Early Intensive Versus Minimally Invasive Approach to Postoperative Hemodynamic Management After Subarachnoid Hemorrhage

Tatsushi Mutoh, MD, DVM, PhD; Ken Kazumata, MD; Shunsuke Terasaka, MD; Yasuyuki Taki, MD, PhD; Akifumi Suzuki, MD; Tatsuya Ishikawa, MD

Background and Purpose—The results of previous studies suggest that early goal-directed fluid therapy (EGDT) reduces delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage, but the effects of EGDT on clinical outcomes are still unclear. This study aimed to determine whether EGDT improves outcomes compared with standard less-invasive hemodynamic therapy.

Methods—This study included 160 patients treated within 24 hours after subarachnoid hemorrhage, randomized to receive either (1) EGDT guided by preload volume and cardiac output monitored by transpulmonary thermodilution (treatment group) or (2) standard therapy guided by fluid balance or central venous pressure, assisted by uncalibrated less-invasive cardiac output monitoring during hyperdynamic therapy in patients with clinical or radiological indications of DCI (control group). DCI determined by clinical or radiological findings and functional outcome determined by the modified Rankin Scale score at 3 months were compared between groups.

Results—For all clinical grades combined, there were no significant differences in the rates of DCI (33% versus 42%; \( P = 0.33 \)) or modified Rankin Scale score of 0 to 3 at 3 months (67% versus 57%; \( P = 0.22 \)) between the 2 groups. For patients with poor clinical grade, those who received EGDT had a significantly lower rate of DCI (5% versus 14%; \( P = 0.036 \)), modified Rankin Scale score of 0 to 3 at 3 months (52% versus 36%; \( P = 0.026 \)), and shorter length of intensive care unit stay (14 versus 17 days; \( P = 0.043 \)) than those who received standard therapy.

Conclusions—EGDT is beneficial for reducing DCI and improving postoperative functional outcome in patients with poor clinical grade.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: UMIN000007509.

Key Words: delayed cerebral ischemia ▪ fluid therapy ▪ hemodynamic management ▪ subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) is one of the main causes of severe disability and death after aneurysmal subarachnoid hemorrhage (SAH).\(^\text{1,2}^\) The pathogenesis of DCI seems to be multifactorial, including factors such as vasospasm, microcirculatory dysfunction, microembolism, and cortical spreading depolarization related to the primary brain injury.\(^\text{4-6}^\) Systemic hemodynamic insufficiency such as decreased intravascular volume and low cardiac output (CO) can contribute to the development of DCI.\(^\text{7-13}^\)

The results of previous studies suggest that early goal-directed fluid therapy (EGDT) reduces the incidence of DCI after aneurysmal SAH,\(^\text{10,14}^\) but the effects of EGDT on clinical outcomes are still unclear. This prospective study aimed to determine whether EGDT improves outcomes compared with standard less-invasive hemodynamic therapy. The outcomes after EGDT were also evaluated in subgroups of patients with poor clinical grade,\(^\text{10,14}^\) or concurrent cardiopulmonary complications,\(^\text{16-18}^\) which are well-known risk factors for DCI and poor outcome.

Methods

Patient Selection

This 2-center, prospective, randomized, nonblinded clinical trial enrolled patients who were admitted for the treatment of SAH at Teine Keijinkai Hospital and the Research Institute for Brain and Blood Vessels-AKITA between April 2009 and September 2013. Patients were screened for enrollment after obliteration of the causative aneurysm. The inclusion and exclusion criteria are shown in Figure I and

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the Methods in the online-only Data Supplement. The study protocol was approved by the institutional ethics committee at each center. After obtaining written informed consent, patients were randomized into 2 groups using a stratification method based on the World Federation of Neurosurgical Societies (WFNS) grade (good: I–III; poor: IV–V), to the control arm who received standard therapy or the treatment arm who received EGDT.

**Treatment Algorithms**

All patients at both study sites were managed in accordance with our predefined SAH treatment protocol (Figure).21,22,23 The general systemic management and therapeutic algorithms used are shown in the Figure II in the online-only Data Supplement. All patients underwent transcranial Doppler ultrasonography every 1 to 2 days by a single investigator to screen for cerebral vasospasm.21 When clinically indicated, patients underwent diffusion-weighted MRI, magnetic resonance angiography, and imaging criteria recommended for use in research studies investigating DCI by the recent expert consensus.3 The primary outcome measure was DCI within 21 days after SAH. DCI was defined as a new focal neurological deficit or global neurological deterioration (a decrease of ≥2 points on the Glasgow Coma Scale) lasting >2 hours, after exclusion of intracranial hemorrhage, hydrocephalus, seizures, metabolic derangements, and infection, with or without radiological signs of cerebral vasospasm. In unconscious patients, DCI was diagnosed when there was a lack of neurological progress in the absence of the

**Outcome Measures**

The outcome measures used in this study were based on the clinical and imaging criteria recommended for use in research studies investigating DCI by the recent expert consensus.3 The primary outcome measure was DCI within 21 days after SAH. DCI was defined as a new focal neurological deficit or global neurological deterioration (a decrease of ≥2 points on the Glasgow Coma Scale) lasting >2 hours, after exclusion of intracranial hemorrhage, hydrocephalus, seizures, metabolic derangements, and infection, with or without radiological signs of cerebral vasospasm. In unconscious patients, DCI was diagnosed when there was a lack of neurological progress in the absence of the

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**Figure.** Study algorithm showing the course of events after the initial aneurysmal subarachnoid hemorrhage (SAH) and aneurysm obliteration. The study included 2 groups: a treatment group who received early goal-directed fluid therapy (EGDT) and a control group who received standard care assisted by less-invasive hemodynamic monitoring. CT indicates computed tomography; CV, central venous; DCI, delayed cerebral ischemia; MRA, magnetic resonance angiography; and mRS, modified Rankin Scale.
confounders described above or other causes of brain damage observed on imaging examinations, and there was evidence of one of the following: cerebral vasospasm on transcranial Doppler ultrasonography, magnetic resonance angiography, or digital subtraction angiography; perfusion deficit on single-photon emission computed tomography; regional cerebral hypoxia on near-infrared spectroscopy; or cerebral infarction on imaging not attributable to other causes.3,12,14,40,41

The secondary outcome measures were modified Rankin Scale (mRS) score (poor: 4–6 or favorable: 0–3) at 1 and 3 months after SAH, radiologically confirmed new infarct (as assessed by diffusion-weighted magnetic resonance images on days 7 and 14 after SAH), persistent or newly diagnosed cardiopulmonary complications (such as pulmonary edema or left ventricular dysfunction based on clinical, chest computed tomography, and echocardiographic findings) at the onset of the DCI risk period (day 4 after SAH), and clinical response to hemodynamic therapy defined as overall neurological improvement on day 14.

An experienced stroke neurologist who was blinded to the treatment allocation and magnetic resonance findings assessed the clinical outcomes of all patients. Two trained board-certified radiologists who were blinded to the treatment allocation and clinical outcomes evaluated the images and reached agreement on all findings.

Statistical Analysis
The initial power calculation was based on an expected incidence of DCI of 40% in the control arm and 15% in the treatment arm and estimated that 69 patients were needed in each group with an α risk of 5% and power of 80%. The primary analysis was performed on an intention-to-treat basis. Normally distributed numeric data were compared between groups using the Mann–Whitney U test. Categorical frequencies were compared using the χ² test or Fisher exact test when a cell size was <5. P<0.05 was considered statistically significant. Subgroup analysis was performed for patients with good (I–III) or poor (IV–V) WFNS grade and for patients with persistent cardiopulmonary complications at the beginning of the DCI risk period. All statistical analyses were performed using SPSS version 22 (SPSS, Chicago, IL).

Results
Table 1 shows the baseline patient characteristics in the EGDT and standard care groups (n=80 per group). Changes in the hemodynamic parameters in each group are shown in the Table and Figure III in the online-only Data Supplement. There were no significant differences in any of the parameters between the 2 groups.

Table 2 shows the primary intention-to-treat analysis and secondary outcome measures. Analysis of all patients in all clinical grades found no significant differences in the incidence of DCI (33% versus 42%; P=0.33) or other outcome measures. However, subgroup analysis of patients with poor WFNS grade showed that those who received EGDT had a significantly lower incidence of DCI (5% versus 14%; P=0.036), higher frequency of favorable functional outcome at 3 months (52% versus 36%; P=0.026), and shorter length of intensive care unit stay (median, 14 versus 17 days; P=0.043) than those who received standard care. In patients with poor WFNS grade, those who received EGDT were more likely to have a clinical response to hemodynamic therapy for DCI (67% versus 36%; P=0.038), had a significantly smaller volume of fluid intake than those who received standard care (Figure IIIID in the online-only Data Supplement), and tended to have a lower incidence of therapy-related pulmonary edema (5% versus 24%; P=0.079). The median indwelling time for monitoring devices was 14 days (interquartile range, 14.0–15.0 days) for patients who received EGDT and 7 days (interquartile range, 6.0–7.0 days) for those who received standard care (P<0.0001).

In the subgroup of 37 patients with coexisting cardiopulmonary complications at the beginning of the DCI risk period (left ventricular ejection fraction <40%, n=18; wall motion abnormality suggestive of takotsubo cardiomyopathy, n=21; pulmonary edema, n=27; and pneumonia, n=10), those who received EGDT had a significantly higher frequency of favorable functional outcome at 3 months (63% versus 38%; P=0.045) and a strong tendency toward a shorter length of intensive care unit stay (median, 15 versus 17 days; P=0.068) compared with those who received standard care. There were no significant differences in the incidence of DCI (P=0.22) or the frequency of mRS score of 0 to 3 after 1 month (P=0.22) between patients who received EGDT and standard therapy.

Discussion
This is the first study to confirm that EGDT can reduce the incidence of DCI and improve functional outcome at 3 months compared with standard postoperative fluid management in patients with SAH, especially those with poor WFNS grade. EGDT may also result in better clinical outcomes in patients with concurrent cardiopulmonary complications who receive treatment for DCI. On the contrary, standard therapy guided by conventional indicators of fluid balance and assisted by less-invasive monitoring of CO is sufficient for patients with good WFNS grade.

Ideal fluid management for the treatment of DCI involves knowing how much hydration patients will tolerate and
Table 2. Outcome Measurements of Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>EGDT (n=80)</th>
<th>Usual Care (n=80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCI</td>
<td>8 (10)</td>
<td>14 (18)</td>
<td>0.17</td>
</tr>
<tr>
<td>Good grade</td>
<td>4</td>
<td>3</td>
<td>0.47</td>
</tr>
<tr>
<td>Poor grade</td>
<td>4</td>
<td>11</td>
<td>0.036*</td>
</tr>
<tr>
<td>CP complications</td>
<td>2</td>
<td>8</td>
<td>0.058</td>
</tr>
<tr>
<td>Response to hemodynamic</td>
<td>19 (70)</td>
<td>17 (58)</td>
<td>0.14</td>
</tr>
<tr>
<td>Good grade</td>
<td>5</td>
<td>8</td>
<td>0.69</td>
</tr>
<tr>
<td>Poor grade</td>
<td>14</td>
<td>9</td>
<td>0.038*</td>
</tr>
<tr>
<td>CP complications</td>
<td>4</td>
<td>3</td>
<td>0.18</td>
</tr>
<tr>
<td>Therapy-related pulmonary</td>
<td>1 (4)</td>
<td>6 (12)</td>
<td>0.089</td>
</tr>
<tr>
<td>edema</td>
<td>Good grade</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Poor grade</td>
<td>1</td>
<td>6</td>
<td>0.079</td>
</tr>
<tr>
<td>CP complications</td>
<td>1</td>
<td>5</td>
<td>0.22</td>
</tr>
<tr>
<td>Length of ICU stay, d</td>
<td>14 (14.0–17.0)</td>
<td>15 (15.0–18.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Good grade</td>
<td>15 (13.0–17.0)</td>
<td>15 (14.0–17.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Poor grade</td>
<td>14 (14.0–17.0)</td>
<td>17 (14.0–18.0)</td>
<td>0.043*</td>
</tr>
<tr>
<td>CP complications</td>
<td>15 (14.0–17.0)</td>
<td>17 (14.3–19.0)</td>
<td>0.068</td>
</tr>
<tr>
<td>mRS score of 0–3 at 1 month</td>
<td>45 (56)</td>
<td>40 (50)</td>
<td>0.43</td>
</tr>
<tr>
<td>Good grade</td>
<td>24 (53)</td>
<td>25 (63)</td>
<td>0.92</td>
</tr>
<tr>
<td>Poor grade</td>
<td>21 (47)</td>
<td>15 (37)</td>
<td>0.26</td>
</tr>
<tr>
<td>CP complications</td>
<td>7 (41)</td>
<td>5 (25)</td>
<td>0.29</td>
</tr>
<tr>
<td>mRS score of 0–3 at 3 months</td>
<td>52 (67)</td>
<td>44 (57)</td>
<td>0.22</td>
</tr>
<tr>
<td>Good grade</td>
<td>25 (48)</td>
<td>28 (64)</td>
<td>0.36</td>
</tr>
<tr>
<td>Poor grade</td>
<td>27 (52)</td>
<td>16 (36)</td>
<td>0.026*</td>
</tr>
<tr>
<td>CP complications</td>
<td>10 (63)</td>
<td>5 (38)</td>
<td>0.045*</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or number (%). CP complications indicate the presence of persisting or newly diagnosed cardiopulmonary complications on day 4 after subarachnoid hemorrhage ictus. Response to hemodynamic therapy was defined as overall neurological improvement on day 14 to maximal hemodynamic protocols used for standard management provide similar results to EGDT with advanced hemodynamic monitoring in patients without complications and good WFNS grade.

This study is limited by the small patient numbers in the subgroups analyses and the restriction to either our EGDT protocol or standard postoperative SAH management. Although a new focal neurological deficit, new infarction, or both are the most significant predictors of severe disability or death at 3 months,40,50 the follow-up period in this study may not have been long enough to assess longer term outcomes adequately. Our results therefore do not answer the question of whether EGDT can be directly substituted for conventional management, although similar management protocols have already been used.96,98 Our results indicate that more studies are warranted to determine whether refinement of the monitoring device and the short-term treatment protocols can reduce complications, enable less-invasive user-friendly monitoring, and improve long-term outcomes.

In conclusion, the results of this study show that EGDT is beneficial for optimizing the complex SAH-induced hemodynamic changes during the treatment of DCI and for improving the prognosis of patients with poor WFNS grade or coexisting cardiopulmonary complications, compared with standard less-invasive hemodynamic therapy.

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Disclosures
None.

References


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Supplemental Methods

Patient Selection Criteria

The inclusion criteria were: (1) age 18 years or older, (2) initial aneurysmal subarachnoid hemorrhage (SAH), (3) pre-morbid modified Rankin Scale (mRS) score of 0 or 1, (4) aneurysm treatment performed during the first 24 hours after the initial hemorrhage (Day 0), and (5) informed consent from the patient or the patient’s legal representative. If the patient was not capable of giving informed consent and no legal representative was available, informed consent was given by an independent physician who was not involved in the patient’s treatment or in conducting the trial.

The exclusion criteria were: (1) SAH of other than aneurysmal origin, (2) no hemorrhage visible on the initial the CT scan (modified Fisher Grade 1), (3) concurrent participation in another interventional trial (participation in an observational trial was not considered grounds for exclusion), (4) life expectancy of less than 1 year for reasons other than the current SAH, and (5) other concomitant severe disease (e.g., intracardiac shunting, long-term cardiac arrhythmia, significant valvular heart disease, or occlusive peripheral arterial disease) that might affect treatment requirements. After screening and recruitment, patients were not enrolled in any other DCI prevention trials.
**Single-Indicator Transpulmonary Thermodilution Technique**

The single-indicator transpulmonary thermodilution system incorporated into the PiCCOplus monitor (version 6.0; Pulsion Medical Systems, Munich, Germany) measures the change in temperature over time induced by a bolus injection of cold saline.² The cardiac output is then calculated by analysis of the thermodilution curve using the Stewart–Hamilton equations.³ The measurement of cardiac output by transpulmonary thermodilution has been previously validated against the pulmonary thermodilution and Fick methods. By using standard equations, the system calculates the flow \( \dot{Q} \) and the mean transit time \( \dot{t} \) for the thermal indicator. By multiplying these two factors, the system can determine the thermal distribution volume between the site of injection and the thermistor. This volume is denoted as intrathoracic thermal volume (ITTV = \( \dot{Q} \times \dot{t} \)). Moreover, the system measures the down-slope time of the logarithmically transformed dilution curve. By multiplying the down-slope time with \( \dot{Q} \), the system calculates the volume of the largest mixing chamber in the serial system comprised of the heart chambers and the lungs, as described by Newman et al.⁴ The largest mixing chamber for the thermal indicator is denoted as pulmonary thermal volume (PTV = DST × \( \dot{Q} \)) and is constituted from the pulmonary blood volume and the lung tissue. By subtracting the PTV from the ITTV, the composite extrapulmonary blood volume between the site of injection and the thermistor is calculated and described as the global end-diastolic volume (GEDV = ITTV − PTV). To calculate the extravascular lung water (EVLW = ITTV − ITBV), the intrathoracic blood volume (ITBV) must be determined so the system uses the empirically established linear relationship between intrathoracic volume and GEDV to calculate ITBV.⁵ The default relationship used by the PiCCO system, ITBV = 1.25 × GEDV, is based on the report by Sakka et al.⁶

The PiCCO system operates in such a way that every time a thermodilution injection is performed, the pulse contour analysis is automatically and immediately self-calibrating from the shape of the arterial pressure wave with the new value of transpulmonary thermodilution to compute each single stroke volume (SV).⁷ As pulse contour analysis continuously measures SV
and arterial pressure, cardiac output (CO = SV × heart rate) and systemic vascular resistance (SVR = mean arterial pressure − central venous pressure × 79.9/CO) are computed simultaneously and displayed for continuous monitoring. The CO, GEDV, EVLW, SV, and SVR were indexed to body surface area (BSA) by means of the DuBois formula (BSA = body weight [kg] × body length [cm]^{0.725} × 71.84), yielding the cardiac index (CI, normal value: 3.0–5.0 L/min/m²), GEDV index (GEDI, 680–800 mL/m²), EVLW index (ELWI, 3–7 mL/kg), SV index (SVI, 40–60 mL/m²), and SVR index (SVRI, 1700–2400 dyn·s/cm⁵/m²).

**Uncalibrated Arterial Pressure Waveform-Based Pulse Contour CO Analysis**

Radial artery access was established with a 20- or 22-gauge catheter connected to a FloTrac sensor kit (MHD8S; Edwards Lifesciences, Irvine, CA) and a plastic splint was placed on the palmar surface of the hand using an elastic bandage to keep the wrist in the neutral position to avoid bending or kinking of the catheter. CO was determined from the arterial pressure waveform using the algorithm of the Vigileo monitor (MHM1; Edwards Lifesciences) using the relationship between pulse pressure and SV and the inverse relationship of pulse pressure with aortic compliance, with calculation performed every 20 s on the basis of the preceding 20-s interval of arterial waveform analysis. A conversion factor (χ) was used to account for dynamic changes in vascular tone, and was calculated from certain pressure waveform characteristics along with patient demographic data (age, sex, height, weight, and BSA) used to estimate large-vessel compliance. The rate of adjustment of the internal variable estimating vascular tone was reduced from 10 min to 60 s with new 3rd-generation software (version 3.02; Edwards Lifesciences) in combination with reduction of pulse wave detection noise.⁸

The FloTrac/Vigileo system also allows a dynamic preload indicator, stroke volume variation (SVV), to be tracked continuously. SVV was assessed using the following equation during a time window of 20 s: SVV (%) = (SVmax − SVmin)/SVmean. The system can detect and eliminate premature ventricular contractions and other arrhythmias for assessment of SVV.
Validity of the Hemodynamic Measurements in Postoperative SAH Patients

The values of CI obtained from the PiCCO system in 16 postoperative SAH patients for a total of 263 data pairs between Days 4 and 14 after SAH were highly correlated ($r^2 = 0.64–0.78$, $P<0.0001$) and had close agreement (bias: 0.05–0.11 L/min/m$^2$; precision: ±0.25 – ±0.33 L/min/m$^2$; percentage error: 13.5–18.0%) with those obtained from the standard pulmonary thermodilution method using a pulmonary artery catheter. With regard to the effects of volume expansion by fluid loading with 500 mL of 6% hydroxyethyl starch for the treatment of clinical deterioration attributable to DCI, there was good correlation between GEDI and SVI ($r^2 = 0.45$; $P<0.0001$), and poor correlation between pulmonary capillary wedge pressure and SVI ($r^2 = 0.06$; $P=0.001$).

On the other hand, the CI values recorded during hyperdynamic therapy for the treatment of clinical DCI in 20 postoperative SAH patients for a total of 95 data pairs showed good correlation between FloTrac-derived CI and transpulmonary thermodilution-derived CI ($r^2 = 0.77$; $P<0.0001$), with bias and precision according to the Bland–Altman plot of 0.33 L/min/m$^2$ ± 0.26 L/min/m$^2$, and an acceptable percentage error of 14.9%. In contrast to GEDI (area under the curve ± SEM: 0.77 ± 0.10; $P=0.04$) or the presence of mechanical ventilation (0.82 ± 0.06; $P<0.0001$), the SVV was inaccurate for predicting changes in SVI after fluid loading in the presence of spontaneous respiratory movements (0.74 ± 0.10; $P=0.069$) in postoperative SAH patients.

These data suggest that CI derived from the PiCCO system is interchangeable with CI derived from pulmonary thermodilution. Uncalibrated CI derived from the less-invasive FloTrac/Vigileo system is acceptable for tracking trends in selected situations (i.e., hyperdynamic therapy for reversing clinical DCI) in postoperative SAH patients, and obtains comparable clinical results compared with using the PiCCO system in these patients. In SAH patients with spontaneous ventilation, GEDI appears to be a superior indicator of fluid balance than cardiac filling pressures (pulmonary artery wedge pressure or central venous pressure) or dynamic preload indicated by SVV.
Table. Changes in hemodynamic and fluid parameters in the two groups throughout the study period

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid balance, mL/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EGDT</td>
<td>865 ± 511</td>
<td>749 ± 278</td>
<td>588 ± 345</td>
<td>770 ± 385</td>
<td>711 ± 437</td>
<td>728 ± 461</td>
<td>741 ± 352</td>
</tr>
<tr>
<td>Usual care</td>
<td>878 ± 362</td>
<td>977 ± 349</td>
<td>921 ± 332</td>
<td>948 ± 368</td>
<td>1,002 ± 339</td>
<td>1,081 ± 465</td>
<td>1,086 ± 524</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>107 ± 13</td>
<td>93 ± 13</td>
<td>92 ± 14</td>
<td>95 ± 12</td>
<td>99 ± 12</td>
<td>103 ± 9</td>
<td>106 ± 10</td>
</tr>
<tr>
<td>Usual care</td>
<td>109 ± 15</td>
<td>96 ± 14</td>
<td>91 ± 10</td>
<td>93 ± 11</td>
<td>95 ± 10</td>
<td>99 ± 10</td>
<td>101 ± 12</td>
</tr>
<tr>
<td>SVRI, dyn·s/cm²/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGDT</td>
<td>1,837 ± 283</td>
<td>1,735 ± 267</td>
<td>1,778 ± 250</td>
<td>1,695 ± 268</td>
<td>1,685 ± 260</td>
<td>1,731 ± 263</td>
<td>1,706 ± 282</td>
</tr>
<tr>
<td>Usual care</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1,760 ± 265</td>
<td>1,731 ± 263</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>EGDT</td>
<td>73 ± 12</td>
<td>73 ± 13</td>
<td>79 ± 14</td>
<td>88 ± 11</td>
<td>88 ± 12</td>
<td>91 ± 15</td>
<td>92 ± 16</td>
</tr>
<tr>
<td>Usual care</td>
<td>78 ± 15</td>
<td>75 ± 13</td>
<td>81 ± 13</td>
<td>89 ± 12</td>
<td>90 ± 11</td>
<td>89 ± 17</td>
<td>93 ± 17</td>
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<tr>
<td>ELWI, mL/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>EGDT</td>
<td>7 ± 2</td>
<td>8 ± 2</td>
<td>7 ± 2</td>
<td>7 ± 2</td>
<td>7 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 3</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
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<td>-</td>
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</tr>
</tbody>
</table>

n=80 per group. EGDT, early goal-directed therapy; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; HR, heart rate.

No statistically significant differences were detected between the EGDT and usual care groups in each time frame.
<table>
<thead>
<tr>
<th></th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
<th>Day 13</th>
<th>Day 14</th>
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<tbody>
<tr>
<td>Fluid balance, mL/d</td>
<td>811 ± 414</td>
<td>909 ± 422</td>
<td>940 ± 456</td>
<td>922 ± 453</td>
<td>809 ± 429</td>
<td>815 ± 484</td>
<td>887 ± 395</td>
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<tr>
<td>EGDT</td>
<td>1,258 ± 520</td>
<td>1,224 ± 382</td>
<td>1,283 ± 388</td>
<td>1,280 ± 374</td>
<td>1,252 ± 479</td>
<td>1,112 ± 380</td>
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<tr>
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<td>811 ± 414</td>
<td>909 ± 422</td>
<td>940 ± 456</td>
<td>922 ± 453</td>
<td>809 ± 429</td>
<td>815 ± 484</td>
<td>887 ± 395</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>106 ±12</td>
<td>107 ± 10</td>
<td>109 ± 13</td>
<td>107 ± 11</td>
<td>110 ± 9</td>
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<td>SVRI, dyn·s/cm²/m²</td>
<td>1,689 ± 295</td>
<td>1,646 ± 267*</td>
<td>1,619 ± 234*</td>
<td>1,641 ± 199*</td>
<td>1,602 ± 216*</td>
<td>1,630 ± 195*</td>
<td>1,659 ± 227</td>
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<tr>
<td>EGDT</td>
<td>1,586 ± 274</td>
<td>1,580 ± 279</td>
<td>1,479 ± 275*</td>
<td>1,540 ± 239*</td>
<td>1,576 ± 212*</td>
<td>1,573 ± 198*</td>
<td>1,601 ± 244</td>
</tr>
<tr>
<td>Usual care</td>
<td>1,689 ± 295</td>
<td>1,646 ± 267*</td>
<td>1,619 ± 234*</td>
<td>1,641 ± 199*</td>
<td>1,602 ± 216*</td>
<td>1,630 ± 195*</td>
<td>1,659 ± 227</td>
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<td>HR, beats/min</td>
<td>92 ± 15*</td>
<td>92 ± 14*</td>
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<td>93 ± 16*</td>
<td>94 ± 16*</td>
<td>94 ± 15*</td>
<td>94 ± 13*</td>
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<td>ELWI, mL/kg</td>
<td>9 ± 3</td>
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</table>

n=80 per group. EGDT, early goal-directed therapy; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; HR, heart rate.

*P< 0.05 versus initial measurement. No statistically significant differences were detected between the EGDT and usual care groups in each time frame.
Supplemental Figure I. Trial profile. EGDT, early goal directed therapy.

Admission

208 SAH patients screened for eligibility

- 48 excluded
  - 29 delayed presentation greater than 24h
  - 9 deterioration prior to recruitment
  - 10 Fisher grade 1
  - 0 refused consent

Aneurysm repair (Day 0)

160 recruited and randomized

- 80 randomized to EGDT
- 80 randomized to control

Postoperative Management (Day 1 – 14)

- 80 analyzed as primary intention to treat analysis
  - 0 lost to outcome follow-up
  - 0 lost to initial secondary outcome follow-up
  - 2 lost to 3-month secondary follow-up

- 80 analyzed as primary intention to treat analysis
  - 0 lost to outcome follow-up
  - 0 lost to initial secondary outcome follow-up
  - 3 lost to 3-month secondary follow-up
Supplemental Figure II-1. The algorithm of baseline hemodynamic management of early goal-directed fluid therapy (EGDT) guided with the transpulmonary thermodilution device (PiCCO) (A) and usual care partially assisted with the radial artery waveform-based pulse contour cardiac output device (FloTrac) (B).
Supplemental Figure II-2. The algorithm of early goal-directed fluid therapy (EGDT) guided with the transpulmonary thermodilution device (PiCCO) (A) and usual care partially assisted with the radial artery waveform-based pulse contour cardiac output device (FloTrac) (B) for treating clinical deterioration attributable to delayed cerebral ischemia (DCI).

A

**Clinical DCI**

- GEDI
  - 800~850 mL/m²
  - Are goals reached?
    - If persisting neurological deficit or further deteriorated
      - CI
        - ≥ 4 L/min/m²
          - ELWI
            - ≤ 12 mL/kg
              - 1. Dobutamine
                - 2. Milrinone
            - If ELWI > 12mL/kg under hypervolemia
              - 1. Furosemide
                - 2. Fluid restriction (option)
        - ≤ 12 mL/kg
          - Are goals reached?

B

**Clinical DCI**

- Fluid balance CVP
  - +750~+1,000 mL
    - 8 – 12 mmHg
      - Are goals reached?
        - If persisting neurological deficit or further deteriorated
          - Insert FloTrac/Vigileo system
          - Volume control
          - CI
            - ≥ 4 L/min/m²
              - ELWI
                - If heart failure suspected under hypervolemia
                  - 1. Furosemide
                    - 2. Fluid restriction (option)
            - If ELWI >12mL/kg under hypervolemia
              - 1. Dobutamine
                - 2. Milrinone
      - > +2,000mL
        - > 12 mmHg
          - Volume control
          - Are goals reached?
**Supplemental Figure III.** Changes in volumetric and hemodynamic parameters in the control (usual care) (○) and the study (early goal-directed fluid therapy; EGDT) (●) group. CI, cardiac index; GEDI, global end-diastolic volume index; ELWI, extravascular lung water index; CVP, central venous pressure.

CI (L/min/m²)

GEDI (mL/m²)

CVP (mmHg)

Fluid intake (mL/day)

Day after SAH onset
Supplemental Figure Legends

**Figure I.** Trial profile. EGDT indicates early goal-directed fluid therapy.

**Figure II-1.** Algorithms for baseline hemodynamic management during (A) early goal-directed fluid therapy (EGDT) guided by transpulmonary thermodilution using the PiCCO system, and (B) standard care assisted by radial artery waveform-based pulse contour cardiac output monitoring (FloTrac).

**Figure II-2.** Algorithms for the treatment of clinical deterioration attributable to delayed cerebral ischemia (DCI) during (A) early goal-directed fluid therapy (EGDT) guided by transpulmonary thermodilution using the (PiCCO) system, and (B) standard care assisted by radial artery waveform-based pulse contour cardiac output monitoring (FloTrac).

**Figure III.** Changes in volumetric and hemodynamic parameters in the control group who received standard care (○) and the treatment group who received early goal-directed fluid therapy (EGDT) (●). CI indicates cardiac index; GEDI, global end-diastolic volume index; ELWI, extravascular lung water index; CVP, central venous pressure.
Supplemental References


10. Mutoh T, Ishikawa T, Nakase T, Yasui N. Performance of the refined FloTrac system (3rd generation device) for uncalibrated continuous cardiac output monitoring during
