Effect of Hypervolemic Therapy on Cerebral Blood Flow After Subarachnoid Hemorrhage
A Randomized Controlled Trial

Laura Lennihan, MD; Stephan A. Mayer, MD; Matthew E. Fink, MD; Avis Beckford, RN; Myunghee C. Paik, PhD; Haiying Zhang, PhD; Ya-Chi Wu, MA; Louise M. Klebanoff, MD; Eric C. Raps, MD†; Robert A. Solomon, MD

Background and Purpose—Cerebral blood flow (CBF) is reduced after subarachnoid hemorrhage (SAH), and symptomatic vasospasm is a major cause of morbidity and mortality. Volume expansion has been reported to increase CBF after SAH, but CBF values in hypervolemic (HV) and normovolemic (NV) subjects have never been directly compared.

Methods—On the day after aneurysm clipping, we randomly assigned 82 patients to receive HV or NV fluid management until SAH day 14. In addition to 80 mL/h of isotonic crystalloid, 250 mL of 5% albumin solution was given every 2 hours to maintain normal (NV group, n=41) or elevated (HV group, n=41) cardiac filling pressures. CBF (133 xenon clearance) was measured before randomization and approximately every 3 days thereafter (mean, 4.5 studies per patient).

Results—HV patients received significantly more fluid and had higher pulmonary artery diastolic and central venous pressures than NV patients, but there was no effect on net fluid balance or on blood volume measured on the third postoperative day. There was no difference in mean global CBF during the treatment period between HV and NV patients (P=0.55, random-effects model). Symptomatic vasospasm occurred in 20% of patients in each group and was associated with reduced minimum regional CBF values (P=0.04). However, there was also no difference in minimum regional CBF between the 2 treatment groups.

Conclusions—HV therapy resulted in increased cardiac filling pressures and fluid intake but did not increase CBF or blood volume compared with NV therapy. Although careful fluid management to avoid hypovolemia may reduce the risk of delayed cerebral ischemia after SAH, prophylactic HV therapy is unlikely to confer an additional benefit. (Stroke. 2000;31:383-391.)

Key Words: blood volume • cerebral blood flow • cerebral vasospasm • subarachnoid hemorrhage

Outcomes in patients with aneurysmal subarachnoid hemorrhage (SAH) have improved over the past 2 decades with advances in neurosurgery and neurocritical care, including an emphasis on early aneurysm clipping to prevent rebleeding.1 However, cerebral ischemia related to vasospasm remains an important cause of morbidity and mortality,2 despite the beneficial effects of the calcium channel blocker nimodipine.3

Excessive natriuresis and intravascular volume contraction occur frequently after SAH and have been implicated as risk factors for delayed cerebral ischemia related to vasospasm.4–6 SAH causes progressive reduction of CBF for up to 3 weeks7–21 and can result in loss of the normal capacity to autoregulate.21–23 Experimental studies indicate that volume expansion can improve CBF in ischemic regions independent of perfusion pressure because of beneficial effects on cardiac output and blood rheology,24–26 and uncontrolled case series27–30 have reported that hypervolemic therapy can reverse ischemic deficits in symptomatic patients.

Accordingly, postoperative hypervolemic therapy is now routinely performed at most medical centers, on the assumption that this intervention may augment CBF, prevent delayed ischemia, and improve clinical outcomes.31,32 However, both increases33,34 and decreases35 in CBF have been reported after volume expansion in SAH patients, and CBF measurements in hypervolemic (HV) and normovolemic (NV) subjects have never been directly compared. We performed this randomized...
controlled study to test the hypothesis that postoperative HV therapy increases CBF after SAH.

Subjects and Methods

Study Population
Patients with aneurysmal SAH admitted to the Neurological Intensive Care Unit (NICU) of Columbia–Presbyterian Medical Center between June 1991 and October 1994 were eligible for enrollment if they had surgery to clip the ruptured aneurysm on or before SAH day 6 (with the calendar day of bleeding referred to as SAH day 0), were Hunt-Hess grades I to IV after surgery, were between the ages of 18 and 80 years, and did not have symptomatic vasospasm. Exclusion criteria included congestive heart failure, pregnancy, and renal insufficiency (creatinine >2.0 mg/dL). Aneurysmal SAH was documented by CT or lumbar puncture and angiography in all patients. Solicitation of study subjects was approved by the Institutional Review Board of Columbia–Presbyterian Medical Center.

Perioperative and ICU Management
All subjects were managed according to a standard treatment protocol. Spinal drainage and mannitol (1 g/kg) were used during surgery for brain relaxation, and standard microsurgical techniques were used to clip the aneurysm and exclude it from the intracranial circulation. Total fluid input on the day of surgery ranged from 4 to 6 liters in most patients. Pulmonary artery catheters were placed at the time of surgery and were replaced with internal jugular venous catheters on the third postoperative day (study day 3) until SAH day 14 to minimize the risks associated with prolonged pulmonary artery catheterization. All patients received nimbodipine throughout the study period; phenytoin and dexamethasone were given perioperatively. All patients were evaluated hourly for signs of neurological deterioration. Transcranial Doppler (TCD) sonography was performed approximately every other day but was not used to diagnose symptomatic vasospasm or guide clinical management.

Stratification and Treatment Randomization
After written consent was obtained on the first postoperative day (study day 0), subjects were classified before randomization into 1 of 3 strata based on the number of days since SAH and on postoperative Hunt-Hess grade: stratum 1, SAH days 0 to 3 and Hunt-Hess grade I or II; stratum 2, SAH days 0 to 3 and Hunt Hess grade III or IV; stratum 3, SAH days 4 to 7 and Hunt Hess grade I or II; and stratum 4, SAH days 4 to 7 and Hunt Hess grade III or IV. These criteria (interval from SAH and Hunt-Hess grade) were selected because they were expected to have a major impact on CBF, vasospasm risk, and clinical outcome. Subjects were randomized using a biased-coin technique,38 in which the probability of assignment to either treatment within each stratum, subsequent subjects were assigned with a probability of 0.50 of assignment to either treatment. After this “baseline” treatment allocation, to ensure assignment of an equal number of patients to each treatment within each stratum, subsequent subjects were randomized with a biased-coin technique,38 in which the probability of randomization to the underrepresented treatment within a given stratum was 0.67.

Fluid Management
All patients received a baseline crystalloid infusion of 80 mL/h 5% dextrose and 0.9% saline preoperatively and postoperatively until SAH day 14. At the time of enrollment on the first postoperative day (study day 0), baseline CBF, blood volume, and cardiovascular hemodynamic measurements were obtained. After these measurements, patients were assigned to receive 250 mL of 5% albumin solution every 2 hours in addition to the baseline crystalloid infusion if cardiac filling pressures fell below the following target levels (pulmonary artery diastolic pressure [PADP] on study days 0 to 3 and central venous pressure [CVP] thereafter): HV group, PADP 14 mm Hg or CVP 8 mm Hg; NV group, PADP 7 mm Hg or CVP 5 mm Hg. This fluid management protocol was strictly adhered to throughout the entire study period unless symptomatic vasospasm was diagnosed, in which case the assigned treatment was stopped and hypertensive hypervolemic therapy (HHT) was given. In these cases HV fluid management was used, and subjects were given vasopressors (dopamine, norepinephrine, or phenylephrine) titrated to the level at which the deficit resolved or a maximal systolic blood pressure of 200 mm Hg. We did not use pulmonary artery wedge pressures to guide volume expansion because our NICU nurses were not certified to perform these measurements.

Primary Outcome Measures
The primary measures of treatment effect were CBF measured serially during the first 14 days after SAH and BV measured at baseline and on the third postoperative day. These measurements were performed and analyzed by investigators blinded to the treatment assignment of the study subjects.

CBF measurements were performed on study day 0 (before treatment assignment), study day 1, and then approximately every 3 days until SAH day 14. CBF was measured after intravenous injection of $^{133}$Xe in saline in 16 symmetrical hemispheric brain regions using 32 external scintillation detectors placed in accordance with skull landmarks (Novo Cerebrogaph 32c, Novo Diagnostic Systems). Each CBF study was evaluated for data quality by a blinded investigator, and poor-quality or uninterpretable studies (due to motion artifact, gas leak, or equipment malfunction) were excluded from the analysis. CBF studies were performed according to the original study schedule in patients with symptomatic vasospasm; there was no attempt to measure CBF immediately before and after the institution of HHT.

Total BV measurements, based on the volume of distribution of chromium-51–labeled autologous red blood cells, were obtained on study day 0 (before treatment assignment), and once again on study day 3. Twenty milliliters of blood were labeled with 20 to 30 mCi of chromium-51, and washed, labeled cells were reinfused. A second 7-mL sample was obtained 20 minutes after the reinfusion. BV was derived from the calculated red blood cell volume (RBCV) as follows: $\text{BV} = \text{RBCV} / 0.9$ (venous hematocrit), expressed in milliliters per kilogram of body weight.

Secondary Outcome Measures
Secondary measures of treatment effect included the frequency of symptomatic vasospasm, medical and neurological complications, and 5 other physiological variables (mean arterial blood pressure [MAPB], PADP, CVP, hematocrit, 24-hour fluid intake, and 24-hour net fluid balance); all were evaluated daily until SAH day 14 except PADP, which was measured during the first 3 days of the study. Outcome was assessed at 14 days and at 3, 6, and 12 months with the Glasgow Outcome Scale (GOS). Secondary outcome measures were recorded by investigators who were not blinded to treatment assignment, because it was not possible to give the treatment in a blinded fashion.

Blood pressure and cardiac filling pressures were measured using fluid-filled catheters with transducers positioned at the level of the right atrium. Complications were classified and defined as follows.

Neurological complications: symptomatic vasospasm (a focal neurological deficit or deterioration in level of consciousness, with either confirmation of infarction on a CT scan or exclusion of other possible causes of deterioration, such as rebleeding, surgical complication, hydrocephalus, cerebral edema, electrolyte disorder, infection, or seizure), cerebral infarction (due to surgery, angiography, or other causes), aneurysm rebleeding, symptomatic hydrocephalus (ventricular enlargement on CT treated with a ventricular drain, lumbar puncture, or ventriculoperitoneal shunt), seizures, or cerebral edema (focal or diffuse on CT); cardiovascular complications: hypertension (systolic blood pressure $>150$ mm Hg in the absence of vasopressors), arrhythmia, or congestive heart failure ($O_2$ saturation by pulse oximetry $<95\%$ on at least 40% oxygen, with clinical and X-ray findings consistent with pulmonary edema); metabolic complications: hyponatremia (plasma sodium measurement $<135$ mEq/L for 2 consecutive days) or hyperglycemia (plasma glucose $>200$ mg/dL); and infectious complications: pneumonia (infiltrate on chest X-ray), urinary tract infection, bacteremia, or meningitis/ventriculitis (all defined by positive cultures).
Statistical Analysis

CBF was analyzed on an intention-to-treat basis. For measurements of CBF on study day 0, correlations of the initial slope index (ISI) between any of the 32 detectors were high (range, R = 0.74 to 0.98).

We measured CBF in 3 ways: global CBF (gCBF), based on the mean ISI of all 32 detectors; hemispheric CBF (hCBF), based on the mean ISI of the 16 hemispheric detectors; and minimum regional CBF (mCBF), based on the lowest ISI among the 32 detectors. CBF measurements on study day 0 are referred to as baseline CBF.

To test whether there was an overall difference in CBF between the 2 treatment groups, we fitted random-effects models using repeated CBF measurements as the outcome variable and using baseline CBF, treatment, stratum, and time as covariates. Because the number of CBF studies performed in each treatment group on any given study day was small, CBF results were grouped into 8 epochs: study days 0, 1, 2 to 3, 4 to 5, 6 to 7, 8 to 9, 10 to 11, and 12 to 14. No subject had CBF study within an epoch. Models were fitted analyzing gCBF, gCBF with patients who received HHT excluded, and mCBF. The random-effects model takes into account correlations among CBF values over time, whereas classical regression assumes that repeated CBF measurements are independent.

To compare other physiological variables, we fitted random-effects models to estimate the magnitude of treatment effect over time, using only time as a covariate. These models assumed no interaction between treatment group and study day. Continuous variables were compared with 2-tailed t tests, and proportions were compared with the χ² or Fisher exact test. Independent risk factors for poor outcome at 3 months (dependent with severe deficit, vegetative, or dead, according to the GOS) were identified by fitting a simple logistic regression model after identification of candidate variables in a univariate analysis. Significance was judged at the P < 0.05 level.

Results

Study Population

Of 286 patients admitted to the NICU for SAH during the study period, 99 met the eligibility criteria, and 82 consented to participate and were enrolled in the study (Figure 1). Forty-one patients were randomized to HV therapy and 41 to NV therapy. Subjects in the 2 treatment groups were similar with regard to age, sex, race/ethnic group, route of admission, Hunt-Hess grade, aneurysm location, and days from SAH to study enrollment (Table 1). The numbers of subjects assigned to each treatment within the 4 strata were not significantly different.

CBF

Of the 82 study subjects, 3 had CBF studies of such poor quality that none were included in the CBF analysis, 6 did not have an adequate CBF study at baseline (study day 0), and 2 had only baseline CBF studies. These 11 subjects (13%) were excluded from the random-effects model that analyzed change in CBF over time. The 71 patients included in the CBF analysis had 320 measurements of good quality (mean 4.5, range 2 to 6 studies per patient); 25 other measurements of poor quality were excluded. Reasons for failure to complete scheduled CBF studies included equipment malfunc-

Table 1. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normovolemia (n=41)</th>
<th>Hypervolemia (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.8±12.7</td>
<td>50.1±13.1</td>
</tr>
<tr>
<td>Female</td>
<td>22 (54)</td>
<td>26 (63)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>16 (39)</td>
<td>15 (37)</td>
</tr>
<tr>
<td>African</td>
<td>9 (22)</td>
<td>14 (34)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15 (37)</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Route of admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency room</td>
<td>13 (32)</td>
<td>13 (32)</td>
</tr>
<tr>
<td>Interhospital transfer</td>
<td>28 (68)</td>
<td>28 (68)</td>
</tr>
<tr>
<td>Hunt-Hess grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>16 (39)</td>
<td>16 (39)</td>
</tr>
<tr>
<td>II</td>
<td>10 (25)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>III</td>
<td>12 (29)</td>
<td>14 (34)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>SAH day of enrollment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>12 (29)</td>
<td>14 (34)</td>
</tr>
<tr>
<td>3</td>
<td>11 (27)</td>
<td>13 (32)</td>
</tr>
<tr>
<td>4</td>
<td>7 (17)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>5</td>
<td>3 (7)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>6</td>
<td>5 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>7</td>
<td>2 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Stratum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (SAH days 0–3, Hunt-Hess grade I or II)</td>
<td>15 (36)</td>
<td>17 (42)</td>
</tr>
<tr>
<td>2 (SAH days 0–3, Hunt-Hess grade III or IV)</td>
<td>9 (22)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>3 (SAH days 4–7, Hunt-Hess grade I or II)</td>
<td>11 (27)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>4 (SAH days 4–7, Hunt-Hess grade III or IV)</td>
<td>6 (15)</td>
<td>7 (17)</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%).

*Day 0 refers to calendar day of SAH onset.
tion, subject refusal or lack of cooperation, and other technical failure.

Mean baseline gCBF on study day 0 (mean 3.4 days after SAH) was 52.3 mL/100 g per minute in the NV group and 48.9 mL/100 g per minute in the HV group (Table 2), a nonsignificant difference. Among the entire study group (Figure 2) and within each stratum (Figure 3), gCBF levels were similar between the 2 treatment groups and were stable over time, with a 5% to 10% reduction from baseline in both groups over the first 2 weeks. Mean baseline gCBF was higher in Hunt-Hess grades I and II patients (strata 1+3) than in grades III and IV patients (strata 2+4) (54.9 versus 43.0 mL/100 g per minute, respectively, \( P \leq 0.0001 \); Figure 3). Baseline gCBF was not different in subjects enrolled between SAH days 0 to 3 (strata 1+2) and SAH days 4 to 7 (strata 3+4) (mean 50.0 versus 51.4 mL/100 g per minute, respectively).

There was no significant difference in gCBF over time between the HV and NV groups in the random effects model after adjusting for stratum, baseline CBF, and study day \( (P=0.55) \) (Table 3). However, baseline gCBF was a significant predictor of subsequent gCBF measurements \( (P<0.001) \). We repeated the random-effects model analysis using mCBF as the outcome variable, and again found no differences between the HV and NV groups. Although it violates the “intention-to-treat” principle, we assessed efficacy of treatment after excluding 13 subjects treated with HHT. There was still no difference in gCBF between the 2 treatment groups. There were no differences in hCBF ipsilateral to the ruptured aneurysm when compared with the contralateral hemisphere in subjects with lateralized aneurysms, or between hemispheres in patients with midline aneurysms.

**Blood Volume**

In the NV group \( (n=32) \), mean BV was 67.9 mL/kg at baseline and 63.4 mL/kg on study day 3, a 6.6% reduction. In the HV group \( (n=35) \), mean BV was 63.5 mL/kg at baseline and 64.8 mL/kg on study day 3, a 2.0% increase (normal range 55 to 80 mL/kg for men and 50 to 75 mL/kg for women). Baseline BV, study day 3 BV, and change in BV were not significantly different between the 2 groups.

![Figure 2](image1.png)

**Figure 2.** Mean global CBF (gCBF) in the hypervolemic and normovolemic treatment groups plotted over the 14-day study period. Error bars represent 95% CIs.

![Figure 3](image2.png)

**Figure 3.** Mean global CBF (gCBF) in the hypervolemic and normovolemic treatment groups within each stratum, plotted over the 14-day study period. Stratum 1: enrolled SAH days 0 to 3, Hunt-Hess grade I or II; stratum 2: enrolled SAH days 0 to 3, Hunt-Hess grade III or IV; stratum 3: enrolled SAH days 4 to 7, Hunt-Hess grade I or II; stratum 4: enrolled SAH days 4 to 7, Hunt-Hess grade III or IV.
TABLE 3. Effect of Treatment on gCBF Over Time, Adjusting for Baseline CBF and Stratum in a Random-Effects Model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimate of gCBF Difference, mL/100 g per min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normovolemia</td>
<td>-0.93±1.57</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypervolemia*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stratum†</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>1 (days 0–3, grade I or II)</td>
<td>-0.43±2.59</td>
<td></td>
</tr>
<tr>
<td>2 (days 0–3, grade III or IV)</td>
<td>-1.22±2.70</td>
<td></td>
</tr>
<tr>
<td>3 (days 4–7, grade I or II)</td>
<td>3.42±2.86</td>
<td></td>
</tr>
<tr>
<td>4 (days 4–7, grade III or IV)*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Baseline gCBF (study day 0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1 mL/100 g per min‡</td>
<td>0.42±0.07</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Values are mean±SE.
*Reference for within-variable comparisons.
†Refers to SAH day and Hunt-Hess grade.
‡For interindividual comparisons, this is the difference in gCBF for every 1 mL/100 g per min difference in baseline gCBF.

Between-individual variance accounts for 35.8% of gCBF variation; within-individual variance accounts for 26.8±7.4% of gCBF variation.

Physiological Variables

Mean PADP (=14 mm Hg) and CVP (=9 mm Hg) were elevated at baseline in both groups (Table 4). Compared with NV patients, HV patients had significantly higher PADP values (mean difference 1.9 mm Hg, P=0.002) during the first 3 days of the study and higher CVP values (mean difference 1.25 mm Hg, P=0.002) and 24-hour fluid intake (mean difference 530 mL, P=0.006) over the entire study period. There were no differences (HV–NV) in MABP (mean difference 0.2 mm Hg, P=0.92) or hematocrit (mean difference -1.7%, P=0.06) between the 2 groups during the study period. The higher mean 24-hour fluid intake in HV patients was accompanied with higher fluid outputs, resulting in no difference in 24-hour fluid balance between the 2 groups (mean difference -28 mL, P=0.81) (Figure 4).

Symptomatic Vasospasm

Eight subjects (20%) in each treatment group developed symptomatic vasospasm during the study period. Cerebral infarction from vasospasm occurred in 4 NV patients (10%) and 7 HV patients (17%). Symptomatic vasospasm was not predicted by age, gender, treatment assignment, Hunt-Hess grade, SAH day at study entry, baseline gCBF, baseline mCBF, or mean gCBF over the entire study period. However, patients with symptomatic vasospasm had lower minimum gCBF values (the lowest CBF recorded in any detector on any study day was 36.2±4.7 versus 39.0±5.8 mL/100 g per minute, P=0.053) and lower minimum mCBF values (the lowest CBF recorded in any detector on any study day was 29.1±7.3 versus 33.3±6.9, P=0.04) than those who did not. The median value for minimum mCBF among all subjects was 33.1 mL/100 g per minute; 8% (3/39) of patients with values above this level developed symptomatic vasospasm compared with 30% (12/40) of those with values below this level (P=0.01).

Thirteen subjects (6 NV, 7 HV) were treated with HHT to treat symptomatic vasospasm during the study period. Because of the small number of cases and lack of temporally appropriate CBF measurements, it was not possible to determine whether HHT had an effect on CBF.

Complications

There were no significant differences in the frequency of any of the complications for which we screened between the 2 treatment groups. Radiographic cerebral edema occurred in 7 NV patients (17%) and 6 HV patients (15%). Congestive heart failure occurred in only 1 patient in the HV group (3%). Hyponatremia (<135 mEq/L) occurred in only 2 patients (5%) in each treatment group.

Outcome

On SAH day 14, 27 of the 41 subjects in each treatment group (66%) were functionally independent, and 1 in each group (2%) was dead (Table 5). Three additional subjects died later during their hospitalization, after the study was completed. GOS scores were not significantly different between the 2 groups at SAH day 14 or at 3 months, and there was little change in outcome status between 3, 6, and 12 months after SAH. There were no differences in 3-month outcome between HV and NV subjects within each of the 4 strata.

In a univariate analysis of the entire study group, significant predictors of poor outcome (dead, vegetative, or dependent with severe deficit) at 3 months included a Hunt-Hess grade of III or IV (43% [13/30] versus 4% [2/49] among Hunt-Hess grade I or II patients, P<0.0001), any neurological complication (38% [13/34] versus 4% [2/45] without, P=0.0002), lower mCBF values during the study period (23.5±5.4 versus 34.7±5.7, P<0.0001), any cardiovascular complication (53% [9/17] versus 10% [6/61] without, P=0.003), and any infectious complication (38% [10/26] versus 9% [5/53] without, P=0.005). In a logistic regression analysis to identify independent predictors of poor outcome, a Hunt-Hess grade of III or IV (odds ratio 16.9, 95% confidence interval [CI] 0.56 to 142.8, P=0.008) and lower mCBF values recorded during the study (odds ratio 0.70, 95% CI 0.56 to 0.86 for each 1.0 mL/100 g per minute increase, P=0.0008) were associated poor outcome at 3 months.

Discussion

In this study, we found that HV treatment after aneurysm surgery did not increase blood volume or CBF compared with NV treatment. Although fluid administration may be important to avoid hypovolemia after SAH, prophylactic HV therapy probably does not confer an additional benefit.

The reduction in CBF that typically develops after SAH has been attributed to 2 causes. Within hours of onset, a primary generalized reduction in cerebral oxidative metabo-
lism occurs, in conjunction with a coupled decrease in CBF that is less prominent.\textsuperscript{7–10,42–44} Although this occurs even in patients in the best clinical condition, these reductions are greatest in patients with depressed levels of consciousness (Hunt-Hess grades III to V).\textsuperscript{7–15} The primary cause of this phenomenon is thought to be a toxic effect of SAH on cerebral metabolism,\textsuperscript{7,10,44} although hydrocephalus, cerebral edema, and increased intracranial pressure may also contribute.\textsuperscript{8,15,16} Over the following 2 weeks, further diminution of CBF may occur as a consequence of cerebral vasospasm, and if ischemic levels are reached, additional reductions in cerebral metabolism may occur. These late reductions in CBF are usually focal or topographically heterogeneous and are most prominent in patients with focal neurological deficits and severe angiographic narrowing.\textsuperscript{7–14,17–21,45}

On the first postoperative day (mean 3.4 days after SAH) we found the expected relationship between poor Hunt-Hess grade and lower gCBF values.\textsuperscript{7–15} However, when plotted from the time of study entry (Figure 1), mean gCBF remained slightly below baseline but did not decline progressively as reported in earlier studies. This lack of CBF decline may be explained by the fact that neither treatment group was allowed to become hypovolemic. Alternately, CBF reductions resulting from vasospasm may have been minimized because symptomatic patients were treated with HHT and nimodipine.

Almost all studies demonstrating progressive reduction in CBF after SAH were published before 1985,\textsuperscript{7–19} when most patients were treated with fluid restriction and delayed surgery. By contrast, studies performed during the volume-expansion era have shown stable CBF levels after SAH. Origitano et al\textsuperscript{33} reported an immediate and sustained increase in CBF after instituting HV therapy with albumin shortly after admission for SAH. They did not measure the baseline volume status of their patients, who may have been hypovolemic before treatment. Although we did not observe a similar increase in CBF between study days 0 and 1 in either treatment group, most of our patients were already hypervolemic.
lemic on the first postoperative day, with elevated PADP values and normal-to-high blood volumes. Similarly, Mori et al. observed a progressive reduction in hemispheric CBF in patients who developed symptomatic vasospasm, which improved after volume expansion with albumin and dextran. These patients were hypovolemic before they started HV therapy, however, with low-normal pulmonary artery wedge pressures and cardiac outputs. Mizuno et al. found stable CBF values within 3 weeks of SAH, as did we, but they administered prophylactic hyperdynamic therapy (hydroxyethyl starch and dobutamine) to most patients.

These findings suggest that CBF is dependent on volume status only when SAH patients are in the hypovolemic-to-normovolemic range. In our study, HV therapy resulted in higher daily fluid intake and cardiac filling pressures than NV therapy but had no effect on net fluid balance, blood volume, or CBF. This observation and those of others indicate that once a state of normovolemia to mild hypervolemia has been attained, additional fluids do not lead to further increases in BV or CBF. This concept is supported by the observation that net fluid balance remained well matched in both groups during the second week of the study, when fluid intake fell from approximately 4 to 2.5 L/d (Figure 4). Progressive BV reduction has been reported in SAH patients given maintenance crystalloid infusions (1.5 to 3.0 L/d) but did not occur in our subjects or in other studies of patients given prophylactic HV therapy.

To our knowledge, fluid supplementation has never been shown to increase BV from normal to hypervolemic levels after SAH.

It is possible that our study intervention—volume expansion guided by target cardiac filling pressures—was not robust enough to increase CBF. Although additional volume may have significantly increased blood volume or CBF in our HV patients, we doubt this, because the additional fluid would probably be matched by equal urinary losses. There was no difference in MABP between the 2 groups in our study, and while no amount of additional volume may have produced an increase in blood pressure, pharmacologically induced hypertension has been shown to improve CBF in ischemic regions in patients with symptomatic vasospasm. Darby et al. found that dopamine-induced hypertension led to increased CBF in ischemic (<25 mL/100 g per minute), noninfarcted territories without producing an increase in mean global CBF. We did not analyze CBF values before and after instituting HHT in our patients with symptomatic vasospasm.

Symptomatic vasospasm was associated with lower mCBF during the study period. The association of symptomatic vasospasm with decreased CBF is well established. Because HV therapy might be able to maintain regional CBF above the ischemic threshold without producing an effect on gCBF, we repeated the random-effects model analysis using mCBF as the outcome variable and again found no difference between the HV and NV groups.

Using logistic regression we identified 2 independent predictors of poor outcome (dependent or dead) at 3 months: a postoperative Hunt-Hess grade of III or IV and lower mCBF values during the study period. Others have also identified poor Hunt-Hess grade and low CBF1,12,54,55 as predictors of poor outcome after SAH.

Several limitations of this study deserve mention. Very-poor-grade patients (Hunt-Hess grades IV and V) were relatively underrepresented, which may limit the generalizability of our findings. However, we found no difference in CBF between the 2 treatment groups even after stratification by Hunt-Hess grade. We analyzed our results according to an intention-to-treat analysis, despite the fact that 13 patients (16%) were switched to HHT at some point during the study period for symptomatic vasospasm. Although we found no difference in CBF between the 2 groups when these patients were removed from the analysis, a significant difference in CBF may have been detected had HHT not been used. We used surface rather than tomographic measurements of CBF, which may have been able to detect clinically relevant areas of ischemia deep in the brain. We were unable to identify predictors of symptomatic vasospasm other than mCBF. However, we did not quantify the amount of SAH on admission CT scans or analyze TCD data, factors that have been predictive of delayed ischemia in other studies.

In summary, we found that HV therapy after aneurysm clipping did not result in increased CBF compared with NV therapy. Although our study was not powered to detect an effect on clinical outcome, our results suggest that postoperative HV therapy probably has no advantage over NV therapy for prevention of delayed ischemia after SAH. However, because invasive hemodynamic monitoring directed toward avoiding hypovolemia may still be of value, we do not feel that our results should change the way patients with SAH are currently treated. Our findings indicate that supplemental albumin given to maintain cardiac filling pressures in the

### Table 5. Clinical Outcome

<table>
<thead>
<tr>
<th></th>
<th>14 d After SAH</th>
<th>3 mo After SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NV</td>
<td>HV</td>
</tr>
<tr>
<td>Independent, minimal deficit</td>
<td>27 (66)</td>
<td>27 (66)</td>
</tr>
<tr>
<td>Independent, moderate deficit</td>
<td>4 (10)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Dependent, severe deficit</td>
<td>9 (22)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Vegetative</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dead</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are n (%).
normal range (CVP >5 mm Hg or PADP >7 mm Hg) is an effective and safe method for preventing volume contraction after SAH. We currently reserve prophylactic CVP-guided volume expansion for patients who are Hunt-Hess grades III to V or for patients with thick cisternal SAH (Fisher grade III) on the admission CT scan. We use PADP-guided volume expansion for patients with left ventricular dysfunction, renal insufficiency, or symptomatic vasospasm. A controlled study is needed to determine whether CVP-guided fluid administration is more safe and effective than scheduled periodic fluid administration for preventing hypovolemia after SAH.

In some centers, pharmacologically induced hypertension is given after surgery to asymptomatic patients with elevated TCD velocities or other risk factors for symptomatic vasospasm. Although postoperative HV therapy does not increase CBF, a more robust intervention might. A controlled study that analyzes the effect of prophylactic HHT on CBF is needed to determine whether this approach might reduce the incidence of symptomatic ischemia in high-risk patients.

Acknowledgements
This study was supported by a grant from the National Institutes of Health (RO1-N27325-01) to Dr Solomon. We thank Marianne Mearon for performing the blood volume measurements; John Mann, MD, and William L. Young, MD, for assistance in analyzing the CBF measurements; Daphne Copeland, MPH, for statistical support; Chris Commichau, MD, for helpful editorial comments; and the nursing staff of the Columbia–Presbyterian Neurological Intensive Care Unit.

References
Effect of Hypervolemic Therapy on Cerebral Blood Flow After Subarachnoid Hemorrhage: A Randomized Controlled Trial
Laura Lennihan, Stephan A. Mayer, Matthew E. Fink, Avis Beckford, Myunghee C. Paik, Haiying Zhang, Ya-Chi Wu, Louise M. Klebanoff, Eric C. Raps and Robert A. Solomon

Stroke. 2000;31:383-391
doi: 10.1161/01.STR.31.2.383
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/2/383