Blood Volume Measurement to Guide Fluid Therapy After Aneurysmal Subarachnoid Hemorrhage
A Prospective Controlled Study

Reinier Hoff, MD; Gabriel Rinkel, MD; Bon Verweij, MD; Ale Algra, MD; Cor Kalkman, MD

Background and Purpose—Conventional parameters used to guide fluid therapy after aneurysmal subarachnoid hemorrhage (SAH) are poorly related to blood volume. In a prospective controlled study we assessed whether fluid management guided by daily measurements of blood volume (BV) reduces the incidence of severe hypovolemia compared to conventional fluid balance guided fluid therapy.

Methods—We used Pulse Dye Densitometry to measure BV daily in 102 patients during the first 10 days after SAH. Fluid management was based on BV-measurements in the intervention group (n=54) and on fluid balance in the control group (n=48). Severe hypovolemia was defined as BV <50 mL/kg.

Results—In the intervention group 6.7% of BV measurements were in the severe hypovolemic range and in the control group 17.1% (mean weighted difference 7.7%; 95% CI: 1.4 to 13.9%). In the intervention group 21 patients (39%) had 1 or more measurements with severe hypovolemia versus 26 (54%) of the controls (RR 0.7; 95% CI: 0.5 to 1.1).

Conclusions—Guiding fluid management on daily measurements of blood volume reduces the incidence of severe hypovolemia after SAH. The effects on neurological outcome should be studied. (Stroke. 2009;40:2575-2577.)

Key Words: aneurysm, brain ischemia, cerebrovascular disease, hemodynamics, subarachnoid hemorrhage, blood volume

Hypovolemia after aneurysmal subarachnoid hemorrhage (SAH) increases the risk of delayed cerebral ischemia (DCI).1,2 DCI occurs in 30% to 40% of patients, usually 4 to 10 days after the hemorrhage, and is a major contributor to poor outcome.3 Fluid management after SAH is usually guided on clinical parameters as heart rate, arterial and central venous blood pressures, pulmonary capillary wedge pressure, fluid balance, or serum sodium concentration. These parameters have a poor relation with actual measured blood volume.2,4–6 In a prospective controlled study we assessed whether fluid management guided by daily measurements of blood volume results in less hypovolemia after SAH than conventional fluid balance guided fluid therapy.

Methods

Study Population
The Medical Ethics Research Committee of the UMC-Utrecht approved the study, and written informed consent was obtained. Patients were eligible if admitted to the UMC-Utrecht within 72 hours after SAH. Patients with accompanying head injury, pregnancy, liver or kidney failure, an allergy for the indicator dye, or with imminent death on admission were excluded. The study period was day 1 to 10 after the onset of SAH.

Study Design
The study was performed in 3 sequential cohorts of patients: first a control group (25% of patients), then an intervention group (50% of patients), and finally again a control group (25% of patients). We measured BV daily in all included patients by means of Pulse Dye Densitometry (PDD). This technique was previously validated and used in patients after SAH.2,6,7 BV values were classified as normal (60 to 80 mL/kg), moderate hypovolemic (50 to 60 mL/kg), severe hypovolemic (<50 mL/kg), or hypervolemic (>80 mL/kg).6,8 The goal of fluid management was to maintain normovolemia. At admission, an infusion of 3 L normal saline per day was installed, in addition to oral intake as desired by the patient.

In the control groups, intravenous fluid administration was adjusted on the basis of the fluid balance, calculated every 6 hours, by subtracting urinary volume from total oral and intravenous intake. The aim was to keep the daily fluid balance at 750 mL positive, compensating for insensible fluid loss. With fever, the desired level for the daily fluid balance was increased by 500 mL for each degree above 37° Celsius.

In the intervention group fluid management was guided by daily BV-measurements. When BV was outside the normovolemic range, fluid management was changed according to a standardized intervention protocol.

Central venous pressure was not routinely monitored in WFNS grade I and II patients. If DCI developed, fluid management was continued according to treatment allocation; no intentional hypervolemia or hemodilution was used. Induced hypertension could be applied.
Outcome Measurements
Primary outcome was the occurrence of severe hypovolemia. Secondary outcomes included daily fluid intake, excretion, and balance, and the clinical diagnosis of DCI (after excluding other causes of neurological deterioration with CT and appropriate laboratory examinations) or pulmonary edema or the use of inotropics on any day during the study period.

Statistical Analysis
Proportions of patients were compared in terms of risk ratios (RR) and differences in continuous variables were reported as mean differences, each with corresponding 95% confidence interval (CI). Because in each patient multiple BV measurements were performed, we used weighted linear regression for comparison of “per patient mean” values, with the inverse of the standard error of the “per patient mean” taken as weight.

Results
During 2006 and 2007, 102 patients were included (intervention n=54; controls n=48). Patient characteristics and outcome measurements were comparable for both control periods, and data from these periods are combined (Table 1).

The Figure presents the results of BV-measurements, divided into the 4 categories of volume status. In the intervention group on average 6.7% of the BV-measurements showed severe hypovolemia as compared with 17.1% in controls (mean weighted difference 7.7%; 95% CI: 1.4 to 13.9%). In the intervention group 21 patients (39%) had 1 or more measurements with severe hypovolemia during the entire 10-day study period versus 26 (54%) of the controls (RR 0.7; 95% CI: 0.5 to 1.1).

Secondary outcomes are presented in Table 2. There were no serious adverse events related to BV measurements.

Discussion
Fluid management guided by daily BV measurements improves volume status after SAH compared with conventional

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>Women</td>
<td>42 (78%)</td>
<td>36 (75%)</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>58±15</td>
<td>56±14</td>
</tr>
<tr>
<td>Length, cm (mean±SD)</td>
<td>171±9</td>
<td>172±10</td>
</tr>
<tr>
<td>Weight, kg (mean±SD)</td>
<td>74±14</td>
<td>77±18</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>23 (43%)</td>
<td>22 (46%)</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>15 (28%)</td>
<td>11 (23%)</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>9 (17%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>7 (13%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>WFNS grade on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22 (41%)</td>
<td>25 (52%)</td>
</tr>
<tr>
<td>II</td>
<td>12 (22%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>III</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>IV</td>
<td>8 (15%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>V</td>
<td>9 (17%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Aneurysm treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coiling</td>
<td>28 (52%)</td>
<td>32 (67%)</td>
</tr>
<tr>
<td>Clipping</td>
<td>18 (33%)</td>
<td>13 (27%)</td>
</tr>
<tr>
<td>Modified rankin scale at 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>1</td>
<td>21 (39%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>2</td>
<td>13 (24%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>3</td>
<td>2 (4%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>4</td>
<td>5 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>5</td>
<td>2 (4%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Dead</td>
<td>10 (19%)</td>
<td>9 (19%)</td>
</tr>
</tbody>
</table>

Data are numbers with percentages or means with standard deviations. SD indicates standard deviation; WFNS, World Federation of Neurological Surgeons.

Table 2. Secondary Outcome Measurements

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Controls</th>
<th>Mean Difference (95% CI) or Risk Ratio (95% CI)</th>
<th>n=54</th>
<th>n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid intake, L/day</td>
<td>5.2 (1.0)</td>
<td>4.7 (1.1)</td>
<td>MD 0.8 (0.3–1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid excretion, L/day</td>
<td>4.2 (1.3)</td>
<td>3.9 (1.3)</td>
<td>MD 0.6 (0.1–1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid balance, L/day</td>
<td>+1.0 (0.8)</td>
<td>+0.8 (0.5)</td>
<td>MD 0.1 (−0.1–0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCI</td>
<td>18 (33%)</td>
<td>19 (40%)</td>
<td>RR 0.8 (0.5–1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>12 (22%)</td>
<td>5 (10%)</td>
<td>RR 2.1 (0.8–5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inotropic support</td>
<td>20 (37%)</td>
<td>11 (23%)</td>
<td>RR 1.6 (0.9–3.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented are mean values in liters per day (with standard deviation) of daily fluid intake/excretion/balance, and No. of patients (with proportions) of newly diagnosed DCI or pulmonary edema or use of inotropic support on any day during the study period.
fluid balance guided therapy. The proportion of measurements indicating severe hypovolemia was more than halved in the intervention group, whereas the proportion of measurements in the hypervolemic range did not increase.

Previous studies on measured BV repeatedly demonstrated hypovolemia after SAH and associations between hypovolemia, DCI, and poor outcome. In these studies fluid therapy was guided by conventional hemodynamic parameters. We found, with BV-guided fluid therapy, a statistically significant reduction in severe hypovolemia, but the incidence of DCI did not decrease to the same extent. Possible explanations are limited power to study DCI and its dependency on other factors such as the severity of vasospasm and global ischemia during the initial event.

We defined normovolemia (60 to 80 mL/kg) in accordance with previous studies, but this is a simplification. Firstly, BV varies with age, sex, and stature. These variables showed no difference between control and intervention groups. Secondly, the changes in BV that occur as a result of illness are incompletely understood. Therefore we conservatively used wide margins in our definition of normovolemia.

A limitation is that DCI and pulmonary edema were clinical diagnoses made by the treating physicians, who may have been biased by their knowledge on treatment allocation. We do not routinely use transcranial doppler because of its suboptimal sensitivity for actual neurological deficits.

Pulmonary edema was considered present more often in the intervention group, albeit not statistically significant. However, there was no increase in measured hypervolemia in the intervention group and no difference in fluid balance between both treatment groups.

Conclusion
Guiding fluid management on daily BV-measurements results in less hypovolemia after SAH. Whether this will lead to improved neurological outcome remains to be studied. The effects on the extracranial circulation must be taken into account in future studies.

Acknowledgments
The authors thank research nurses Joanna Schinkel and Etienne Sluis and anesthesiology-resident Joep Scholten for performing BV measurements and data collection, and neurology-resident Sanne Dorhout Mees for her assistance in patient inclusion.

Sources of Funding
This study was supported by a grant of ZonMw—the Netherlands Organization for Health Research and Development (project number 945-05-035) and by the Department of Perioperative & Emergency Care, University Medical Center Utrecht, The Netherlands.

Disclosures
None.

References
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Stroke. 2009;40:2575-2577; originally published online May 7, 2009;
doi: 10.1161/STROKEAHA.108.538116

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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