Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage*

Elke Muench, MD; Peter Horn, MD; Christian Bauhuf, MD; Harry Roth, MD; Mark Philipps, MD; Peter Hermann, DrScHum; Michael Quintel, MD, PhD; Peter Schmiedek, MD; Peter Vajkoczy, MD

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Define "triple-H" therapy.
2. Explain the usefulness of triple-H therapy.
3. Use this information in a clinical setting.

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Objective: **Hypertensive, hypervolemic, hemodilution therapy (triple-H therapy) is a generally accepted treatment for cerebral vasospasm after subarachnoid hemorrhage. However, the particular role of the three components of triple-H therapy remains controversial. The aim of the study was to investigate the influence of the three arms of triple-H therapy on regional cerebral blood flow and brain tissue oxygenation.**

Design: **Animal research and clinical intervention study.**

Setting: **Surgical intensive care unit of a university hospital.**

Subjects and Patients: **Experiments were carried out in five healthy pigs, followed by a clinical investigation of ten patients with subarachnoid hemorrhage.**

Interventions: **First, we investigated the effect of the three components of triple-H therapy under physiologic conditions in an experimental pig model. In the next step we applied the same study protocol to patients following aneurysmal subarachnoid hemorrhage. Mean arterial pressure, intracranial pressure, cerebral perfusion pressure, cardiac output, regional cerebral blood flow, and brain tissue oxygenation were continuously recorded. Intrathoracic blood volume and central venous pressure were measured intermittently. Vasopressors and/or colloids and crystalloids were administered to stepwise establish the three components of triple-H therapy.**

Measurements and Main Results: **In the animals, neither induced hypertension nor hypervolemia had an effect on intracranial pressure, brain tissue oxygenation, or regional cerebral blood flow. In the patient population, induction of hypertension (mean arterial pressure 143 ± 10 mm Hg) resulted in a significant ($p < .05$) increase of regional cerebral blood flow and brain tissue oxygenation at all observation time points. In contrast, hypervolemia/hemodilution (intrathoracic blood volume index 1123 ± 152 mL/m^2) induced only a slight increase of regional cerebral blood flow while brain tissue oxygenation did not improve. Finally, triple-H therapy failed to improve regional cerebral blood flow more than hypertension alone and was characterized by the drawback that the hypervolemia/hemodilution component reversed the effect of induced hypertension on brain tissue oxygenation.**

Conclusions: **Vasopressor-induced elevation of mean arterial pressure caused a significant increase of regional cerebral blood flow and brain tissue oxygenation in all patients with subarachnoid hemorrhage. Volume expansion resulted in a slight effect on regional cerebral blood flow only but reversed the effect on brain tissue oxygenation. In view of the questionable benefit of hypervolemia on regional cerebral blood flow and the negative consequences on brain tissue oxygenation together with the increased risk of complications, hypervolemic therapy as a part of triple-H therapy should be applied with utmost caution. (Crit Care Med 2007; 35:1844–1851)**

KEY WORDS: subarachnoid hemorrhage; triple-H therapy; hypertension; hemodilution; vasospasm

Aneurysmal subarachnoid hemorrhage (SAH) is a potentially disastrous illness that leads to severe disability and a high mortality rate. One of the most important determinants of outcome after SAH is delayed cerebral ischemia from vasospasm (1–3). Studies of cerebral blood flow (CBF) showed that cerebral vasospasm is associated with reduced CBF (4–7). Experimental and clinical studies suggest that changes in CBF are coupled to changes in oxygen delivery so that cerebral hypoperfusion leads to inadequate oxygen delivery capacity (8–11). More than 20 yrs ago, hypertensive, hypervolemic, hemodilution therapy was introduced into clinical care. The so-called "triple-H" therapy improves cerebral perfusion, because the only way to increase blood flow through the narrowed vessels is to increase perfusion pressure or to decrease blood viscosity. Several studies described the effectiveness of triple-H therapy for preventing neurologic deficits due to cerebral vasospasm (6, 12–15). However, the efficacy of triple-H therapy has not been proven in controlled trials. Furthermore, triple-H therapy has serious side effects, such as pulmonary edema and cardiac arrhythmias. Particularly elderly patients with poor cardiac reserve may not tolerate induced hypertension with vasopressor agents or volume loading (16). Nevertheless, triple-H therapy is widely accepted in the clinical management of patients after SAH, mainly because of the lack of alternative treatment options.

It is unclear which components of the triple-H therapy are crucial for the treatment of cerebral hypoperfusion and hypoxia. Studies investigating the efficacy of the three arms of triple-H therapy in treating cerebral hypoperfusion are rare. Recent studies have shown that hypervolemia may carry more risks than benefits (16, 17).

In consideration of the fact that each component of the triple-H therapy is associated with major medical complications, the effectiveness of the individual arms of triple-H therapy on cerebral perfusion and oxygenation has to be evaluated. Therefore, we undertook the present study to investigate the efficacy of catecholamine-induced arterial hypertension, hypervolemia/hemodilution, and hypervolemic arterial hypertension on intracranial pressure (ICP), regional CBF (rCBF), and brain tissue oxygenation ($Ptio_2$). In the first part of the study, multimodal monitoring was performed in a healthy porcine model under physiologic conditions, serving as a control with preserved cerebral autoregulation. In the second part of the study, the experimental protocol was transferred to the clinical setting and the three components of triple-H therapy were investigated in patients after aneurysmal SAH.

MATERIALS AND METHODS

Experimental Part

Animal Preparation. The study was approved by the animal care and use committee of the local government authorities. Experiments were performed in five healthy female pigs (34.6 ± 2.3 kg of body weight), and animal preparation was described previously in detail (18). In brief, anesthesia was induced using ketamine and midazolam and was maintained by fentanyl and midazolam. Neuromuscular paralysis was achieved by vecuronium bromide. Animals were tracheotomized and ventilated in a volume control mode, adjusted to yield a $Paco_2$ of 35–40 mm Hg. Fio_2 was set to 0.4. Positive end-expiratory pressure was set to 5 cm H_2O. After the animal was placed in the supine position, a central venous catheter, an arterial catheter, and a thermistor catheter (Pulsiocath PV 2014L13; Pulsion Medical Systems, Munich, Germany) were placed. Mean arterial blood pressure (MAP) was continuously monitored, and cerebral perfusion pressure (CPP) was calculated according to the following equation: CPP = MAP − ICP. Body temperature was maintained between 36°C and 37°C. A crystalloid solution (5 mL/kg of body weight/hr) was given continuously. The animals were turned to the prone position, and an intraparenchymal sensor for ICP measurement (Codman, Raynham, MA), a polarographic microprobe for $Ptio_2$ recordings (Licox, Kiel, Germany), and a thermal diffusion rCBF microprobe (Hemedex, Cambridge, MA) were placed intracerebrally.

Clinical Part

Patient Population. The prospective observational study was approved by the local research ethics committee and institutional review board. Ten patients with aneurysmal SAH were enrolled in the study. Inclusion criteria consisted of age 18–75 yrs, SAH grade II–V according to the Hunt and Hess classification (19) and grade III according to the Fischer scale (20), surgical clip occlusion of a ruptured saccular aneurysm, and informed consent obtained from the patient or their relatives.

Exclusion criteria were congestive heart failure, electrocardiographic abnormalities, pulmonary complications, and renal insufficiency. All patients underwent surgical clipping of their anterior circulation aneurysms on the day of their bleeding. An internal jugular venous catheter and a radial artery catheter were placed directly after admission for administration of drugs and blood pressure control. A 4-Fr thermistor catheter (Pulsiocath PV 2014L13) was placed in one femoral artery for extended hemodynamic monitoring. At the time of surgery, an external ventricular catheter was implanted in all patients. Microprobes to measure subcortical rCBF (21) and $Ptio_2$ (22) were inserted into the vascular territory at risk for developing cerebral vasospasm, defined as the ipsilateral middle cerebral artery territory in patients with a middle cerebral artery or internal carotid artery aneurysm and in the right anterior communicating artery territory in the case of an anterior communicating artery aneurysm. Thereafter, correct probe position was documented by computed tomography (CT) scanning, and a stable xenon CT was performed to validate the rCBF measurements (21, 23). All patients were maintained in 30° head-up position and were treated according to a standard treatment protocol, which includes sedation with midazolam and fentanyl and ventilation in a volume control mode with tidal volume of 6–7 mL/kg of body weight. Positive end-expiratory pressure was set to 5 cm H_2O, and respiration rate was adjusted to maintain a $Paco_2$ of 35–40 mm Hg.

***See also p. 1985.**

Consultant, Intensive Care Medicine, Department of Anesthesiology, University Hospital Mannheim, Mannheim, Germany (EM); Neurosurgeon, Department of Neurosurgery, Klinikum Eppendorf, University of Hamburg, Germany (P Horn); Neurosurgeon, Department of Neurosurgery, Krankenhaus Barmherzige Brüder, University of Regensburg, Germany (CB); Director, Department of Anesthesiology and Intensive Care, Community Hospital, Erbach, Germany (HR); Neurosurgeon, Department of Neurosurgery, Johannes-Gutenberg University, Mainz, Germany (MP); Medical Bioengineer, Department of Anesthesiology and Intensive Care Medicine, University of Göttingen, Germany (P Hermann); Professor Dr. Medicine, Director of Anesthesiology II—Operative Intensive Care Medicine, University of Göttingen, Göttingen, Germany (MQ); Professor and Director, Department of Neurosurgery, University Hospital Mannheim, Mannheim, Germany (PS); Professor and Director, Department of Neurosurgery, Charité University of Medicine, Berlin, Germany (PV).

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Address requests for reprints to: Elke Muench, MD, Department of Anesthesiology and Critical Care Medicine, Klinikum Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, D-68167 Mannheim, Germany. E-mail: elke.muench@t-online.de

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Definition of Vasospasm

Transcranial Doppler sonography was performed daily over the temporal bone windows. If mean blood flow velocity was >120 cm/sec or increased by >50 cm/sec within 24 hrs, stable xenon-enhanced CT study and cerebral angiography were performed. In case of negative transcranial Doppler studies, a stable xenon-enhanced CT study and a cerebral panangiography were routinely performed on day 7 after bleeding. In neurologically assessable patients, vasospasm was defined as delayed ischemic neurologic deficit combined with a stable xenon-enhanced CT study and angiographically verified vasospasm. In comatose or sedated patients, the definition of vasospasm was based only on the stable xenon-enhanced CT study and cerebral angiography. A hemodynamic relevant vasospasm was defined by an angiographic vessel narrowing >33% in comparison with baseline angiography and a mean cerebral blood flow of <32 mL/100 g/min measured by stable xenon CT.

Study Protocol

First, we investigated the effect of the three components of triple-H therapy on regional cerebral blood flow and oxygen supply under physiologic conditions in an experimental pig model. In the next step we applied the same study protocol to patients following aneurysmal SAH. In the latter setting, the study protocol was applied on days 1, 3, and 7 after bleeding. After induction of anesthesia and a 30-min accommodation period, baseline recordings of MAP, ICP, CPP, $Ptio_2$, rCBF, end-tidal CO_2 tension, cardiac output, intrathoracic blood volume index (ITBVI), extravascular lung water index (EVLWI), cardiac index (CI), cardiac function index (CFI), central venous pressure (CVP), and blood gases were performed. ICP, CPP, $Ptio_2$, rCBF, end-tidal CO_2 tension, and cardiac output were continuously recorded with a sampling rate of 10 Hz and were calculated by averaging the data samples acquired over 90 secs after each stabilization period. Blood gases, ITBVI, EVLWI, CI, CFI, and CVP were measured intermittently.

Following the baseline recordings, hypertension was induced by norepinephrine infusion to achieve a MAP >130 mm Hg. Regional CBF, ICP, and $Ptio_2$ recordings as well as hemodynamic measurements were recorded after monitoring variables had stabilized. Following induced hypertension, norepinephrine infusion was terminated. When normotension was reestablished and all other hemodynamic and cerebral variables returned to baseline values, hypervolemia/hemodilution was induced by infusion of hydroxyethyl-starch (1000 mL) and crystalloids (1000–3000 mL) to achieve the target ITBVI of >1000 mL/m^2. Hemodilution was passively achieved through volume expansion when hypervolemia was established. Monitoring of hemodilution was accomplished with repeated blood samples at baseline and after induction of hypervolemia and hypertension to check the hemoglobin values. Measurements were taken after a 10-min stabilization period. To achieve hypervolemia/hemodilution and hypertension, norepinephrine was administered additionally to reach a MAP >130 mm Hg.

In addition to the monitoring variables, cerebrovascular autoregulation was assessed by calculating the cerebral autoregulatory index (AI) as the ratio of the percentage change in rCBF and the corresponding percentage change in MAP (AI = ΔrCBF [%]/ΔMAP[%]) (24).

Statistics

Descriptive statistics, including mean, SD, and range, were calculated for continuous variables. Physiologic variables, CBF, and $Ptio_2$ values are given as mean ± SD. Both rCBF and $Ptio_2$ are expressed in absolute values or as the difference from baseline readings that were defined at the beginning of each experiment. The level of significance was set to 5%. Data analysis was performed using the statistical analysis system program (version 8.1; SAS Institute, Cary, NC).

RESULTS

Experimental Part

To achieve induced hypertension, MAP was increased in a stepwise manner by norepinephrine administration from 99.4 ± 5.3 mm Hg to 140 ± 6.7 mm Hg ($p < .05$). ITBVI measurements revealed a normovolemic state in all animals (882 ± 57 mL/m^2). After norepinephrine administration was stopped and normotension was reestablished, hypervolemia was induced by infusion of fluid boluses (1000–3000 mL) to reach an ITBVI of 1260 ± 202 mL/m^2 ($p < .05$). Induction of hypervolemia resulted only in a slight increase of MAP from 99.6 ± 23 mm Hg to 108.5 ± 14.7 mm Hg. To induce hypervolemia and hypertension, norepinephrine was administered additionally in the hypervolemic state and MAP was increased from 108.5 ± 14.7 mm Hg to 138.4 ± 15.5 mm Hg ($p < .05$). Baseline hemodynamic values measured were CI 4.1 ± 1 L/min/m^2, CFI 5.7 ± 1 1/min, and EVLWI 9.2 ± 1 mL/m^2. Induced hypervolemia resulted in a significant increase of CVP from 16 ± 4 mm Hg to 25 ± 6 mm Hg ($p < .05$), while all other variables (CI, CFI, EVLWI) did not change significantly with induced hypertension and hypervolemia. Neither induced hypertension nor hypervolemia had an effect on ICP (3.7 ± 2.5 mm Hg), $Ptio_2$ (19.1 ± 5.6 mm Hg), or rCBF (32.9 ± 9.6 mL/100 g/min) in the healthy porcine model. All animals presented with an intact cerebrovascular autoregulation (AI <0.2).

Patient Characteristics

Ten patients (eight female, two male) with a mean age of 53 ± 12 yrs (range 32–67 yrs) had aneurysmal SAH—grade II–V according to the Hunt and Hess classification (19) and grade III according to the Fischer scale (20)—were entered into the study. Aneurysms were located at the middle cerebral artery (n = 3), anterior communicating artery (n = 5), and pericallosal artery (n = 2). Angiography, stable xenon CT studies, and rCBF measurements revealed the presence of hemodynamically relevant vasospasm in six of the ten patients on day 7.

Clinical Part

To induce hypertension, MAP was increased by vasopressors from 95.3 ± 7.2 mm Hg to 143 ± 9.7 mm Hg ($p < .05$). At baseline, all patients were in a normovolemic state (ITBVI 933 ± 117 mL/m^2; CVP 14 ± 7 mm Hg). The patients received 1000- to 3000-mL fluid boluses to reach a hypervolemic state (ITBVI 1123 ± 152 mL/m^2; CVP 20 ± 7 mm Hg; $p < .05$), but hypervolemia did not result in an increase of MAP (96.6 ± 12.1 mm Hg). The stepwise induced components of triple-H therapy with the corresponding MAP and ITBVI values are presented in Figure 1. CI, CFI, and EVLWI remained unchanged during induced hypertension and hypervolemia (Fig. 2). As demonstrated in Table 1, induced hypertension and hypervolemia had a statistically significant impact on ICP. However, ICP elevation was clinically not relevant because the effect on ICP could be treated by cerebrospinal fluid drainage in all patients. CPP increased as MAP was elevated by vasopressors.

With hypervolemia, the hemoglobin values decreased from 10.6 ± 1.5 g/dL to 8.6 ± 1.3 g/dL on day 1, from 9.4 ± 0.7 g/dl to 8.1 ± 0.9 g/dL on day 3, and from 9.9 ± 0.9 g/dL to 8.4 ± 0.9 g/dL on day 7.

Mean baseline rCBF on study day 1 was 30.4 ± 19.1 mL/100 g/min. Baseline rCBF levels were similar on day 3 (34.1 ± 14.9 mL/100 g/min) and decreased

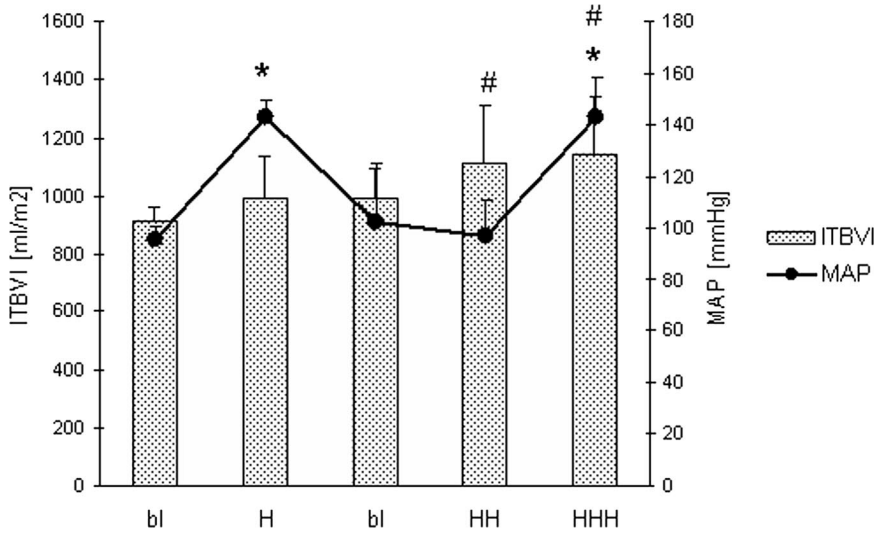

Figure 1. The clinical protocol in subarachnoid hemorrhage patients and the measurements of mean arterial pressure (*MAP*) and intrathoracic blood volume index (*ITBVI*) under baseline (*bl*), induced hypertension (*H*), hypervolemic/hemodilution (*HH*), and hypertensive/hypervolemic/hemodilution therapy (*HHH*). Data are expressed as mean ± SD. *$p < .05$ vs. baseline in mean arterial pressure; #$p < .05$ in intrathoracic blood volume index.

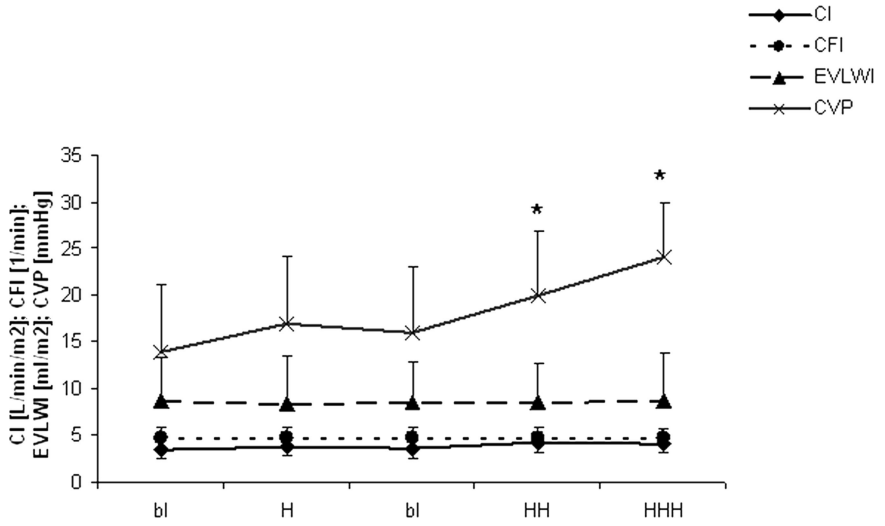

Figure 2. Hemodynamic measurements in subarachnoid hemorrhage patients showed no effect of triple-H therapy on cardiac index (*CI*), cardiac function index (*CFI*), and extravascular lung volume index (*EVLWI*). Central venous pressure (*CVP*) increased significantly with hypervolemic therapy. Data are expressed as mean ± SD. *$p < .05$ vs. baseline. *bl*, baseline; *H*, hypertension; *HH*, hypervolemia/hemodilution; *HHH*, hypervolemia/hemodilution/hypertension.

slightly on study day 7 to 23.1 ± 14.1 mL/100 g/min. An elevation of MAP >130 mm Hg by vasopressors (catecholamine-induced arterial hypertension) resulted in a statistically significant increase of rCBF on all observation time points (Fig. 3). In contrast, changes in rCBF following hypervolemia and hemodilution were rather moderate (Fig. 3). Induced hypervolemia/hemodilution combined with arterial hypertension led to a further increase of rCBF. However, the effect of the three components of triple-H therapy was statistically significant compared with baseline, but the additional effect of hypervolemia/hemodilution and hypertension compared with induced hypertension alone was rather moderate (not significant).

In parallel, vasopressor-induced hypertension induced a significant increase of $Ptio_2$ on day 1 from 21.3 ± 9.2 to 24.8 ± 9.9 mm Hg ($p < .05$), on day 3 from 29.3 ± 9 to 33.5 ± 9.5 mm Hg ($p < .05$), and on day 7 from 18.2 ± 9.4 to 22.3 ± 10.9 mm Hg ($p < .05$). However, after induction of hypervolemia, $Ptio_2$ remained unchanged or even decreased slightly. With hypervolemia/hemodilution and hypertension, no changes in $Ptio_2$ compared with baseline were noted. In summary, the positive effect of induced arterial hypertension on $Ptio_2$ was resolved when hypervolemia was added to the therapy (Fig. 3).

These results prompted us to compose the AI in healthy animals and patients. While the AI in animals was in the normal range, it revealed a disturbed cerebrovascular autoregulation for all patients during the study period. The calculated AI of the patients was 1.6 ± 0.8 on day 1, 1.7 ± 0.7 on day 3, and 1.7 ± 0.7 on day 7 of the study period.

DISCUSSION

Since 1976, when Kosnik and Hunt (25) reported on the reversal of neurologic deficits by use of induced hypertension and hypervolemia in seven patients who had deteriorated due to vasospasm, the use of triple-H therapy in the management of patients with cerebral vasospasm after SAH has been widely accepted. However, based on the existing experimental and clinical data, the efficacy of this therapy remains unproven. Induced hypertension in combination with volume expansion is not always effective in reversing neurologic deficits and may cause intracranial and medical complications (3, 16, 26). It remains unclear whether all three components of triple-H therapy optimize brain perfusion.

This is the first human study investigating the three arms of triple-H therapy with multimodal neuromonitoring, including continuous measurements of regional cerebral blood flow and cerebral oxygenation. In the first part of the study, we used a healthy porcine model to investigate the effects of triple-H therapy on cerebral hemodynamics in subjects with preserved cerebral autoregulation. We are aware that an experimental animal control does not further support the findings of the human study. However, the results of the experimental part showed that triple-H therapy does not lead to changes in rCBF or $Ptio_2$ in healthy subjects with preserved cerebral autoregulation. In contrast, patients with SAH presented with a disturbed cerebral autoregulation at each study period, including the first day after SAH. As a consequence, rCBF was dependent on MAP so that rCBF increased with induced hy-

pertension on days 1, 3, and 7 after bleeding. Our results demonstrate that cerebral autoregulation is disturbed in patients after SAH from the beginning and that, therefore, cerebral perfusion is directly dependent on cerebral perfusion pressure.

Both the experimental and clinical parts of our study demonstrate that the stepwise investigation of triple-H therapy—including a) induced hypertension; b) induced hypervolemia with accompanying hemodilution; and c) added induced hypertension to the hypervolemic state—is a practicable method. The hemodynamic measurements show that guidance of volume therapy with pulse contour cardiac output monitoring is a feasible method to optimize hemodynamics and to achieve therapeutic goals under control of cardiopulmonary complications (27).

Table 1. Intracranial perfusion pressure (ICP) and cerebral perfusion pressure (CPP) in patients with triple-H therapy

	ICP	CPP
Day 1		
bl	16.6 ± 8.6	79.9 ± 11.4
H	22.9 ± 9.1[a]	118.8 ± 13.2
HH	20.8 ± 5.7	75.5 ± 8.1
HHH	26.7 ± 9.2[a]	118 ± 9.9[a]
Day 3		
bl	15.5 ± 8.4	82.3 ± 9.4
H	18.5 ± 9.4	129.6 ± 12.9
HH	18.8 ± 5.2[a]	80.1 ± 13.7
HHH	25.6 ± 6.8[a]	118.9 ± 9.5
Day 7		
bl	15.4 ± 7.1	76.3 ± 10.5
H	19.2 ± 7.6	120.1 ± 9.5
HH	17.3 ± 4	68.6 ± 28.8
HHH	22.5 ± 6.3[a]	104.4 ± 40.4

bl, baseline; H, hypertension; HH, hypervolemia/hemodilution; HHH, hypervolemia/hemodilution/hypertension.

[a] $p < .05$. Data are mean ± SD mm Hg.

Induced Hypertension

There are several reports on the effectiveness of induced hypertensive therapy to prevent vasospasm-related delayed ischemic neurologic deficit and infarcts. Most studies focused on the reversal of vasospasm-related deficits, and only a few investigated the direct effects of induced hypertension on CBF (4, 6, 7, 28, 29). Studying the effect of dopamine- or phenylephrine-induced hypertension, the authors reported on a drug-induced improvement of rCBF in ischemic regions in patients with SAH (4, 6, 7, 28). Darby et al. (28) could not observe changes in global CBF, and Joseph et al. (17) demonstrated a MAP-dependent increase of CBF only in the setting of vasospasm.

In our study, we observed a MAP-dependent increase of rCBF in all patients. The observed improvement of rCBF with induced hypertension is likely to be a result of the impaired autoregulation, so that CBF increases passively following the elevation of cerebral perfusion pressure. Due to technical limitations of the regional CBF monitoring method, we were not able to elucidate the effects of induced hypertension on different cerebral regions in a patient. Although MAP was elevated with induced hypertension alone to the same level (mean 143 mm Hg) as with the combination of hypervolemia/hemodilution and induced hypertension by norepinephrine, the greatest increase in rCBF was achieved with hypervolemia/hemodilution and hypertension. One possible explanation might be the reduced hematocrit and blood viscosity that have been demonstrated in experimental settings to correlate inversely with cortical blood flow and lead to a reduced cortical vascular resistance (30). On the other hand, the further increase in rCBF by hypervolemic/hemodilution hypertension did not lead to an improvement in $Ptio_2$ compared with hypertension alone. This might be due to a reduced oxygen delivery in the setting of hypervolemia and

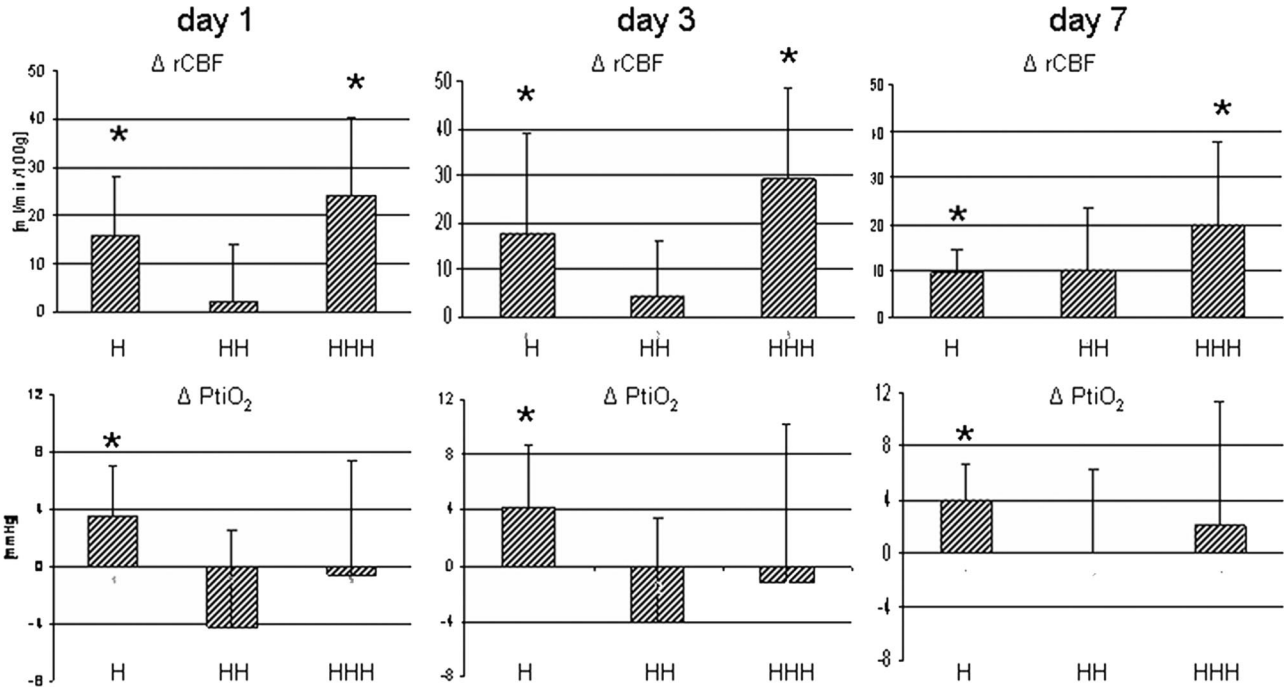

Figure 3. Effects of vasopressor-induced hypertension (*H*), induced hypervolemia/hemodilution (*HH*), and hypertensive/hypervolemic/hemodilution therapy (*HHH*) on regional cerebral blood flow (*rCBF*) and brain tissue oxygenation ($Ptio_2$) in patients 1, 3, and 7 days following aneurysmal subarachnoid hemorrhage. Data are presented as the difference from baseline (Δ) in mL/100 g/min (rCBF) and mm Hg ($PtiO_2$). Data are expressed as mean ± SD. *$p < .05$.

reduced hematocrit. One of the major findings of our study is that the best effect on rCBF was achieved with induced hypertension and additional institution of hypervolemia, but the beneficial effects of induced hypertension on $Ptio_2$ were reversed when hypervolemia was added.

Induced Hypervolemia/ Hemodilution

Hypervolemia and hemodilution are probably the most controversial parts of triple-H therapy. In theory, hemodilution achieved by volume expansion may prevent cerebral ischemia by increasing cardiac filling pressures and cardiac output, which elevates blood pressure and cerebral blood flow (31, 32). Furthermore, volume expansion may improve CBF, especially the microcirculation of ischemic regions independent of perfusion pressure, by lowering blood viscosity and decreasing cerebrovascular resistance, leading to improved blood rheology (33–35). Indeed, uncontrolled case series have reported on a reduced incidence of delayed ischemia and an improved clinical outcome after SAH with hypervolemic therapy (12, 36, 37). However, the results of clinical investigations are conflicting, as there also exist a number of studies showing no additional benefit from hypervolemic therapy (17, 38, 39). Hypervolemic therapy may carry more risks than benefits because initiation of hypervolemia is associated with significant side effects, including cardiac failure, electrolyte abnormalities, cerebral edema, and bleeding abnormalities (15, 16). Furthermore, Lennihan et al. (39) demonstrated that the fluid management is associated with higher costs.

There are conflicting results in the literature concerning the effect of hypervolemic therapy on CBF. Increases (33), decreases (40), and no changes (39) in cerebral blood flow have been reported after hypervolemic therapy. Lennihan et al. (39) investigated the effect of prophylactic hypervolemic therapy on CBF in 82 SAH patients and reported neither an increased regional CBF with hypervolemic therapy nor a difference in mean global CBF values between the hypervolemic and normovolemic subjects. Using a xenon blood flow tomography-based system, Joseph et al. (17) showed that hypervolemia does not increase CBF. Furthermore, in a clinical series, Ekelund et al. (41) demonstrated no effect of hypervolemic therapy on rCBF and a pronounced reduction in oxygen delivery capacity.

The main difference between the older investigations reporting on a successful use of hypervolemic therapy and the newer publications showing no effect of hypervolemia is the volume status of the patients. Formerly, SAH patients were kept rather dehydrated and volume status was not monitored consequently. Today, the hypovolemic state of SAH patients and its associated increased risk of developing delayed ischemic neurologic deficit are well known, and restoration of normovolemia has become an integral part in the management of SAH patients.

Since our patients were in a normovolemic state at baseline, the volume expansion did not further increase CFI or MAP, reflecting the relationship between cardiac output and left ventricular preload, where increasing left ventricular preload is more effective in increasing cardiac output at low values of left ventricular preload than at high values (42).

In our study, volume expansion from normovolemia to hypervolemia monitored by ITBVI and CVP resulted in a slight increase of rCBF on all observation time points. However, the elevated rCBF did not result in an improved cerebral oxygenation measured by $Ptio_2$ monitoring. Furthermore, $Ptio_2$ decreased with hypervolemic therapy, possibly due to hemodilution and the accompanying decrease of hemoglobin. The $Ptio_2$ decrease we observed is likely a direct effect of the reduced oxygen delivery, since other variables that may affect $Ptio_2$, such as Fio_2 and arterial oxygen saturation, did not change and CPP increased with volume load.

Several experimental studies have demonstrated that isovolemic hemodilution results in a significant reduction in blood viscosity that correlated almost linearly with the decrease in hematocrit and that isovolemic hemodilution can improve cerebral blood flow (43–47). However, when hematocrit is reduced to $<30\%$, insufficient oxygen delivery to the brain may promote ischemia (47). On the basis of the current literature, hematocrit levels between 30% and 35% corresponding to hemoglobin of 10–12 g/dL are recommended by most authors (48). Usually the hematocrit of SAH patients is in this range after restoration of a normovolemic state and after aneurysm surgery. In our study, hemoglobin levels decreased with hypervolemic therapy <10 g/dL, which indicated hematocrit levels $<30\%$. Studies investigating the effect of different hemoglobin levels on $Ptio_2$ and their consequences on local oxygen delivery to ischemic cerebral tissues are rare. Several studies in nonneurosurgical patients demonstrated that a selective increase in oxygen delivery by augmentation of red blood cell transfusion and oxygen-carrying capacity did not improve tissue oxygen utilization (49, 50). Smith and coworkers (51) investigated the effect of packed red blood cell transfusion on $Ptio_2$ in patients with SAH and traumatic brain injury. They observed an increase of $Ptio_2$ in 74% and a decrease in the remaining 26% of the patients with an associated significant increase in hemoglobin and hematocrit. Irrespective of the legitimate considerations regarding the several limitations of this study, their results imply that $Ptio_2$ monitoring may be considered as a red blood cell transfusion trigger to correct cerebral hypoxia. In our study we could demonstrate that hypervolemic therapy leads to a slight increase in rCBF, but improvement of rCBF did not result in an improved local cerebral oxygenation. We are aware that brain tissue monitoring carries several methodological limitations and that the relationships between brain oxygen tension and other physiologic variables, such as MAP, CPP, CBF, and Fio_2, have to be investigated in further studies. However, $Ptio_2$ reflects cerebral oxygen concentration, and in combination with rCBF monitoring, integrated in a multimodal neuromonitoring system, it provides the best possible monitoring to guide treatment protocols at the time (52). In summary, our results support the current evidence that hypervolemic therapy as a part of triple-H therapy does not add any benefit. Further research has to clarify if hypervolemic therapy without an accompanying decrease in hematocrit and hemoglobin will lead to beneficial effects on both rCBF and $Ptio_2$.

Limitations

One major limitation of this study is the nonrandomized, observational protocol. Our intention was to evaluate the three arms of triple-H therapy in a clinical setting and to demonstrate that the applied therapeutic maneuvers should be monitored carefully for their effectiveness. It was not our intention to perform a randomized outcome study. We are aware that the study protocol does not represent triple-H therapy over a longer

period of time. For that reason, we could evaluate neither cerebral hemodynamics over a longer time period nor the consequences of sustained hypervolemia or vasopressor administration. Furthermore, we could not observe different effects of triple-H therapy on rCBF between patients with and without vasospasm or between vasospastic and nonvasospastic hemispheres. This is likely a result of the small sample size and the high variations in rCBF values in the patients. However, we believe that our data demonstrate impressively that triple-H therapy should only be performed under online monitoring of several cerebral and hemodynamic variables so that in the future, we hope, more data over longer time periods will be available. Due to the short time periods that triple-H therapy was performed in most of our patients and possibly due to careful monitoring, no therapy-related complications were observed. The adverse effects often reported for hypervolemic therapy, like pulmonary edema and fluid overload, could be minimized by adequate hemodynamic monitoring with the pulse contour cardiac output monitor, which provides exact information on intravascular volumes and extravascular lung water to help titrate the fluid management.

In this study, the achieved MAP for hypertensive therapy was aggressively high. We chose this high MAP because of methodological reasons. Of course, lower MAP levels might be sufficient to increase CBF in most patients, but there remains the question to which level MAP should be elevated to provide adequate cerebral perfusion. As demonstrated in our study, the optimal level of hypertension can only be evaluated by CBF monitoring.

CONCLUSIONS

Vasopressor-induced elevation of MAP causes a significant increase of cerebral perfusion and cerebral oxygenation in SAH patients. While volume expansion results in an increase of cerebral perfusion, hypervolemia reverses the hypertension-induced benefit on $Ptio_2$. In view of the questionable effect of hypervolemia on brain tissue oxygenation and the increased risk of complications, hypervolemic therapy should be applied with utmost caution in SAH patients. The results of our study further support the important value of CBF and $Ptio_2$ measurements to prove the response to therapeutic interventions employed for the treatment of SAH patients.

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REFERENCES

1. Baldwin ME, Macdonald RL, Huo D, et al: Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in-hospital complications and poor outcome. *Stroke* 2004; 35:2506–2511
2. Claassen J, Bernardini GL, Kreiter K, et al: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: The Fisher scale revisited. *Stroke* 2001; 32:2012–2020
3. Solenski NJ, Haley EC Jr, Kassell NF, et al: Medical complications of aneurysmal subarachnoid hemorrhage: A report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med* 1995; 23:1007–1017
4. Mendelow AD, Dharker S, Patterson J, et al: The dopamine withdrawal test following surgery for intracranial aneurysms. *J Neurol Neurosurg Psychiatry* 1986; 49:35–38
5. Meyer CH, Lowe D, Meyer M, et al: Progressive change in cerebral blood flow during the first three weeks after subarachnoid hemorrhage. *Neurosurgery* 1983; 12:58–76
6. Muizelaar JP, Becker DP: Induced hypertension for the treatment of cerebral ischemia after subarachnoid hemorrhage. Direct effect on cerebral blood flow. *Surg Neurol* 1986; 25:317–325
7. Origitano TC, Wascher TM, Reichman OH, et al: Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. *Neurosurgery* 1990; 27:729–739
8. Critchley GR, Bell BA: Acute cerebral tissue oxygenation changes following experimental subarachnoid hemorrhage. *Neurol Res* 2003; 25:451–456
9. Prunell GF, Mathiesen T, Svendgaard NA: Experimental subarachnoid hemorrhage: Cerebral blood flow and brain metabolism during the acute phase in three different models in the rat. *Neurosurgery* 2004; 54:426–436
10. Fandino J, Kaku Y, Schuknecht B, et al: Improvement of cerebral oxygenation patterns and metabolic validation of superselective intraarterial infusion of papaverine for the treatment of cerebral vasospasm. *J Neurosurg* 1998; 89:93–100
11. Schneider GH, von Helden A, Lanksch WR, et al: Continuous monitoring of jugular bulb oxygen saturation in comatose patients—Therapeutic implications. *Acta Neurochir (Wien)* 1995; 134:71–75
12. Pritz MB, Giannotta SL, Kindt GW, et al: Treatment of patients with neurological deficits associated with cerebral vasospasm by intravascular volume expansion. *Neurosurgery* 1978; 3:364–368
13. Awad IA, Carter LP, Spetzler RF, et al: Clinical vasospasm after subarachnoid hemorrhage: Response to hypervolemic hemodilution and arterial hypertension. *Stroke* 1987; 18:365–372
14. Kassell NF, Peerless SJ, Durward QJ, et al: Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension. *Neurosurgery* 1982; 11:337–343
15. Levy ML, Giannotta SL: Cardiac performance indices during hypervolemic therapy for cerebral vasospasm. *J Neurosurg* 1991; 75: 27–31
16. Raabe A, Beck J, Keller M, et al: Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg* 2005; 103:974–981
17. Joseph M, Ziadi S, Nates J, et al: Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: A study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery* 2003; 53:1044–1051
18. Muench E, Bauhuf C, Roth H, et al: Effects of positive end-expiratory pressure on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation. *Crit Care Med* 2005; 33:2367–2372
19. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28: 14–20
20. Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery* 1980; 6:1–9
21. Vajkoczy P, Roth H, Horn P, et al: Continuous monitoring of regional cerebral blood flow: Experimental and clinical validation of a novel thermal diffusion microprobe. *J Neurosurg* 2000; 93:265–274
22. Kiening KL, Hartl R, Unterberg AW, et al: Brain tissue pO2-monitoring in comatose patients: Implications for therapy. *Neurol Res* 1997; 19:233–240
23. Vajkoczy P, Horn P, Thome C, et al: Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2003; 98:1227–1234
24. Dirnagl U, Pulsinelli W: Autoregulation of cerebral blood flow in experimental focal brain ischemia. *J Cereb Blood Flow Metab* 1990; 10:327–336
25. Kosnik EJ, Hunt WE: Postoperative hypertension in the management of patients with

intracranial arterial aneurysms. *J Neurosurg* 1976; 45:148–154
26. Shimoda M, Oda S, Tsugane R, et al: Intracranial complications of hypervolemic therapy in patients with a delayed ischemic deficit attributed to vasospasm. *J Neurosurg* 1993; 78:423–429
27. Segal E, Greenlee JD, Hata SJ, et al: Monitoring intravascular volumes to direct hypertensive, hypervolemic therapy in a patient with vasospasm. *J Neurosurg Anesthesiol* 2004; 16:296–298
28. Darby JM, Yonas H, Marks EC, et al: Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. *J Neurosurg* 1994; 80:857–864
29. Touho H, Karasawa J, Ohnishi H, et al: Evaluation of therapeutically induced hypertension in patients with delayed cerebral vasospasm by xenon-enhanced computed tomography. *Neurol Med Chir (Tokyo)* 1992; 32:671–678
30. Wood JH, Simeone FA, Kron RE, et al: Experimental hypervolemic hemodilution: Physiological correlations of cortical blood flow, cardiac output, and intracranial pressure with fresh blood viscosity and plasma volume. *Neurosurgery* 1984; 14:709–723
31. Wood JH, Fleischer AS: Observations during hypervolemic hemodilution of patients with acute focal cerebral ischemia. *JAMA* 1982; 248:2999–2304
32. Archer DP, Shaw DA, Leblanc RL, et al: Haemodynamic considerations in the management of patients with subarachnoid haemorrhage. *Can J Anaesth* 1991; 38:454–470
33. Mori K, Arai H, Nakajima K, et al: Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 1995; 26: 1620–1626
34. Matsui T, Asano T: The hemodynamic effects of prolonged albumin administration in beagle dogs exposed to experimental subarachnoid hemorrhage. *Neurosurgery* 1993; 32: 79–83
35. Tranmer BI, Keller TS, Kindt GW, et al: Loss of cerebral regulation during cardiac output variations in focal cerebral ischemia. *J Neurosurg* 1992; 77:253–259
36. Solomon RA, Fink ME, Lennihan L: Prophylactic volume expansion therapy for the prevention of delayed cerebral ischemia after early aneurysm surgery. Results of a preliminary trial. *Arch Neurol* 1988; 45:325–332
37. Solomon RA, Fink ME, Lennihan L: Early aneurysm surgery and prophylactic hypervolemic hypertensive therapy for the treatment of aneurysmal subarachnoid hemorrhage. *Neurosurgery* 1988; 23:699–704
38. Medlock MD, Dulebohn SC, Elwood PW: Prophylactic hypervolemia without calcium channel blockers in early aneurysm surgery. *Neurosurgery* 1992; 30:12–16
39. Lennihan L, Mayer SA, Fink ME, et al: Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. *Stroke* 2000; 31: 383–391
40. Yamakami I, Isobe K, Yamaura A: Effects of intravascular volume expansion on cerebral blood flow in patients with ruptured cerebral aneurysms. *Neurosurgery* 1987; 21:303–309
41. Ekelund A, Reinstrup P, Ryding E, et al: Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)* 2002; 144:703–712
42. Bendjelid K, Romand JA: Fluid responsiveness in mechanically ventilated patients: A review of indices used in intensive care. *Intensive Care Med* 2003; 29:352–360
43. Kiyohara Y, Fujishima M, Ishitsuka T, et al: Effects of hematocrit on brain metabolism in experimentally induced cerebral ischemia in spontaneously hypertensive rats (SHR). *Stroke* 1985; 16:835–840
44. Stone HO, Thompson HK Jr, Schmidt-Nielsen K: Influence of erythrocytes on blood viscosity. *Am J Physiol* 1968; 214:913–918
45. Tohgi H, Yamanouchi H, Murakami M, et al: Importance of the hematocrit as a risk factor in cerebral infarction. *Stroke* 1978; 9:369–374
46. Tu YK, Heros RC, Candia G, et al: Isovolemic hemodilution in experimental focal cerebral ischemia. Part 1: Effects on hemodynamics, hemorheology, and intracranial pressure. *J Neurosurg* 1988; 69:72–81
47. Tu YK, Heros RC, Karacostas D, et al: Isovolemic hemodilution in experimental focal cerebral ischemia. Part 2: Effects on regional cerebral blood flow and size of infarction. *J Neurosurg* 1988; 69:82–91
48. Janjua N, Mayer SA: Cerebral vasospasm after subarachnoid hemorrhage. *Curr Opin Crit Care* 2003; 9:113–119
49. Conrad SA, Dietrich KA, Hebert CA, et al: Effect of red cell transfusion on oxygen consumption following fluid resuscitation in septic shock. *Circ Shock* 1990; 31:419–429
50. Dietrich KA, Conrad SA, Hebert CA, et al: Cardiovascular and metabolic response to red blood cell transfusion in critically ill volume-resuscitated nonsurgical patients. *Crit Care Med* 1990; 18:940–944
51. Smith MJ, Stiefel MF, Magge S, et al: Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 2005; 33: 1104–1108
52. Stiefel MF, Spiotta A, Gracias VH, et al: Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg* 2005; 103:805–811