transcranial Doppler sonography.
Hypercapnia in SAH

Methods

The study was approved by the University of Wuerzburg institutional ethics committee. The approval contained the explicit assignment of an intermediate analysis of the safety and effectiveness of the study intervention after it was applied in 4 cases. To detect a significant increase of CBF by an elevation of PaCO₂ from 40 to 50 mm Hg and from 40 to 60 mm Hg, a number of 6 patients was calculated. This calculation was based on the experimental data of Diringer et al.⁵ and Schmieder et al.²⁰ This Phase 1 clinical trial was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration number is NCT01799525.

Inclusion Criteria

The patients were included in the study on Day 4 after SAH. They were eligible for recruitment if they had suffered severe aSAH and had undergone placement of an external ventricular drainage device due to occlusive hydrocephalus as well as early treatment of the ruptured aneurysm (coiling or clipping) within the first 72 hours after rupture. The severity of aSAH was classified a) by the 5-grade clinical classification introduced by Hunt and Hess;¹² and b) by the 4-grade radiological classification of Fisher.⁷,⁸ Only patients of poor clinical grades (Hunt and Hess Grade III–V) and diffuse thick subarachnoid blood clots (Fisher Grade 3) with or without intraventricular or intracerebral hemorrhage were included in the study. As all patients who met the inclusion criteria were unable to give informed consent, the rapid appointment of a legal guardian was obtained, and this individual’s written consent was required for inclusion into the study.

Exclusion Criteria

Patients were not eligible for inclusion if they were under 18 years of age, suffered from chronic obstructive pulmonary disease, or had an intracranial pressure (ICP) of more than 20 mm Hg. The criteria to interrupt the trial intervention were an arterial pH value under 7.25, an ICP higher than 25 mm Hg for more than 2 minutes, and spontaneous breathing under controlled hypoventilation with constant analgesodation.

Respirator Settings

All patients were intubated and mechanically ventilated in a volume-controlled ventilation mode (SERVO-i, Maquet GmbH). Prior to the intervention, PaCO₂ values were kept within the normal range (36–44 mm Hg). Before the beginning of the PaCO₂ intervention, arterial blood gases were obtained for baseline. At first, the respiratory minute ventilation was increased by increasing the respiratory rate to reach a PaCO₂ level of 30 mm Hg. Subsequently, the respiratory rate and minute ventilation were reduced gradually in 15-minute intervals to reach target PaCO₂ values of 40, 50, and 60 mm Hg. Thereafter, the respirator settings were returned to baseline parameters to obtain normal PaCO₂ levels. Apart from the respiratory rate, all other respirator settings (tidal volume, inspiratory-expiratory ratio, and inspiratory fraction of oxygen) remained unchanged.

Arterial Blood Gases and Hemodynamic Parameters

A 15-minute period was allowed for equilibration between each modification. Arterial blood gases, hemoglobin, glucose, sodium, and potassium concentrations were measured by standard blood gas electrodes (RapidLab 700, Siemens Health Care). Heart rate, mean arterial blood pressure, and peripheral oxygen saturation were continuously monitored throughout the intervention period.

Monitoring of Cerebral Vasospasm and Cerebral Infarction

Transcranial Doppler sonography (TCD) of the intracranial vessel trunks was performed every day. For measurement of the internal carotid artery and the middle and anterior cerebral arteries, a temporal ultrasound window was used. For measurement of the basilar artery, a suboccipital ultrasound window was used. A mean flow velocity over 140 cm/sec in the anterior circulation and over 90 cm/sec in the basilar artery was considered indicative of cerebral vasospasm. CT and perfusion CT scans were performed at 3-day intervals to monitor for newly appearing hypodensities in the brain tissue representing secondary infarction and areas with perfusion deficits. In case of suspected vasospasm, the patients were transferred to the angiography suite for diagnostic angiography. If short-segment proximal vasospasm was detected, balloon dilation was performed. In case of diffuse peripheral vasospasm, pharmacological vasospasmolysis with nimodipine was performed.¹⁵

Target Parameters

Cerebral blood flow was measured by an intracerebral thermodilution probe (Q-Flow 500, Hemedex) positioned in the right frontal cortex 1.5 cm anterior to the external ventricular drain and was monitored by a Bowman Perfusion Monitor (Hemedex). Cerebral tissue oxygen saturation (S₅0₂) was measured by near-infrared spectroscopy (NIRS) (INVOS, Covidien). The probes were attached bilaterally on the forehead skin. At the beginning of each intervention, a baseline value was established, to which the following measurements were compared.

Protocol and Statistical Analysis

For the baseline value, and each further measurement point, CBF, ICP, S₅0₂, respiratory settings, arterial blood gas values, and hemodynamic parameters were written into an examination protocol. The values were transferred to electronic datasheets. Testing for normal distribution was performed by a D’Agostino-Pearson normality test. Since normality testing was not passed for all data columns and measurement points, a Friedman test was used for nonnormally distributed data; this was followed by post hoc testing using Dunn’s multiple comparison test. Statistical analyses were performed using GraphPad Prism 4.0 statistical software.

Results

All patients had suffered from SAH and had poor clinical grades. One patient was classified as Hunt and Hess Grade III, 3 patients as Grade IV, and 2 as Grade V.
All patients had thick diffuse subarachnoid blood clots, representing Grade 3 on the Fisher scale. Altogether, the trial intervention was performed 60 times in these 6 patients (Table 1).

Clinical and Radiological Course

All patients had developed early occlusive hydrocephalus and were treated with external ventricular drainage. According to the study protocol and ethics vote, the aneurysm was occluded within the first 3 days. None of the 6 patients regained appropriate consciousness for extubation and spontaneous ventilation, so anesthesia was continued and an intracerebral probe was placed for CBF measurement. Thus, these patients met the inclusion criteria for the study. Since the patient in Case 4 intermittently had ICP values above 20 mm Hg on Days 4 and 5 after SAH, the first trial intervention was performed on Day 6. Daily TCD showed a significant increase of mean flow velocity in each patient. In 5 of 6 cases the patients underwent additional angiographic examinations during the course of the hospital stay due to suspected vasospasm. The angiographic findings are presented in Table 2. Serial CT scans did not show evidence of secondary infarction in any of the patients.

Side Effects

Since all patients were being treated with external ventricular drainage prior to entry into the study and the device was kept open for continuous CSF drainage during the intervention, no patient experienced a relevant elevation of ICP. However, the potential elevation of ICP was reflected in a surplus drainage of CSF when PaCO\(_2\) was elevated to 50 and 60 mm Hg. During the decrease of PaCO\(_2\) from 30 mm Hg to 15 mm Hg, the CSF drainage was 2.2 ± 2.8 ml over 15 minutes. During the increase of PaCO\(_2\) to 40, 50, and 60 mm Hg, the CSF drainage was 4.4 ± 2.8 ml over 15 minutes, respectively; PaO\(_2\) was not markedly influenced by the alterations of the respiratory settings.

Ventilation and PaCO\(_2\)

The baseline PaCO\(_2\) was 39.1 ± 3.9 mm Hg at a respiratory minute ventilation of 7.8 ± 1.3 L/min. After increasing the respiratory rate and minute ventilation to 12.2 ± 2.0 L/min for 15 minutes, PaCO\(_2\) decreased to 32.1 ± 1.4 mm Hg. Thereafter, the respiratory minute ventilation was decreased in 15-minute intervals to 6.4 ± 1.5, 4.3 ± 1.0, and 2.9 ± 0.7 L/min, resulting in PaCO\(_2\) values of 41.1 ± 2.5, 50.1 ± 2.5, and 61.3 ± 4.0 mm Hg, respectively.

Cerebral Blood Flow

The mean baseline CBF measured in the right frontal lobe was 19.0 ml/100 g/min. Hypocapnia (PaCO\(_2\) 32.1 ± 1.4 mm Hg) resulted in a decrease of CBF to a mean of 15.1 ml/100 g/min (79% of baseline). Increasing PaCO\(_2\) to 41.1 ± 2.5, 50.1 ± 2.5, and 61.3 ± 4.0 mm Hg resulted in an increase of CBF to 18.7, 23.6, and 27.1 ml/100 g/min, respectively (98%, 124%, and 143% of baseline) (Fig. 1).

In 30 measurements, the course of CBF was followed for more than 1 hour after the termination of the trial interventions. In this subset of measurements, the mean baseline CBF was 17.3 ml/100 g/min. At PaCO\(_2\) values of 30, 40, 50, and 60 mm Hg, CBF was 13.0 (75% of baseline), 17.1 (99%), 21.0 (121%), and 24.8 (143%). Thereafter, the trial intervention was terminated, and the respiratory settings were returned to normal. At 15, 30, 45, and 60 minutes after the respirator was reset to baseline parameters (i.e., 75, 90, 105, and 120 minutes after initiation of the trial), the mean CBF was 24.9 (144%), 22.6 (131%), 20.6 (119%), and 19.3 (112%) (Fig. 2).

Cerebral Tissue Oxygenation

The baseline S\(_{\text{O}}\(_2\) measured by NIRS over the right forebrain was 67.0%. It decreased to 62.0% (93% of baseline) at a PaCO\(_2\) of 32.1 ± 1.4 mm Hg and increased to 65.9% (98% of baseline), 69.7% (104% of baseline), and 74.2% (111% of baseline) at PaCO\(_2\) values of 41.1 ± 2.5, 50.1 ± 2.5, and 61.3 ± 4.0 mm Hg (Fig. 3). At 15, 30, 45, and 60 minutes after resetting the respiratory settings, a S\(_{\text{O}}\(_2\) of 73.0% (109% of baseline), 70.8% (106% of baseline), 70.0% (104% of baseline) and 67.6% (101% of baseline) was measured (Fig. 4).

On the left side, the baseline S\(_{\text{O}}\(_2\) was 70.5%. It decreased to 66.3% (94% of baseline) at a PaCO\(_2\) of 32.1 ± 1.4 mm Hg and increased to 69.9% (99% of baseline), 73.9% (105% of baseline), and 78.1% (111% of baseline) at PaCO\(_2\) values of 41.1 ± 2.5, 50.1 ± 2.5, and 61.3 ± 4.0 mm Hg (Fig. 3). At 0.15, 30, 45, and 60 minutes after resetting the res-
pirator to baseline parameters, the mean $S_tO_2$ values were 77.5% (110% of baseline), 74.8% (106% of baseline), 73.0% (104% of baseline), and 71.3% (101%) (Fig. 4).

**Discussion**

The present data indicate that CBF and $S_tO_2$ can be enhanced by graded hypercapnia in patients with high-grade SAH. The effect outlasts the period of hypercapnia and does not turn into a rebound perfusion deficit. Measurements of CBF and $S_tO_2$ were conducted by thermodilution and transcutaneous NIRS, respectively. Measurement of the regional CBF by the thermodilution method is based on the temperature difference between a temperature input and a temperature measurement point. The difference decreases with higher CBF and has been validated by comparison with invasive measurement of brain tissue oxygen tension. NIRS measures the content of oxygenated hemoglobin in tissues and depends on arterial partial pressure of oxygen (PaO$_2$) on the one side and CBF on the other side. Transcutaneous NIRS measurement has been validated by comparison with xenon and perfusion CT. PaCO$_2$ was the only variable parameter in the present study. In particular, the arterial oxygen saturation and PaO$_2$ remained constant. We recorded a nonsignificant but marked difference between the left and right NIRS measurements, which is probably due to technical reasons.

**Table 2: Angiographic findings and neurological outcome**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Aneurysm Location</th>
<th>Repeat Angiography (time post-SAH)</th>
<th>Angiographic Findings/Interventions</th>
<th>Secondary Infarction (CT)</th>
<th>GOS Score (3 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>right MCA</td>
<td>Day 5, Day 12</td>
<td>PTA of left ICA, MCA, &amp; ACA</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>left ICA (choroid artery)</td>
<td>Day 9, Day 13</td>
<td>PTA of right ICA &amp; MCA</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>left ICA (PCoA)</td>
<td>Day 6</td>
<td>moderate peripheral spasms, spasmolysis w/ intraarterial nimodipine</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>ACoA</td>
<td>Day 9</td>
<td>PTA of left ICA, MCA, &amp; ACA</td>
<td>none</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>ACoA</td>
<td>Day 11</td>
<td>PTA of right ICA, MCA, ACA, &amp; BA</td>
<td>none</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>left MCA</td>
<td>—</td>
<td>—</td>
<td>none</td>
<td>4</td>
</tr>
</tbody>
</table>

* Due to repeat vasospasm, 5 of 6 patients underwent repeat angiography with the possibility of interventional treatment (balloon dilatation or pharmacological angioplasty). No patient suffered secondary cerebral infarction. ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; GOS = Glasgow Outcome Scale score (with 5 indicating no neurological deficit or low disability, 4 indicating moderate disability, and 3 indicating severe disability); ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; PTA = percutaneous transluminal angioplasty.

**Fig. 1.** Percent changes of intracerebral CBF measurement and the respective PaCO$_2$ values during the period of hypercapnia. The probe for CBF monitoring was placed into the right frontal lobe in the territory supplied by the right middle and anterior cerebral arteries. The decrease of PaCO$_2$ resulted in a concomitant reduction of CBF. Controlled hypercapnia resulted in an increase of CBF.

**Fig. 2.** Course of CBF during and after controlled hypercapnia. CBF remained elevated after resetting the respirator to baseline parameters and slowly returned to pre-hypercapnia levels without a negative rebound effect. *p < 0.05, ***p < 0.001 (all for comparison with baseline values). Resp. = respiratory.
arachnoid blood distribution over the frontal lobes might influence the transcranial NIRS measurement that reads the presence of hemoglobin. Apart from one right middle cerebral artery aneurysm (Case 1), all aneurysms in this series had domes directed to the left side causing a corresponding increase in subarachnoid blood on that side.

In the present study, the trial end points, CBF and brain tissue oxygenation (S$_{\text{O}_2}$), were gathered by measurements in only one or two points, respectively, which makes it susceptible to false-negative measurements. The CBF probe was placed into the border zone of the right middle and anterior cerebral arteries in an attempt to cover 2 vascular territories. The NIRS probes were placed bilaterally on the forehead over the territories supplied by the anterior cerebral artery. The CBF probe was placed in a noneloquent area. The placement of the NIRS probes was chosen on the basis of practical considerations; placement on the forehead does not require additional removal of hair and allows the probe to adhere to a broad and flat skin area. Since both CBF and S$_{\text{O}_2}$ measurement are regional measurements, a redistribution of blood in terms of a "steal phenomenon" into other territories that are not monitored cannot be excluded. Our measurements do not suggest a left-right shift since relative changes of bilateral NIRS measurements had an absolutely parallel course. In contrast, the fact that all PaCO$_2$ interventions resulted in an elevation of CBF and bilateral S$_{\text{O}_2}$ rather suggests that the elevation of PaCO$_2$ causes a global increase of brain perfusion and oxygen supply, even in the territory supplied by the most affected vessel and within the period of maximum vascular narrowing. Ideally, each vascular territory should be supplied with a probe, but this was not justifiable in this clinical study. Thus, it is possible that territories with reduced CO$_2$ reactivity may have been missed by the monitoring tools. In the 6 cases reported here, maximum elevations of flow velocities in TCD and maximum angiographic vessel narrowing were found in the territories supplied by the internal carotid arteries that were covered by the monitoring probes.

The CBF and bilateral NIRS measurements showed a concomitant decrease and increase during the period of hypercapnia as well as after the resetting of the respirator to baseline parameters. Therefore, it can be concluded that both monitoring tools—invasive CBF measurement as well as noninvasive transcutaneous NIRS—are suitable methods for following short-term changes of CBF. Both are methods of bedside monitoring and, in comparison with TCD or radiological examinations, allow continuous measurement of relative changes of CBF.

Several days after aSAH, a variety of local factors lead to contraction and finally to structural changes of the vessel wall.$^{11}$ However, arterial vasospasm seems not to be the only factor for the development of delayed cerebral ischemia (DCI) after aSAH. DCI can occur without significant cerebral vasospasm$^{2}$ and many patients with arterial vasospasm do not develop DCI.$^{12}$ Dreier et al.$^6$ and Pluta et al.$^{17}$ suggested a double-hit model of secondary ischemia in which ion disturbances and hypermetabolism are superimposed on arterial narrowing and, in combination, cause DCI. Although the etiology of DCI is not exactly known, all pathophysiological factors are likely to finally turn into a discrepancy between the supply and demand of oxygen in the brain. The CO$_2$ reactivity of CBF after SAH has been examined by several groups in experimental models and in SAH patients. In animal studies, Diringer et al. and Schmieder et al. demonstrated that the reactivity of CBF upon changes of PaCO$_2$ is still intact after SAH, whereas autoregulation on blood pressure changes is deranged after SAH.$^{1,20}$ Hassler and Chioffi found that downstream of segmental vasospasm, small peripheral vessels are in a compensatory state of near-maximum dilation. They concluded that the dilatational capacity of small blood vessels during hypercapnia is low and hyperventilation is hazardous because a contraction of peripheral vessels may rapidly cause ischemia in the presence of a spastic proximal vessel.

![Figure 3](image-url)  
**Fig. 3.** Percent changes of transcutaneous NIRS measurement during hypercapnia. NIRS probes were positioned bilaterally on the forehead. Controlled hypercapnia decreased at lower PaCO$_2$ values and increased during hypercapnia.

![Figure 4](image-url)  
**Fig. 4.** Brain tissue oxygen saturation remained elevated after hypercapnia. Similar to the course of CBF, values only gradually returned to baseline suggesting a sustained CBF-enhancing effect. *p < 0.05, **p < 0.01, ***p < 0.001 (all for comparison with baseline values).
Hypercapnia in SAH

Recently, Carrera and coworkers have reported on a clinical trial assessing the predictive value of various extents of CO$_2$ reactivity of CBF after aSAH. They found that the loss of normal CO$_2$ reactivity predicts a high risk for the eventual development of DCI. In that study, the end-tidal CO$_2$ was elevated 6 mm Hg by inhalation of an air-oxygen mixture enriched with 5% CO$_2$. The patients who showed only a small increase of CBF were more prone to develop DCI. In our study, hypercapnia was confirmed by arterial blood gas measurement. PaCO$_2$ was elevated by a mean of 22.0 mm Hg. All patients showed an increase of CBF and StiO$_2$ in each measurement after this high increase of PaCO$_2$. The therapeutic potential of hypercapnia to enhance CBF after SAH has not been evaluated in humans until now. Schatlo et al. reported no reactivity of CBF upon alterations of PaCO$_2$ in a primate study of experimental cerebral vasospasm. This is in discordance with our finding in human patients, as we observed reproducible increases of CBF and StiO$_2$ upon an elevation of PaCO$_2$ in all trial interventions, including the days of maximum flow velocities in TCD in all 6 patients (Fig. 5). The course of CBF and StiO$_2$ after the period of hypercapnia indicates that there is a sustained CBF-enhancing effect with a slow return to baseline values and without a rebound effect. The CBF-enhancing effect lasts much longer than the amount of time that would be expected for PaCO$_2$ to return to baseline values. This sustained effect may be mediated by the CSF pH. Buffer systems influence the CSF pH during the period of hypercapnia, leading to a slow adaptation to an elevated PaCO$_2$, and may, on the other hand, slow down the recovery of CSF pH. This could result in a delayed return of CBF to baseline. The period of hypercapnia was still relatively short in the present study, as it was the purpose of this study to assess in principle whether hypercapnia can be used to enhance CBF. The optimum duration and intensity of hypercapnia and especially whether longer periods of hypercapnia result in an even more sustained elevation of CBF still need to be investigated. The treatment may be optimized by a longer duration of hypercapnia. In theory, the ideal duration is until CSF starts decreasing again due to the action of buffer systems in blood and CSF. If this length of time is exceeded, a rebound effect can be expected after returning to baseline respirator settings. The next step, a trial assessing this critical time limit, is currently being conducted.

Although the study was planned with strict criteria for patient exclusion and trial termination, we did not have to interrupt a single PaCO$_2$ intervention or exclude any patient from the study after the beginning. The reproducible elevation of CBF and StiO$_2$, the sustained effect, and the obvious absence of negative side effects in patients who are being treated with external ventricular drainage for ICP compensation suggest a therapeutic potential of hypercapnia in patients with aSAH.

**Conclusions**

The controlled alteration of PaCO$_2$ by modification of the respiratory minute ventilation interferes with a very basic physiological regulatory mechanism. The intervention is easy to perform and arterial blood gas levels can be maintained on the basis of repeated arterial blood gas analyses. The present data show that it is safely feasible in SAH patients who are mechanically ventilated. Since increased intracranial blood volume can cause an elevation of ICP and thus may potentially be harmful, hypercapnia should not be induced without continuous CSF drainage or at least continuous ICP measurement. The enhancement of CBF and StiO$_2$ by this nonpharmacological
therapeutic approach of controlled hypercapnia is highly reproducible and sustained and might yield a high therapeutic potential in this state of critical brain perfusion.

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Disclosure

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