Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage

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Object. Hypervolemia and hypertension therapy is routinely used for prophylaxis and treatment of symptomatic cerebral vasospasm at many institutions. Nevertheless, there is an ongoing debate about the preferred modality (hypervolemia, hypertension, or both), the degree of therapy (moderate or aggressive), and the risk or benefit of hypervolemia, moderate hypertension, and aggressive hypertension in patients following subarachnoid hemorrhage.

Methods. Monitoring data and patient charts for 45 patients were retrospectively searched to identify periods of hypervolemia, moderate hypertension, or aggressive hypertension. Measurements of central venous pressure, fluid input, urine output, arterial blood pressure, intracranial pressure, and oxygen partial pressure (PO$_2$) in the brain tissue were extracted from periods ranging from 1 hour to 24 hours. For these periods, the change in brain tissue PO$_2$, and the incidence of complications were analyzed.

During the 55 periods of moderate hypertension, an increase in brain tissue PO$_2$ was found in 50 cases (90%), with complications occurring in three patients (6%). During the 25 periods of hypervolemia, an increase in brain oxygenation was found during six of the intervals (24%), with complications occurring in nine patients (36%). During the 10 periods of aggressive hypervolicmic hypertension, an increase in brain oxygenation was found during six of the intervals (60%), with complications in five patients (50%).

Conclusions. When hypervolemia treatment is applied as in this study, it may be associated with increased risks. Note, however, that further studies are needed to determine the role of this therapeutic modality in the care of patients with cerebral vasospasm. In poor-grade patients, moderate hypertension (cerebral perfusion pressure 80–120 mm Hg) in a normovolemic, hemodiluted patient is an effective method of improving cerebral oxygenation and is associated with a lower complication rate compared with hypervolemia or aggressive hypertension therapy.

KEY WORDS • subarachnoid hemorrhage • cerebral vasospasm • hypervolemia hypertension hemodilution therapy

Hypertension, hypervolemia, hemodilution therapy refers to the hyperdynamic protocol used at many institutions for the prophylaxis and treatment of symptomatic cerebral vasospasm. Note, however, that there is ongoing debate about the indication (prophylactic or therapeutic), modality (hypervolemia, hypertension, or both), degree (moderate or aggressive), and risk/benefit ratio of HHH in patients following SAH.

Analysis of available data is complicated by the variability in applying the treatment clinically. In a recent trial in patients with aneurysmal SAH, prophylactic HHH was used in 59 to 75% of all patients, although the modalities of HHH were applied differently: hypervolemia in 50 to 69%, hypertension in 24 to 29%, and hemodilution in 35 to 43%. Likewise, therapeutic HHH was instituted in 24 to 34% of patients; that is, hypervolemia was used in 18 to 31%, hypertension in 12 to 23%, and hemodilution in 14 to 16% of these patients.

In two recent trials, prophylactic hypervolemia and hypertension produced no clinical benefit and were associated with a higher rate of complications and increased costs. No author has yet compared the different treatment modalities and the degree of therapy in regard to the effect on cerebral circulation and the complication rate. Nonetheless, such data are clinically important given that HHH is currently used in a variety of ways for which its effectiveness has been questioned. Moreover, HHH can be potentially harmful and is associated with a complication rate of 20 to 30%.

In the present study, we investigated in 45 patients with SAH and angiographically verified cerebral vasospasm the effects of hypervolemia and hypertension on brain tissue PO$_2$, which was used to evaluate brain oxygenation. Our ob-

Abbreviations used in this paper: ABP = arterial blood pressure; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CT = computed tomography; CVP = central venous pressure; HHH = hypertension, hypervolemia, hemodilution therapy; ICP = intracranial pressure; ICU = intensive care unit; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; SSEP = somatosensory evoked potential; TCD = transcranial Doppler.
Objective was to compare the efficacy of hypervolemia, moderately induced arterial hypertension, and aggressively induced arterial hypertension to increase brain tissue PO$_2$ and to analyze the complication rates associated with each of these treatment modalities.

Clinical Material and Methods

Study Population

Between January 1999 and July 2003, 419 patients of all clinical grades (Hunt and Hess Grades I–V) were admitted to our hospital for the treatment of aneurysmal SAH. The assigned Hunt and Hess Grade in 198 patients was poor (Grades IV–V) and in 221 was good (Grades I–III). All patients were treated according to a standardized protocol. A ventricular drain was placed in patients with Hunt and Hess Grades IV and V and in those with hydrocephalus and Hunt and Hess Grade III. Whenever possible, surgery (75% of patients) or coil embolization (25% of patients) was performed within 72 hours of hemorrhage. Symptomatic cerebral vasospasm developed in 28 good-grade patients (13% of all good-grade patients) and 84 poor-grade patients (42% of all poor-grade patients). All patients received nimodipine (Nimotop; Bayer, Leverkusen, Germany) and underwent a stepwise protocol of HHH (Fig. 1). Invasive monitoring of brain tissue oxygenation was performed in patients who were not able to cooperate for an adequate neurological assessment, for example, poor-grade patients (Hunt and Hess Grade IV) or those with a Hunt and Hess Grade I to III (24 patients) in whom intubation and analgosedation was required for complications and clinical deterioration.

A tissue oxygenation probe was inserted either after aneurysm application or at the time of clinical deterioration and intubation of the patient. Exclusion criteria for HHH consisted of established cerebral infarction, tentorial herniation, intracerebral hemorrhage, brain edema causing a medically refractory ICP increase greater than 25 mm Hg, pulmonary edema, congestive heart failure, and myocardial infarction. All patients with a World Federation of Neurosurgical Societies Grade V (25 patients) met the exclusion criteria for HHH (for example, tentorial herniation, intracerebral hemorrhage, or brain edema causing a medically refractory ICP increase > 25 mm Hg); thus, they were not included in our study. Patients in whom there was a technical defect of the brain tissue oxygenation probe (three patients) or in whom dislocation of the probe occurred during transportation or nursing (five patients) were also excluded. Another 10 poor-grade patients were treated with HHH but without a tissue oxygenation probe.

Data were collected prospectively in 45 patients with reliable brain tissue PO$_2$ measurements; 29 patients were fe-
Figure 2. Boxplot showing the association between the change in CPP when performing moderate hypertension with a target value of 80 to 120 mm Hg. The values of the x axis indicate the increase in CPP achieved during hypertension therapy, and the y axis indicates the change in brain tissue oxygenation. The increase in brain tissue PO₂ is greatest when increasing CPP more than 20 mm Hg. N = number of periods of moderate hypertension.

It was part of our basic protocol strictly to avoid hypovolemia and hypotension and to maintain normovolemia and normotension. Likewise, the hematocrit value was checked daily for abnormalities, that is, those levels less than 0.30 and greater than 0.45. After starting the specified treatment, hematocrit was kept between 0.25 and 0.40 in all patients regardless of whether we performed hypervolemia, moderate hypertension, or aggressive hypertension. This factor is important because differences in hemodilution among the treatment groups would make the interpretation of the findings very difficult.

The first step of HHH was usually induced hypertension to achieve a CPP of more than 80 mm Hg but less than 120 mm Hg. We did not include hypervolemia at this step because we believe that normovolemia in the high-normal range (CVP ≥ 5 mm Hg) provides an acceptable intravascular volume state for the administration of vasopressor agents. Induced hypertension was started with 5 to 12 μg/kg/min dopamine and, if necessary, supplemented with 0.1 to 0.5 μg/kg/min norepinephrine to maintain a mean CPP between 80 and 120 mm Hg. If moderate hypertension failed to improve clinical vasospasm, tissue oxygenation, or SSEP amplitude or latency or if the patient already had a CPP between 80 and 120 mm Hg, aggressive hypertension was induced by increasing the dose of vasopressor agents to raise the mean CPP to greater than 120 mm Hg. Systolic pressures of more than 220 mm Hg were avoided.

Alternatively, in cases of a poor response to catecholamines (CPP < 120 mm Hg with reasonable catecholamine doses), the patient was included in the hypervolemia group. The target of hypervolemia was a CVP of 10 mm Hg or greater by using crystalloid agents, hydroxyethyl-starch to a maximum of 1000 ml/day, erythrocytes and, rarely, albumin. We are aware that CVP is not an adequate assessment of volume status. Nonetheless, it is widely used in the clinical care of patients with SAH and in prospective studies of hypervolemia.

The goal of intervention was to increase focal tissue oxygenation to a value of more than 10 mm Hg, which is the reported ischemic threshold for the frontal white matter at a depth of 22 to 27 mm when using an oxygenation probe. All patients underwent CT scanning between 24 and 72 hours after treatment and on Day 14 post-SAH to distinguish between infarctions caused by treatment and those caused by cerebral vasospasm.

Data Acquisition

Monitoring of brain tissue oxygenation was performed using a tissue oxygenation probe (Licox; GMS, Kiel, Germany) implanted in the white matter in the territory of the aneurysm’s parent vessel (middle cerebral artery: 1 cm in front of the coronal suture, 6 cm paramedian; anterior cerebral artery: 1 cm in front of the coronal suture, 2 cm paramedian).

Real-time analog signals from tissue oxygenation monitoring, ABP, and ICP were collected, averaged every 2 seconds, and digitized using an AD converter card (DC DT-300; Data Translation, Marlboro, CA). Multimodal monitoring software (BioSan, Biological Signal Analyzer, P. Smielewski, M. Czosnyka, Cambridge, United Kingdom) was used for data storage and online or offline analysis (time resolution 0.5 Hz).
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Outcome Measures

The primary indication of the treatment effect was the change in cerebral oxygenation occurring during the different components and intensities of HHH. Secondary outcome measures included the occurrence of medical and neurological complications, the occurrence of cerebral infarctions caused by vasospasm, and the patient outcome according to the mRS 6 months after SAH.

Data Analysis

The multimodal monitoring data and patient charts were retrospectively searched to identify the time point at which moderate hypertension, aggressive hypertension, or hypervolemia commenced. Measurements of CVP, fluid input, urine output, ABP, ICP, and brain tissue PO2 were extracted from periods ranging from 1 hour to 24 hours. For these periods, the change in cerebral oxygenation was analyzed during a moderate CPP increase (moderate hypertension), a further increase in CPP during aggressive hypertension, and hypervolemia treatment. Side effects and complications that occurred during these treatment periods were registered from each patient’s daily assessment and complications record, which is a separate data sheet that must be filed daily for all patients during their stay in the ICU.

The associations between continuous variables were analyzed using the Pearson correlation coefficient. Continuous variables were compared using two-tailed t-tests, and proportions were compared using the chi-square or Fisher exact test. Significance was reached at a probability level less than 0.05.

Results

Ninety periods of induced moderate hypertension, aggressive hypertension, or hypervolemia were analyzed in 45 patients. We identified 55 periods of moderate hypertension, 10 of aggressive hypertension, and 25 of induced hypervolemia therapy.

Moderate Hypertension Therapy

During the 55 periods of moderate hypertension (38 patients, one–three periods per patient), an increase in brain tissue PO2 (median 6 mm Hg, interquartile range 3–10 mm Hg) occurred in 50 cases (90%). There was a significant correlation between the change in brain oxygenation and the difference in CPP (CPPduring moderate hypertension – CPPbefore moderate hypertension). The treatment effect was less pronounced when CPP was increased less than 20 mm Hg (p < 0.05). When plotting the change in brain tissue PO2 as a function of CPP change, moderate hypertension treatment was found to be more effective when CPP had been increased more than 20 mm Hg (Fig. 2). There was no correlation between brain tissue PO2 and the absolute values of CPP before or after treatment.

The positive effect on brain oxygenation was more frequent in cases with low brain tissue PO2 (< 15 mm Hg), which indicated ischemia in the territory of the implanted oxygenation probe (Fig. 3). In these cases an increase in tissue oxygenation was found in 29 (97%) of 30 periods compared with 18 (72%) of 25 periods in cases with a brain tissue PO2 of 15 mm Hg or more (p < 0.05, Fisher exact test).

Complications of moderate hypertension therapy were observed in three patients (8%); hyponatremia developed in one patient and cardiac arrhythmia in the other two patients.

Aggressive Hypertension Therapy

During the 10 periods of aggressive hypertension (10 patients, one period per patient), an increase in brain tissue oxygenation occurred during six (60%). Tissue oxygenation increased between 2 and 9 mm Hg (median 4 mm Hg). There was no association between the relative increase in CPP and the change in brain tissue PO2 (p = 0.76). Complications of aggressive hypertension were observed in five patients (50%), with multiple complications in all cases. Pulmonary fluid overload occurred in two cases, pulmonary edema and hyponatremia in one case each, cardiac arrhythmia and brain edema in two cases each, and sepsis in three cases.

Hypervolemia Therapy

During the 25 periods of hypervolemia (17 patients, one–two periods per patient), an increase in brain oxygenation was demonstrated during three (12%). In these three cases, tissue \(O_2\) increased between 3 and 5 mm Hg. Complications of hypervolemia were observed in nine patients (53%), with multiple complications in six. Pulmonary fluid overload occurred during eight periods of hypervolemia, pulmonary edema during three, hyponatremia during three, cardiac arrhythmia during three, congestive heart failure during two, and brain edema during two.

Vasospastic Cerebral Infarctions and Outcome

Using our stepwise treatment protocol, the rate of vasospastic cerebral infarctions in this high-risk group of most-
ly poor-grade patients with angiographically proven vasospasm was greater than 50%, and impending cerebral ischemia was 36% (16 of 45 patients). Patients without cerebral infarction had a favorable outcome (mRS 0–2) in 13 cases (45%) and an unfavorable outcome (mRS 3–6) in 16 cases (55%). Patients with cerebral infarctions had a favorable outcome (mRS 0–2) in four cases (25%) and an unfavorable outcome (mRS 3–6) in 12 cases (75%).

**Discussion**

**Fundamental Issues of HHH**

The use of HHH in patients with cerebral vasospasm is based on the following assumptions: 1) cerebral ischemia induced by vasospasm can be prevented or reversed by increasing CBF; 2) HHH increases CBF by elevating cardiac output or CVP or decreasing viscosity, or a combination of these factors; 3) the benefits of increased CBF outweigh the risks of adverse effects such as fluid overload, cardiac failure, and pulmonary or cerebral edema.

There are many reports in the literature that HHH instituted at the first sign of clinical vasospasm is effective in improving CBF and reversing delayed neurological deficits. Nonetheless, there are critical comments on the benefits of HHH, especially regarding the role of hypervolemia. Moreover, an analysis of clinical trials of HHH revealed that only a few prospective and comparative studies have been focused on the question of this therapy’s efficacy or harm, that there are major limitations related to inadequate internal and external validity of these trials, and that there are only small study samples for randomized controlled trials.

**Role of Hypervolemia**

There are conflicting results in the literature: both increases and decreases in CBF have been reported after hypervolemia therapy. Origiano, et al., reported an increase in CBF after instituting hypervolemia therapy shortly after admission for SAH. Note, however, that these authors did not measure the baseline volume status in their patients, who may have been hypovolemic before treatment. Another report about an increase in CBF during hypervolemia therapy, Egge, et al., described in the report of Kassel, et al., further discussed by others. It is often difficult to raise the pulmonary capillary wedge pressure to 14 mm Hg or the CVP to greater than 5 mm Hg in patients who do not have cardiac or renal disease, no matter how much fluid is given. Until now, there has been no report on the failure rate in trying to achieve sustained hypervolemia and hypertension.

**Complications of HHH**

The adverse effects most often reported for HHH include fluid overload (10–40%), pulmonary edema (2–34%), congestive heart failure (5–20%), cardiac arrhythmias (5%), and aggravation of brain edema (8–20%). But hypertensive encephalopathy, hemorrhagic infarction, hypoxia, rebleeding, coagulopathy, myocardial infarction, hemothorax, and intraabdominal bleeding also have been observed. In these studies, a relationship between the degree of therapy and the occurrence of adverse effects has been assumed.

Complications also occur during prophylactic HHH. In the only prospective, randomized trial on normotension/normovolemia compared with prophylactic hypertension/hypervolemia therapy, Egge, et al., included 16 patients in each treatment arm and compared clinical outcomes, clinically evident and TCD ultrasonography–proven vasospasm, single-photon emission computerized tomography findings, complications, and costs. These authors found no difference between the two treatment groups with respect to cerebral vasospasm or regional CBF. One-year postintervention clinical follow-up data, including patient outcome, single-photon emission computerized tomography findings, complications, and costs. These authors found no difference between the two treatment groups with respect to cerebral vasospasm or regional CBF. One-year postintervention clinical follow-up data, including patient outcome, single-photon emission computerized tomography findings, and neuropsychological function results, demonstrated no significant group differences. Note, however, that costs were higher and complications occurred more frequently in the prophylactic hypertension/hypervolemia treatment group.

Authors of recent studies have shown a decrease in treatment-related complications when using a protocol focusing on normovolemia and cardiac output enhancement.
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This therapeutic approach has been verified to be effective\(^a\) and may play a greater role in future concepts of the hemodynamic treatment of patients with cerebral vasospasm.

**Interpretation of Study Findings**

In this study, moderate hypertension induced in a normovolemic patient yielded the highest rate of improvement of cerebral oxygenation (90%) and was associated with the lowest rate of complications (8%). This risk/benefit ratio is very acceptable in the context of a symptomatic patient with cerebral vasospasm. The degree of therapy necessary to achieve the greatest increase in cerebral oxygenation involved a rise in CPP of approximately 20 to 30 mm Hg, which can be used as a target value. Nevertheless, we recommend monitoring CBF or tissue oxygenation in these situations to tailor therapeutic intensity in an individual patient. Aggressive hypertension treatment may help to increase brain oxygenation in approximately 60% of cases in which moderate hypertension has failed. Note, however, that the risk/benefit ratio is approximately 1 and the decision to use aggressive hypertension should be made only when the clinical situation justifies taking a higher risk, for example, in young good-grade patients.

Hypervolemia alone carries the highest risk with the lowest benefit for the patient. We must emphasize, however, that only periods with an increase in the fluid load and an increase in CVP greater than 10 mm Hg without a concomitant rise in blood pressure were included in our analysis. This is a critical point when analyzing studies that have demonstrated an increase in CBF with hypervolemia. One could argue that increasing blood pressure is part of the treatment goal when using hypervolemia; however, this part of the goal confounds the nomenclature and increasing blood pressure can be achieved with higher efficacy and fewer complications by using catecholamines.

Although it is part of the term HHH and often referred to when analyzing the physiological principle of this therapy, hemodilution requires specific measures less often to achieve a hematocrit value in the therapeutic range. In our ICU (all 45 patients included in our study were poor-grade patients treated in the ICU), we were especially careful to avoid hypovolemia and every patient was treated with fluid loading to maintain or reestablish normovolemia in the high-normal range. This strategy may be one reason for our finding that we were within the therapeutic target range for hemodilution in the three treatment groups after initiating hypertension or hypervolemia. This result is in agreement with our previous finding that it is rarely necessary to institute specific measures to achieve hemodilution beyond those for maintaining normovolemia or performing hypertension or hypervolemia therapy. To interpret our study results, it is important to know that there was no difference in hemodilution between the groups.

**Study Limitations**

The major limitations of this study consist of the retrospective design and the stepwise protocol without randomization of patients into the three different treatment arms. The stepwise protocol left for the next treatment modality (aggressive hypertension and/or hypervolemia) those patients whose condition did not improve through moderate hypertension. It is likely that these patients represent the more severe cases with a higher rate of treatment failure, despite the underestimation of the success rate and, probably, an overestimation of the complication rate of aggressive hypertension and hypervolemia. Nevertheless, we believe that these limitations do not affect the main study findings and the subsequent conclusions because no patient had experienced a complication when we started hypervolemia or aggressive hypertension, and because the amount of time a patient was treated with hypervolemia (median 4 days) or aggressive hypertension (median 5 days) was less than that for moderate hypertension (median 8 days).

Although the measurement of focal brain tissue oxygenation may provide a useful tool for assessing the effect of therapeutic interventions,\(^b\) there are limitations in the methodology of single-probe determination of brain tissue oxygenation. First, white matter tissue PO\(_2\), monitoring is a local monitoring technique. Heterogeneity is important, although measurement values are regarded as being less heterogeneous in the white matter than in the gray matter.\(^c\) Therefore, one should not place too much emphasis on the absolute values of brain tissue PO\(_2\), and attempts to identify an exact critical threshold value of brain tissue PO\(_2\), should be viewed with caution. Second, the presence of microhemorrhages around the oxygenation probe may influence the values measured.\(^d\) We therefore recommend routine CT studies of the position of the PO\(_2\) sensor. The catheter itself shows a negligible zero drift and a low sensitivity drift.\(^e\) With these limitations in mind, if one inserts the O\(_2\) probe in an undamaged area of the brain after SAH and if local complicating factors are absent, the recorded values can be considered representative of the territory of the vessel in spasm while taking the known heterogeneity of brain oxygenation into account.\(^f\)

**Conclusions**

When hypervolemia treatment is applied as in our protocol, it may be associated with increased risks. Nonetheless, further studies are needed to determine its role in the care of patients with cerebral vasospasm. In poor-grade patients, moderate hypertension (CPP 80–120 mm Hg) in a normovolemic, hemodiluted patient is an effective method of improving cerebral oxygenation and is associated with a lower complication rate compared with hypervolemia therapy or aggressive hypertension therapy.

**References**


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