Prophylactic Hyperdynamic Postoperative Fluid Therapy after Aneurysmal Subarachnoid Hemorrhage: A Clinical, Prospective, Randomized, Controlled Study

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OBJECTIVE: To investigate the role of prophylactic hyperdynamic postoperative fluid therapy in preventing delayed ischemic neurological deficits attributable to cerebral vasospasm.

METHODS: We designed a prospected, randomized, controlled study and included 32 patients with subarachnoid hemorrhage. Sixteen patients received hypervolemic hypertensive hemodilution fluid therapy; the other 16 patients received normovolemic fluid therapy. All patients were monitored for at least 12 days, with clinical assessments, transcranial Doppler recordings, single-photon emission computed tomographic (SPECT) scanning, and routine computed tomographic scanning. For fluid balance monitoring, a number of blood samples were obtained on a daily basis and continuous central venous pressure and mean arterial blood pressure measurements were performed for both groups. All patients received intravenous nimodipine infusions between Day 1 and Day 12. End points of this study were clinical outcomes, clinically evident and transcranial Doppler sonography-evident vasospasm, SPECT findings, complications, and costs. Clinical examinations (using the Glasgow Outcome Scale) performed 1 year after discharge, together with neuropsychological assessments and SPECT scanning, were the basis for the evaluation of clinical outcomes.

RESULTS: No differences were observed between the two groups with respect to cerebral vasospasm (as observed clinically or on transcranial Doppler recordings). When regional cerebral blood flow was evaluated by means of SPECT analysis performed on Day 12 after subarachnoid hemorrhage, no differences were revealed. One-year clinical follow-up assessments (with the Glasgow Outcome Scale), including SPECT findings and neuropsychological function results, did not demonstrate any significant group differences. Costs were higher and complications were more frequent for the hyperdynamic therapy group.

CONCLUSION: Neither early nor late outcome measures revealed any significant differences between the two subarachnoid hemorrhage treatment models. (Neurosurgery 49:593–606, 2001)

Key words: Cerebral blood flow, Cerebral vasospasm, Hyperdynamic therapy, Induced hypertension, Neurological outcome, Subarachnoid hemorrhage

Outcomes for patients with aneurysmal subarachnoid hemorrhage (SAH) have improved with advances in neurosurgery and neurocritical care, including an emphasis on early aneurysm clipping or coiling to prevent rebleeding (19). However, cerebral ischemia related to vasospasm remains an important cause of morbidity and death (23), despite the beneficial effects of the calcium channel blocker nimodipine (9). Intravascular volume contraction and excessive natriuresis occur frequently after SAH and have been implicated as risk factors for delayed ischemia related to vasospasm (34, 59, 69).

During the past few decades, several reports from uncontrolled studies described the resolution of deficits resulting from vasospasm after blood pressure elevation, volume expansion, and/or hemodilution (hypertensive hypervolemic hemodilution therapy [“triple-H therapy”]) (3, 22, 25, 26, 29, 44), with improved outcomes with respect to vasospasm, compared with historical control results. However, the effi-
cacy of triple-H therapy has not been demonstrated in controlled trials, and studies of cerebral blood flow (CBF) after the initiation of therapy have been equivocal (38). In addition, studies have not been performed to determine which component of this therapy is most important. Recently, Lennihan et al. (28) found prophylactic hypervolemic therapy to be unlikely to confer an additional benefit after SAH.

We performed this prospective, randomized, controlled clinical study with 32 patients who were surgically treated within 72 hours after SAH. The aim of the study was to evaluate the role of hyperdynamic triple-H therapy in preventing delayed ischemic neurological deficits after SAH.

PATIENTS AND METHODS

We performed a prospective, randomized, controlled study between January 1997 and April 1999, with 32 patients who were surgically treated within 72 hours after aneurysmal SAH. All patients were in Hunt and Hess Grade I to III condition (17). Patients in Hunt and Hess Grade IV or V condition were excluded, because of late surgery (>72 h). Additional exclusion criteria were age of more than 75 years, congestive heart failure, pregnancy, and renal insufficiency. Aneurysmal SAH was documented by computed tomographic (CT) scanning, followed by cerebral angiography, for all patients. The patients or relatives were required to provide their written consent for participation, and the regional research ethics committee approved the study.

Perioperative and intensive care unit management

All patients were treated according to a standard treatment protocol. Mannitol (1 g/kg) was used during surgery for brain relaxation, and standard microsurgical techniques were used to clip the aneurysm and exclude it from the intracranial circulation. Spinal drainage was not routinely used. Total fluid input on the day of surgery ranged from 4.5 to 7 L for most patients. Arterial cannulae and internal jugular venous catheters were placed at the time of surgery. All patients received nimodipine, administered intravenously, throughout the study period. Phenytoin and dexamethasone were not administered perioperatively. All patients were evaluated hourly for signs of neurological deterioration. Transcranial Doppler (TCD) sonography was performed on a daily basis.

Stratification and treatment randomization

Written consent was obtained on study Day 1. Prerandomization stratification was performed according to the amount of blood observed in the initial CT scans (Fisher grade) (10). The Fisher grade was selected as a criterion because it is expected to have major effects on vasospasm risks and clinical outcomes. Prerandomization stratification on the basis of age, sex, preexisting arterial hypertension, Hunt and Hess grade at admission, or aneurysm location was not performed.

The included patients were distributed into two groups (Groups A and B) and received fluid management in the postoperative period according to two different protocols. The first included patient in each Fisher grade was randomly entered into one of the groups. Thereafter, consecutive patients were entered alternately into the two groups. The diagnosis of clinical or TCD-detected vasospasm did not alter the management. All included patients completed the study protocol, and there was no crossover between the two groups.

Fluid management

Group A patients (n = 16) received normovolemic fluid therapy, including a baseline crystalloid infusion of 1000 ml of 5% dextrose and 1000 ml of 0.9% saline solution every day until Day 12. Albumin solution or other colloids were not administered. The aim of the normovolemic fluid management (including free oral intake) was a neutral fluid balance.

Group B patients (n = 16) received triple-H fluid management therapy. The fluid management strictly maintained the central venous pressure (CVP) between 8 and 12 cm H2O, venous hematocrit (Hct) between 30 and 35%, and mean arterial blood pressure (MAP) more than 20 mm Hg greater than the preoperative MAP value.

A baseline crystalloid infusion of 2000 ml of 5% dextrose and 2000 ml of 0.9% saline solution and an infusion of 1000 to 1500 ml of colloids (500 ml of 4% albumin solution and/or 500–1000 ml of Rheomacrodex, Pharmalink AB, Spånga, Sweden) were administered on a daily basis until Day 12. Approximately two-thirds of the fluid infusion was administered as crystalloids and one-third as colloids. Vasopressor administration (dopamine, 5–15 μg/kg/min) was titrated to yield MAP values more than 20 mm Hg greater than the preoperative MAP value.

All 32 patients received continuous intravenous nimodipine infusions (0.2 mg/ml, 10 ml/h) for the entire study period (Days 1 to 12), followed by oral administration (360 mg/d) for 10 to 14 days. Blood pressure monitoring was performed via an arterial catheter.

We did not use pulmonary artery wedge pressures to guide volume expansion because the nurses in the neurological ward were not certified to perform these measurements. Postoperative angiography, papaverine infusion, and angioplasty were not performed.

Early outcome measures

Physiological parameters

MAP and CVP were measured hourly, and median 24-hour values were used for analysis. Hct, fluid intake, and fluid balance were measured every 24 hours.

Scandinavian Neurological Stroke Scale assessments

The patients were monitored with daily clinical neurological evaluations using a standardized scoring system, namely the Scandinavian Neurological Stroke Scale (SNSS) (55).

TCD sonography

Daily TCD recordings were made for all patients (1). Increased flow velocities, indicating cerebral vasospasm, were evaluated by using the index described by Lindegaard et al. (31), based on the following formula: flow velocity in the middle cerebral artery (MCA) divided by flow velocity in the internal carotid artery (ICA). A value of more than 3 indicates...
vasospasm, and a value of more than 6 indicates severe vasospasm. A MCA/ICA ratio of more than 4 for 3 days or more was defined as TCD-evident vasospasm in this study. TCD recordings were conducted transtemporally using a 2-MHz transducer, and examinations of the neck were performed using a 4-MHz probe (DWL Multi Dop X; DWL, Sipplingen, Germany).

**CT scanning**

Routine CT scanning was performed on Day 8 after SAH, for evaluation of ventricular size, cerebral edema, and early signs of ischemic lesions.

**Single-photon emission computed tomographic scanning**

The early measures of treatment effect were assessed with a mean of 2.7 (range, 1–5) single-photon emission computed tomographic (SPECT) measurements on Days 4, 8, and 12 after SAH. The SPECT measurements performed on Day 12 after SAH were used in the evaluation of early outcome measures. Thirty-two patients were examined. CBF was measured with a brain-dedicated imaging system (Siemens Neurofocal SPECT camera; Siemens Medical Systems, Erlangen, Germany) with an in-plane resolution of 12 mm. Each patient received an intravenous injection of 750 MBq of 99mTc-hexamethylpropylamine oxime (Ceretec; Amersham, Oslo, Norway) with eyes open during and after the injection. Each patient was positioned in the camera with the orbitomeatal line as the reference. The scanning procedure lasted 20 minutes. Twelve transaxial images, 6.6 mm thick (two pixels) and covering the whole brain, were reconstructed using filtered back-projection and linear attenuation correction. To perform quantitative estimations of the regional CBF distribution, we first subtracted from all slices 30% of the measured activity, which was considered general background activity. The slices then had defined boundaries both laterally and internally, compared with the ventricles, and covered essentially cortical tissue. An automated template with 16 symmetrical sectors was applied to all slices for computation of regional activity. Side-to-side reductions in activity of 15% or more were defined as abnormal CBF reductions. In an extensive SPECT study in normal human subjects, Waldemar et al. (65) demonstrated that CBF values in homologous bilateral brain regions did not differ by more than 10%. In this study, we used the same method but slightly different equipment. Therefore, we thought it prudent to be somewhat more conservative, and we used a 15% side difference to distinguish between normal and abnormal CBF values.

**Evaluation of early outcome measures**

Daily SNSS and TCD evaluations were performed without blinding to the treatment assignments. CT and SPECT measurements were performed and evaluated by clinicians blinded to the treatment assignments of the study subjects.

**Evaluation of late outcome measures**

Late outcome measures of treatment effects included clinical examinations performed 1 year after SAH, using the Glasgow Outcome Scale (GOS) (20). This examination was performed by one of the authors (AE), who was thus not blinded to the treatment assignments of the study subjects. On the same day, SPECT measurements and neuropsychological assessments were performed. Investigators blinded to the treatment assignments of the study subjects performed these analyses.

**Neurobehavioral assessments**

For neuropsychological testing, only standardized, commonly used tests were applied. They were chosen to assess cognitive dysfunctions usually observed after diffuse brain damage as well as focal damage, because SAH involves the likelihood of diffuse as well as more localized disruption of brain cortices. One year after SAH, all patients underwent a battery of seven main conventional tests and four computerized tests. The areas of neuropsychological functioning examined and the specific tests administered were as follows: 1) attention: digit span test from the Wechsler Adult Intelligence Scale (66) and Seashore Rhythm Test (52); 2) psychomotor speed: trail-making test, Parts A and B (52), and Stroop Color-Word Test (reading speed) (60, 61), modified version (12, 33); 3) memory: immediate recall and 30-minute delayed recall of two subtests from the Wechsler Memory Test-Revised (67), namely the verbal paired associates and visual paired associates subtests; 4) language (word fluency): Controlled Oral Word Association test (30, 60); 5) cognitive flexibility: Stroop Color-Word Test (interference) (60, 61) and a computerized version of the Wisconsin Card Sorting Test (14); 6) speed of information-processing: California Computerized Assessment Package, abbreviated version, containing a measure of simple reaction time and three measures of complex choice reaction time (41). Furthermore, to evaluate intellectual functions, the similarities (verbal function), block design (visuospatial construction), and picture arrangement (nonverbal functions) subtests from the Wechsler Adult Intelligence Scale were used (66). Mood was measured with the Beck Depression Inventory (BDI), which was included because of the confounding effects depressed mood can have on cognitive performance (4). The BDI is a widely used depression questionnaire with good reliability and validity (68).

A trained test technician, blinded regarding to which group the patients belonged, conducted all examinations. All patients were tested individually. The technician scored all tests, after which they were sent to another technician, who reviewed the findings for accuracy. An experienced neuropsychologist (KW), also blinded regarding to which group the patients belonged, coded the test scores and performed data analyses.

The 2.5- to 3-hour neuropsychological test battery was administered in two sessions. Two patients were lost to follow-up monitoring, and the follow-up examinations included 30 patients. Factors known to influence neuropsychological performance, including drug or alcohol abuse, learning disabilities, and previous psychiatric or neurological trauma or disease, were analyzed by review of patient...
records; there was no history of these factors among the patients with SAH.

Complications
All complications observed during the study period were prospectively recorded on a daily basis.

Costs
Additional costs for fluid management with triple-H therapy were calculated. Additional costs for patient treatment with triple-H therapy (e.g., prolonged hospital stays, evacuation of postoperative hematomas, and additional nursing work) were not taken into account.

Statistical analyses
Results are presented as means and standard deviations. Data analyses included Student’s unpaired t test (two-tailed) or analysis of variance to test differences between group means and differences between two or more groups of quantitative data and the \( \chi^2 \) test to test differences among groups of qualitative data. Because of multiple comparisons, a Bonferroni-corrected significance threshold of \( P < 0.01 \) was considered appropriate, to reduce the risk of Type I errors.

Simple and multiple regressions were used to analyze quantitative factors associated with neuropsychological parameters, with the test score as the continuous dependent variable and demographic and SAH-associated factors as the independent variables. Differences between groups and times in repeated physiological measures (MAP, CVP, and Hct) were assessed using repeated-measures analysis of variance. Differences were considered significant at \( P \leq 0.05 \). Data were analyzed using SPSS for Windows (Release 10.0; SPSS International BV, Gorinchem, The Netherlands) and Statview Graphics (Version 5.0; SAS Institute, Inc., Cary, NC).

RESULTS

Early outcome measures

Physiological variables

Table 1 presents baseline characteristics such as age, sex, Hunt and Hess grade at admission, Fisher grade at admission, and aneurysm location. Fisher grades were (according to the randomization strategy) equal in the two groups. There was no significant difference in Hunt and Hess grades at admission between the groups. Aneurysm locations were equal in the two groups.

Physiological parameters (MAP, CVP, and Hct) are presented in Table 2 and Figures 1 to 3. Median 24-hour MAP and CVP values were used for all patients. MAP was significantly higher for Group B patients on Days 2 to 12 (\( P = 0.001 \)). Induced hypertensive therapy (dopamine, 5–15 \( \mu g/kg/min \)) was used for Group B patients, to obtain MAP values more than 20 mm Hg greater than preoperative values. No patient in Group A underwent induced hypertensive therapy.

Mean CVP values for Group B patients were \( 9.7 \pm 2.1 \text{ cm H}_2\text{O} \), compared with \( 7.2 \pm 2.8 \text{ cm H}_2\text{O} \) for Group A patients. The difference with respect to Group A patients was statistically significant between Day 5 and Day 12 (\( P = 0.005 \)). The CVP values for Group A patients were within the normal range (5–10 cm H\textsubscript{2}O) throughout the study period (Fig. 2).

Hct levels were significantly lower for Group B patients between Day 5 and Day 12 (\( P = 0.03 \) (Table 2)). As demonstrated in Figure 3, no significant initial difference was observed, and the Hct levels were decreased for both groups on Days 1 to 3. Fluid administration differed between the groups, with significantly greater fluid intake for Group B (\( P < 0.0001 \)) (Fig. 4).

Clinical vasospasm evaluated by daily SNSSS assessments

The severity of clinical symptoms did not differ significantly (Fisher exact test) between the two groups. Five patients (31.5%) in Group A and four patients (25%) in Group B demonstrated clinical symptoms of vasospasm (Table 3). The clinical symptoms were reduced levels of consciousness (two patients in Group A and two patients in Group B) and hemiparesis (three patients in Group A and two patients in Group B). Appearance of headache during the study period was not considered a symptom of vasospasm.

TCD sonography

Ten patients in each group demonstrated MCA/ICA ratios of more than 4 for more than 3 days, indicating TCD-evident

<table>
<thead>
<tr>
<th>No. of Patients</th>
</tr>
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<tbody>
<tr>
<td>Hunt and Hess Grade</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Group B</td>
</tr>
</tbody>
</table>

* Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH. AComA, anterior communicating artery; PComA, posterior communicating artery; MCA, middle cerebral artery.

* Values represent group means, and ranges.

* Hunt and Hess grade at admission (17).

* Amount of blood (Fisher grade) evaluated on the initial computed tomographic scans (10).
vasospasm (Table 3). Six subjects in each group exhibited no TCD-evident vasospasm (MCA/ICA ratios of <4). Five patients in Group A and six patients in Group B exhibited TCD-evident vasospasm for more than 3 days without clinical deterioration. Flow velocities reached the highest levels during the second week after SAH.

TABLE 2. Physiological Parameters

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td></td>
<td>Admittance</td>
<td>Days 2–12</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>86.0 ± 10.3</td>
<td>87.6 ± 7.8</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>37.4 ± 3.9</td>
<td>33.4 ± 3.7</td>
</tr>
<tr>
<td>CVP (cm H2O)</td>
<td>7.2 ± 2.8</td>
<td></td>
</tr>
</tbody>
</table>

*a Mean ± standard deviation values for mean arterial blood pressure (MAP), hematocrit (Hct) levels, and central venous pressure (CVP) were determined at admission and on Days 2 to 12. The Hct levels were significantly lower for Group B patients between Day 5 and Day 12 (*P* = 0.03). Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH.

b *P* = 0.001.

c *P* = 0.03.

d *P* = 0.01.

FIGURE 1. Plot demonstrating MAP values for Group A (■) and Group B (○) patients during the 12-day study period. MAP values were significantly higher for Group B patients on Days 2 to 12 (*P* = 0.001).

FIGURE 2. Plot demonstrating mean CVP values for Group A (■) and Group B (○) patients during the 12-day study period. CVP values were significantly higher for Group B patients (*P* = 0.005).

FIGURE 3. Plot demonstrating mean Hct levels for Group A (■) and Group B (○) patients during the 12-day study period. Hct values were significantly lower for Group B patients between Day 5 and Day 12 (*P* = 0.03).

FIGURE 4. Plot demonstrating mean daily fluid intake for Group A (■) and Group B (○) patients during the 12-day study period. The fluid administration differed between the groups, with significantly greater fluid intake for Group B (*P* < 0.0001).
apy for 12 days after aneurysmal SAH. Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH.

SPECT measurements

No mean group differences were demonstrated when SPECT measurements obtained 1 year after SAH were compared (Table 4). Compared with early SPECT measurements, the volumes of the regional CBF reductions were significantly increased in both groups (Group A, \( P = 0.006 \); Group B, \( P = 0.02 \)). Only a few patients in the two groups demonstrated normal regional CBF distribution.

Neurobehavioral outcomes

There were no statistically significant differences in performance between the two patient groups exceeding the 0.01 level, as summarized in Table 6. Furthermore, there were no group differences between mean scores on the BDI. Seventy-one percent of BDI scores for patients in Group A were within the not-depressed range (scores of 0–9), whereas 29% of patients exhibited scores in the mild-to-moderate depression range (scores of 10–19). For patients in Group B, 64% of the scores were within the normal range (scores of 0–9), whereas 36% of the scores were between 10 and 19. There was no significant association between BDI scores and the scores on any individual neuropsychological test.

In multiple-regression equations with neuropsychological test scores as the dependent variables and the neurologic (Hunt and Hess) grade at admission, severity of the initial bleeding (Fisher grade), vasospasm, age, and education as independent variables, the effects on the Stroop test (color-word interference) results were observed to be attributable to age (\( b = 3.0, P = 0.02 \)). The performance on the complex reaction time test (California Computerized Assessment Package) was significantly influenced by the severity of the initial bleeding (Fisher score) (\( b = 141.3, P = 0.004 \)). No other demographic factor or disease-associated factor had significant effects on the performance on any test.

Complications

There were significant differences in the frequencies of complications between the treatment groups (\( P < 0.001 \)). Most of the complications (82%) were observed for Group B patients during the study period (Table 7). Two patients in Group B developed acute extradural hematomas, and one required surgical intervention. Three patients, all in Group B, experienced coagulation failure, leading to a tendency for bleeding complications at cannula sites and wounds and prolonged menstruation.

Congestive heart failure combined with arrhythmia and pulmonary edema occurred in two Group B patients. Local infections (cannulae or wounds) occurred in a total of four patients.

Costs

The additional costs for hypervolemic therapy (including induced hypertension), compared with normovolemic therapy, were a mean of $250/d.

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### Table 3. Clinical Vasospasm (Evaluated by Daily Scandinavian Neurological Stroke Scale Scores) and Transcranial Doppler-evident Vasospasm

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both clinical and TCD-evident vasospasm</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>TCD-evident but not clinical vasospasm</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>No TCD-evident vasospasm, no clinical vasospasm</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

* TCD, transcranial Doppler sonography (1), as evaluated by using the Lindegaard index (31). Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH.
### TABLE 4. Volume of Cerebral Blood Flow Reduction, as Measured with $^{99m}$Tc-Hexamethylpropylene Oxime Single-photon Emission Computed Tomography, 12 Days and 12 Months after Subarachnoid Hemorrhage$^a$

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume of CBF Decrease on Day 12 after SAH</th>
<th>No. of Patients with Hyperemia on Day 12 after SAH$^b$</th>
<th>Volume of CBF Decrease 12 mo after SAH$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3.5 (range, 0–16)</td>
<td>4</td>
<td>10.1 (range, 0–38)</td>
</tr>
<tr>
<td>B</td>
<td>3.1 (range, 0–29)</td>
<td>8</td>
<td>11.9 (range, 0–49)</td>
</tr>
</tbody>
</table>

$^a$ CBF, cerebral blood flow. Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH. For number of cortical sectors with CBF decrease, see Patients and Methods.

$^b$ Number of patients demonstrating hyperemia in single-photon emission computed tomographic (SPECT) measurements. No significant group differences were demonstrated.

$^c$ No significant group differences were detected. Compared with early SPECT measurements, the volume of the regional CBF reductions was significantly increased in both groups (Group A, $P = 0.006$; Group B, $P = 0.02$).

### TABLE 5. Clinical Outcomes$^a$

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14 d after SAH</td>
</tr>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>Good recovery</td>
<td>10</td>
</tr>
<tr>
<td>Moderately disabled</td>
<td>6</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>0</td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td>0</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Clinical outcomes were evaluated 14 days and 1 year after subarachnoid hemorrhage (SAH), using the Glasgow Outcome Scale (20). Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal SAH; Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH.

### DISCUSSION

Hypervolemic therapy is now routinely used after surgery at most medical centers, with the assumption that this intervention may increase CBF, prevent delayed ischemia, and improve clinical outcomes (40, 57, 58). However, both increases (43, 47) and decreases (70) in CBF have been reported after volume expansion among patients with SAH. An uncontrolled series suggested that therapy might be more effective if initiated prophylactically before the onset of symptoms, preferably after aneurysm clipping (57). In most centers, triple-H treatment is usually continued beyond the period of risk for vasospasm or until the reduction of vasospasm, as assessed by clinical and TCD parameters.

This randomized controlled study evaluated triple-H therapy as prophylactic treatment for vasospasm after SAH. Both Group A and B patients were treated according to the protocol for 12 days, with daily neurological examinations and TCD measurements to detect eventual signs of vasospasm. One major drawback of this study was the small number of patients included. Furthermore, this study does not answer the question of whether triple-H treatment is effective for symptomatic clinical vasospasm, for which it is mostly recommended.

### Stratification and treatment randomization

A stratified randomization was performed on the basis of the amount of blood (Fisher grade) evident on the initial CT scans. The strong relationship between the amount of extravasated blood and the final outcome seems to be one of the few truly reliable prognostic factors in aneurysmal SAH (10, 54). The clinical syndrome of vasospasm was elaborated in detail by Fisher et al. (11). Kapp et al. (21) established that the development of vasospasm and its clinical significance could be clearly predicted by early CT scans. In brief, severe cerebral vasospasm with clinical manifestations occurs mostly among patients with thick blood clots in the basal cisterns, and the vasospasm is more severe where the blood clots are the thickest.

### End points

#### Physiological variables

The goal of increasing MAP by more than 20 mm Hg, compared with preoperative levels, was achieved, as demonstrated in Figure 2. This significant group difference was observed between Day 2 and Day 12, demonstrating a clear difference in postoperative hyperdynamic treatment strategies.

In this study, the fluid management (hypervolemic treatment) was strictly followed to achieve CVP values between 8 and 12 cm H$_2$O for triple-H patients (Group B). We were able to achieve these values for all Group B patients during the study period. The difference with respect to Group A patients was statistically significant between Day 5 and Day 12. The CVP values for Group A patients decreased after study Day 4 but were still within the normal range.

Hct measurements demonstrated a statistically difference between the two groups. After the initial decrease for both groups between Day 1 and Day 3, the Hct levels remained stable for Group A patients, whereas a daily decrease was observed for Group B patients. Ekelund et al. (7) retrospectively evaluated hemodilution for 36 patients who were surgically treated for aneurysmal SAH, and they observed no difference between active hemodilution therapy and normal postoperative treatment.
In 1998, Mayer et al. (39) reported a study of 43 patients with aneurysmal SAH who were treated with two different fluid protocols. For one group of patients, albumin was administered in sufficient amounts to maintain the CVP at approximately 8 mm Hg. For the second group, the CVP was maintained at approximately 5 mm Hg. Supplemental 5% albumin administered to maintain the CVP above 8 mm Hg prevented sodium and fluid losses but did not have an effect on blood volume. Blood volume was decreased by 10% in both groups.

Lennihan et al. (28) evaluated the effect of hypervolemic therapy on CBF after SAH for 82 patients. Those authors used a stratified treatment randomization including the number of days since SAH and the postoperative Hunt and Hess grade, whereas other factors that have been predictive of delayed ischemia, such as the amount of SAH on admission CT scans or TCD data, were not taken into account. CBF values for hypervolemic and normovolemic subjects were compared. Hypervolemic patients received significantly more fluid and exhibited higher pulmonary artery diastolic pressure and CVP, compared with normovolemic patients. There was no difference in mean global CBF values during the treatment period between the groups. Symptomatic vasospasm occurred in 20% of the patients in each group and was associated with reduced minimal regional CBF values ($P = 0.04$).

Patients receiving triple-H treatment are usually monitored in an intensive care unit with a Swan-Ganz catheter, arterial line, and frequent serum electrolyte determinations. In many

### TABLE 6. Neuropsychological Function 12 Months after Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Tests</th>
<th>Group A (n = 15)</th>
<th>Group B (n = 15)</th>
<th>$P$ Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual function</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Verbal function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS, similarities$^{1,b}$</td>
<td>50.3 ± 8.9</td>
<td>57.4 ± 5.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonverbal function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS, picture arrangement$^{1,b}$</td>
<td>44.8 ± 10.1</td>
<td>43.8 ± 9.5</td>
<td>0.8</td>
</tr>
<tr>
<td>WAIS, block design$^{1,b}$</td>
<td>49.7 ± 12.4</td>
<td>47.2 ± 13.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST, persever. responses$^{1,b}$</td>
<td>37.4 ± 9.3</td>
<td>38.1 ± 10.7</td>
<td>0.9</td>
</tr>
<tr>
<td>WCST, % concept level$^{1,b}$</td>
<td>37.3 ± 8.4</td>
<td>37.4 ± 9.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroop test (s)</td>
<td>101.4 ± 60.0</td>
<td>103.0 ± 74.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COWA, total words$^{2,b}$</td>
<td>20.1 ± 10.2</td>
<td>24.1 ± 11.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-making test Part A$^{1,b}$</td>
<td>38.5 ± 8.9</td>
<td>37.3 ± 8.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Trail-making test Part B$^{1,b}$</td>
<td>37.6 ± 8.1</td>
<td>37.1 ± 11.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMS-R, verbal paired ass., immediate$^{2,b}$</td>
<td>12.5 ± 5.5</td>
<td>15.4 ± 4.6</td>
<td>0.1</td>
</tr>
<tr>
<td>WMS-R, verbal paired ass., delayed$^{2,b}$</td>
<td>4.7 ± 2.1</td>
<td>5.6 ± 2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>WMS-R, visual reprod., immediate$^{2,b}$</td>
<td>8.7 ± 3.7</td>
<td>9.5 ± 5.1</td>
<td>0.7</td>
</tr>
<tr>
<td>WMS-R, visual reprod., delayed$^{2,b}$</td>
<td>3.2 ± 2.1</td>
<td>2.9 ± 2.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span test$^{1,b}$</td>
<td>40.8 ± 7.8</td>
<td>35.9 ± 6.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Seashore Rhythm Test$^{1,b}$</td>
<td>41.9 ± 12.0</td>
<td>35.5 ± 8.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Speed of information processing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CalCAP, complex RT, digits (ms)</td>
<td>546.9 ± 139.7</td>
<td>573.3 ± 168.4</td>
<td>0.6</td>
</tr>
<tr>
<td>CalCAP, complex RT, Seq. 1 (ms)</td>
<td>658.8 ± 122.7</td>
<td>704.0 ± 147.9</td>
<td>0.4</td>
</tr>
<tr>
<td>CalCAP, complex RT, Seq. 2 (ms)</td>
<td>736.7 ± 132.8</td>
<td>773.3 ± 169.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Mood self-evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI score$^a$</td>
<td>5.5 ± 3.7</td>
<td>7.1 ± 4.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

$^a$ ass, associates; reprod, reproduction; WMS-R, Wechsler Memory Scale-Revised; CalCAP, California Computerized Assessment Package; RT, reaction time; Seq, sequential reaction time; Stroop test, Stroop Color-Word Test; WCST, Wisconsin Card Sorting Test; persever, perseverative; WAIS, Wechsler Adult Intelligence Scale; BDI, Beck Depression Inventory; COWA, Controlled Oral Word Association test. Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH. The results are given as mean ± standard deviation. The test results are presented as standardized $t$ scores (1) or raw scores (2).

$^b$ Higher scores indicate better performance.
Hyperdynamic Postoperative Fluid Therapy after SAH

 protocols, measurements of left ventricular end diastolic pressure and cardiac output are used to optimize hemodynamics according to the Starling curve (29). Unfortunately, we were not able to obtain pulmonary artery wedge pressure measurements to guide volume expansion, because our neurointensive care nurses were not certified to perform these measurements.

Muizelaar and Becker (44) retrospectively evaluated induced arterial hypertension among patients who postoperatively developed clinical signs of cerebral ischemia attributable to vasospasm. Using intravenous phenylephrine treatment, they documented an effect of such treatment on CBF measurements, combined with an immediate and obvious positive clinical effect, for all patients. Darby et al. (6) observed that dopamine-induced hypertension led to increased CBF in ischemic noninfarcted territories, without producing an increase in mean global CBF. Mizuno et al. (42) administered prophylactic hyperdynamic therapy (including induced hypertension) to most patients and observed stable CBF values within 3 weeks after SAH. We used hypervolemic therapy (including induced hypertension) as a prophylactic intervention for vasospasm but were not able to confirm these findings. However, our study included only 16 patients receiving triple-H therapy, and the dopamine dose administered was low (5–15 μg/kg/min). With the use of induced hypertension, we aimed to increase MAP by more than 20 mm Hg during the entire study period, compared with preoperative MAP values. We also achieved a significant difference in MAP values between the two study groups. However, additional increases in MAP could be more effective prophylactic therapy.

Clinical vasospasm evaluated by daily SNSs assessments

There was no difference in the frequency or severity of clinical symptoms of vasospasm between the groups. Five patients in Group A and four patients in Group B demonstrated clinical symptoms of vasospasm.

TCD assessments

TCD-evident vasospasm is one important factor that has been predictive of delayed ischemia after aneurysmal SAH. Flow velocities of more than 120 cm/s in the MCA and daily increases in MCA flow velocity of more than 50 cm/s have been established as indicators of cerebral vasospasm (8, 13). However, Vora et al. (64) recently concluded that, for individual patients, only low (<120 cm/s) or very high (>200 cm/s) MCA flow velocities reliably predicted the absence or presence of clinically significant vasospasm. With the use of the MCA/ICA ratio (Lindegaard index), a more accurate evaluation of increased flow velocities can be performed (31). Hyperemia can be differentiated from vasospasm; a ratio of more than 3 indicates vasospasm, whereas a ratio of more than 6 indicates severe vasospasm. We observed no differences between the two groups with respect to TCD-evident vasospasm during the study period. In both groups, a ratio of more than 4 was demonstrated for 10 patients. A ratio of less than 3 (no TCD-evident vasospasm) was observed for six patients in each group. Five patients in Group A and six patients in Group B exhibited TCD-evident vasospasm but no clinical signs of vasospasm.

Early clinical outcomes

All patients in Group A exhibited early favorable outcomes (GOS scores of 4 or 5), whereas three patients in Group B were considered severely disabled (GOS scores of 3).

SPECT scanning

Experimental studies indicated that volume expansion may improve CBF in ischemic regions independently of perfusion pressure, because of beneficial effects on cardiac output and blood rheology (24, 36, 62), and uncontrolled case series reported that hypervolemic therapy could reverse ischemic deficits among patients with symptoms (3, 22, 26, 51). SPECT scanning provides an estimate of regional CBF or global CBF, which (with a few exceptions) is closely associated with brain metabolism (35). A major exception involves patients with focal ischemia. SPECT scanning with hexamethylpropylamine oxime is not a measure of absolute CBF but is well suited for the detection of regional CBF abnormalities (35). No mean group differences in SPECT measurements were demonstrated either 12 days or 1 year after SAH. Interestingly, when early SPECT measurements were compared with late measurements, the volume of the regional CBF reductions was significantly increased in both groups. Both Group A and B patients with normal CBF distribution on Day 12 after SAH exhibited large regional CBF reductions 1 year later. Regional hyperemia was present in both Group A and B patients up to 12 days after SAH, probably as a sign of “luxury perfusion” (27). This is a phenomenon linked to unstable CBF, and it often appears before late infarctions (46).

Neurobehavioral outcomes

Neurobehavioral assessment provides an objective and sensitive method for delineating changes in cerebral functions and has been demonstrated to be a useful diagnostic proce-

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**TABLE 7. Complications during the Entire Study Period for Groups A and B**

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>Extradural hematomas</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic diatesis</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure/arrhythmia</td>
<td>0</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>2</td>
</tr>
</tbody>
</table>

*There were significant differences in the frequency of complications between the two treatment groups (P < 0.001). Group A, 16 patients who received normovolemic therapy for 12 days after aneurysmal subarachnoid hemorrhage (SAH); Group B, 16 patients who received hyperdynamic therapy for 12 days after aneurysmal SAH.*
dure for assessment of organic brain dysfunction (30, 52). Although many survivors of SAH experience excellent neurological recoveries, several studies of cognitive outcomes noted that a large proportion do not fully regain their pre-morbid status (5, 18, 32, 37). Memory dysfunction after SAH has attracted particular attention, both because of the importance of memory as a factor in the patient’s daily life and because of the many studies reporting long-term memory dysfunctions after SAH (5, 18, 32). Although memory problems seem to be the most frequent cognitive deficits resulting from SAH, other areas of cognition also suffer; dysfunctions in attention, psychomotor and information-processing speed, and cognitive flexibility have been reported (5, 18, 32).

No global cognitive disturbances were observed and no significant group differences in cognitive function were observed for patients who received hypervolemic fluid therapy according to the triple-H model, compared with patients who received normovolemic fluid therapy. The neurological grade at admission (Hunt and Hess grade) could not predict the extent of cognitive dysfunction 1 year after SAH, whereas the severity of the initial bleeding (Fisher grade) had a significant effect on the speed of information-processing, which is in agreement with other studies (18). The age of the patients at the time of SAH proved to be a significant predictor of cognitive flexibility dysfunction. In 12-month assessments after SAH, older patients were significantly more disturbed in this area of cognitive functioning than were younger patients. Similar results were reported by Hütter and Gilksdach (18) and Bornstein et al. (5). No other demographic factor or disease-associated factor had significant effects on performance on any test.

**Late clinical outcome measures**

It is a commonly held opinion that some factors affect outcomes more than others for patients with aneurysmal SAH. Greater age, poor clinical condition at admission, history of arterial hypertension, low CBF, and greater amounts of blood on the initial CT scans have all been considered negative prognostic factors (2, 16, 43, 45, 49, 53, 54). The Hunt and Hess grade at admission did not differ between the groups in this study. Clinical outcomes, as assessed by means of GOS scores measured 12 months after SAH, indicated 14 patients with favorable outcomes in Group A and 13 patients with favorable outcomes in Group B. The rates of unfavorable outcomes were similar for the two groups. One patient in each group died before the late follow-up examination.

**Complications**

Eighty-two percent of the complications during the study period occurred among Group B patients. This difference in frequency was statistically significant ($P < 0.001$). The most serious complications were extradural hematomas (observed for two patients), which required surgical evacuation in one case. These had no effects on outcomes. Further complications were treated conservatively; however, complications prolonged the hospital stay for four patients.

Shimoda et al. (56) retrospectively concluded that hypervolemic therapy might be very harmful in the early phase after SAH. Among patients who received hypervolemic therapy, 68 patients (72%) experienced no intracranial complications, whereas 18 (19%) exhibited aggravation of brain edema and 8 (9%) developed hemorrhagic infarctions. Trumble et al. (63) evaluated the use of colloidal agents to achieve hypervolemia for the prevention and treatment of vasospasm after SAH. Among a series of 65 patients with recent aneurysmal SAH, 26 developed clinical symptoms of vasospasm. Fourteen of the 26 patients were treated with hetastarch for volume expansion, whereas the other 12 received plasma protein fraction. Clinically significant, bleeding-associated pathological conditions were noted for six patients who received hetastarch as a continuous intravenous infusion. Hetastarch increased partial thromboplastin times for all patients who received this agent, whereas no effect was noted for the 12 patients who received plasma protein fraction infusions.

**Costs**

A comparison of costs for Group A and B patients demonstrated a mean additional cost of $250/24 h for the fluid management. When used, triple-H therapy is administered for a period of 7 to 14 days at most centers. Therefore, 10 days of triple-H therapy would yield an additional fluid cost of at least $2500.

**Practical aspects**

In a recent review of hyperdynamic therapy, Pritz (50) presented practical aspects of the treatment of cerebral vasospasm. Successful medical treatment of neurological symptoms attributable to vasospasm requires vigilance, accurate diagnoses, and prompt intervention. The results of TCD assessments performed routinely at regular intervals after SAH, coupled with neurological decline in the absence of electrolyte and/or cardiovascular or pulmonary abnormalities, should suggest that these symptoms result from vasospasm. CT scans can exclude cerebral edema, hydrocephalus, stroke attributable to vessel occlusion, and hematomas as the causes of these deficits. Cerebral angiography can document the vessels affected by vasospasm, as well as satisfactory aneurysm clipping and vessel patency.

There has been an extraordinary amount of laboratory work studying the pathogenesis and possible pharmacological treatment of vasospasm, but no treatment has been proven to be useful in clinical practice (15). Recently, Polin et al. (48) raised significant doubts regarding the long-term effectiveness of endovascular therapy for vasospasm.

However, only a proportion of patients with vasospasm respond to triple-H therapy, with vasospasm-related stroke and death rates approaching 15% in the series with the best outcomes (3, 44). Initiation of triple-H therapy is associated with significant risks, including the possibilities of cardiac failure, electrolyte abnormalities, cerebral edema, bleeding abnormalities, and rupture of unsecured aneurysms (29). These complications were confirmed in our study. Furthermore, we found triple-H therapy to be associated with higher costs. In summary, we observed that prophylactic triple-H therapy after aneurysm clipping did not result in increased regional CBF (as
assessed by means of SPECT scanning), less clinically evident or TCD-evident vasospasm, or differences in neurocognitive impairment, compared with normovolemic therapy.

CONCLUSION

This study does not support the idea that hyperdynamic postoperative fluid therapy (triple-H therapy) prevents delayed ischemic neurological deficits, compared with normovolemic fluid therapy, among patients with SAH. Our results demonstrated no significant differences in clinically evident or TCD-evident vasospasm between the two groups. When regional CBF disturbances were evaluated, no group differences were observed. Follow-up examinations using GOS assessments, SPECT scanning, and neuropsychological function evaluations did not reveal any significant differences. There were additional costs and more complications for the hyperdynamic treatment group. In summary, the outcome measures did not reveal any significant differences between the two SAH treatment models.

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REFERENCES

This prospective, randomized study compares the efficacy of early induced hypertensive hypervolemic hemodilution combination therapy (triple-H therapy) in a group of patients with aneurysmal subarachnoid hemorrhage (SAH) with a control group with normovolemic, normotensive treatment and normal hematocrit after aneurysmal SAH. All of the patients received intravenous nimodipine. Each group comprised 16 patients, and the treatment period lasted until Day 12 after the SAH. The stratification was according to Fisher grade, and the other important prognostic measures such as Hunt and Hess grade at arrival, patient’s age, and the location of the aneurysm were evenly distributed. The patients who received triple-H therapy showed no difference in outcome at the time of discharge or 1 year after therapy. Other outcome measures, clinically and transcranial Doppler sonography-detected vasospasm, early or late single-photon emission computed tomography findings, and neuropsychological variables did not show any differences either. There were more complications in the active treatment group, and this care was more expensive, even without taking into account the heavy nursing protocol. The authors conclude that prophylactic triple-H treatment does not improve patient outcome or prophylaxis of this problem with hypervolemia makes no sense, because blood volume and cardiac output are not diminished blood flow and oxygen delivery. Treatment or prophylaxis of this problem with hypervolemia makes no sense, because blood volume and cardiac output are not represented in the Poiseuille viscosity coefficient, and manipulation of these factors does not increase cerebral blood flow or oxygen delivery. However, hypervolemia is still used, because with hypovolemia, it would be difficult to induce arterial hypertension if that became necessary. In addition, it might prevent blood pressure decreases—short-lived but deleterious nonetheless—associated with the use of nimodipine. In this respect, one should keep in mind that slow, continuous intravenous administration of nimodipine (as used in this study) is not available in the United States. Thus, in the United States, a certain degree of vasospasm might be more beneficial than it would be in Europe, but it is certainly not worth provoking cardiac failure and pulmonary edema.

In this interesting study, the authors conclude that prophylactic triple-H therapy does not lead to improved patient outcome after aneurysmal SAH but is associated with a higher complication rate and increased costs. The authors recognize that there were only a few patients in this study and that there is considerable chance of β-type error. Nevertheless the results of this study are rather convincing. Why, then, are the results of management of SAH thought to be better now than they were 20 years ago? Neurosurgeons assume that vasospasm leads to diminished blood flow and oxygen delivery to the brain. Treatment or prophylaxis of this problem with hypervolemia makes no sense, because blood volume and cardiac output are not represented in the Poiseuille viscosity coefficient, and manipulation of these factors does not increase cerebral blood flow or oxygen delivery. However, hypervolemia is still used, because with hypovolemia, it would be difficult to induce arterial hypertension if that became necessary. In addition, it might prevent blood pressure decreases—short-lived but deleterious nonetheless—associated with the use of nimodipine. In this respect, one should keep in mind that slow, continuous intravenous administration of nimodipine (as used in this study) is not available in the United States. Thus, in the United States, a certain degree of hypervolemia might be more beneficial than it would be in Europe, but it is certainly not worth provoking cardiac failure and pulmonary edema.

As for hemodilution, I note that in the treatment group, hematocrit was well below my ideal of 33 to 35, whereas in the
control group, it was exactly in this range. It is at a hematocrit level of approximately 34 that a further reduction in hematocrit does not lead to any significant further reduction in blood viscosity (i.e., no further effect on blood flow according to the Poiseuille viscosity coefficient), but the decrease in oxygen carrier capacity easily amounts to 10 to 15%. Hence, I transfuse patients who have a hematocrit level less than 31 and are within the time window for vasospasm (which would apply here to the treatment group from Days 7 through 11).

Finally, with regard to hypertension, I do not believe that many clinicians advocate the use of prophylactic hypotension, partly because of the development of tachyphylaxis for α-adrenergic drugs by the time they become really crucial (i.e., the appearance of delayed ischemic deficits). Nevertheless, many of my patients are administered these agents in low doses early on, not to induce hypertension but to treat hypertensive episodes.

In summary, this thought-provoking study in no way proves that the judicious use of prophylactic hypervolemia, hemodilution to a hematocrit level of 34, and use of hypotension only in case of delayed ischemic deficits have led to better outcomes for patients today as compared with 20 years ago. This article is not sufficient reason to abandon these treatment modalities at this time.

J. Paul Muizelaar
Sacramento, California

The authors prospectively studied two patient cohorts after surgical treatment of aneurysmal SAH. One patient group received prophylactic triple-H therapy and was compared with a group of patients who were administered normovolemic fluid therapy with normotension. The authors found no significant differences between the two groups according to a variety of short- and long-term outcome measures.

This study is rated Level of Evidence II (data from randomized trials with high false-positive [α] and high false-negative errors [β]) according to American Heart Association criteria (1, 2). It has been comprehensively analyzed. Unfortunately, as with any single-institution clinical study, its statistical power is limited because of the small sample size, and the finding of no difference between study groups, although suggestive, remains unproved. Nevertheless, the American Heart Association’s evidence-based review (2) of the treatment of patients with SAH did not identify any controlled clinical trials that demonstrated the efficacy of triple-H therapy but did recommend the use of this therapy on the basis of uncontrolled studies. This report from Egge et al. suggests that the primary effect of triple-H therapy is to increase morbidity and cost, which should prompt a critical reappraisal of this treatment modality.

Christopher L. Taylor
Warren R. Selman
Cleveland, Ohio


Although carefully designed, this study does not answer the question whether prophylactic triple-H therapy after aneurysmal SAH is efficacious for reducing deficits related to cerebral vasospasm. In modern series with calcium channel blockers, the incidence of neurological deficits from vasospasm in patients with Hunt and Hess Grades I through III lesions (the same as patients enrolled in this study) is approximately 15% or less (1). Thus, a poor outcome because of vasospasm might have been expected in only 2 of the 16 controls used. Obviously, these numbers are too small for any meaningful comparison. This study should not be considered as proof for or against the use of triple-H therapy, but rather should be viewed as a template for the design of an adequately powered, prospective, randomized trial.

Marc R. Mayberg
Cleveland, Ohio


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“The Congress of Neurological Surgeons exists for the purpose of promoting the public welfare through the advancement of neurosurgery, by a commitment to excellence in education, and by dedication to research and scientific knowledge. The Congress of Neurological Surgeons maintains the vitality of our learned profession through the altruistic volunteer efforts of our members and the development of leadership in service to the public, to our colleagues in other disciplines, and to the special needs of our fellow neurosurgeons throughout the world and at every stage of their professional lives.”

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