Performance of Bedside Transpulmonary Thermodilution Monitoring for Goal-Directed Hemodynamic Management After Subarachnoid Hemorrhage

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Background and Purpose—Early goal-directed hemodynamic therapy is of particular importance for adequate cerebral circulation of patients with vasospasm after subarachnoid hemorrhage but is often precluded by the invasiveness of established cardiac output determination using a pulmonary artery catheter. This study was undertaken to validate the usefulness of less invasive goal-directed hemodynamic monitoring by transpulmonary thermodilution technique in patients after subarachnoid hemorrhage.

Methods—One hundred sixteen patients with subarachnoid hemorrhage who underwent surgical clipping within 24 hours of ictus were investigated. Validation of transpulmonary thermodilution-derived intermittent/continuous cardiac output and cardiac preload (global end diastolic volume) were compared with pulmonary artery catheter-derived reference cardiac output and pulmonary capillary wedge pressure or central venous pressure in 16 patients diagnosed with vasospasm. In a subsequent trial of 100 consecutive cases, clinical results between the new and standard management paradigms were compared.

Results—Transpulmonary thermodilution-derived intermittent cardiac output and transpulmonary thermodilution-derived continuous cardiac output showed close agreement to catheter-derived reference cardiac output with high correlation (r=0.85 and 0.77) and low percentage error (13.5% and 18.0%). Fluid responsiveness to defined volume loading was predicted better with global end diastolic volume than with pulmonary capillary wedge pressure and central venous pressure for larger receiver operating characteristic curve area. Patients receiving early goal-directed management by transpulmonary thermodilution experienced reduced frequencies of vasospasm and cardiopulmonary complications compared with those managed with standard therapy (P<0.05), whereas their functional outcomes at 3 months were not different (P=0.06).

Conclusions—Goal-directed hemodynamic management guided by transpulmonary thermodilution appears to have a therapeutic advantage for optimizing the prognosis of patients with subarachnoid hemorrhage with vasospasm over conventional methods. (Stroke. 2009;40:2368-2374.)

Key Words: cerebral vasospasm ■ hemodynamic monitoring ■ method comparison ■ subarachnoid hemorrhage ■ transpulmonary thermodilution

Aneurysmal subarachnoid hemorrhage (SAH) is one of the most devastating neurological diseases accounting for approximately one fourth of all cerebrovascular deaths. In the postoperative phase after aneurysm occlusion, cerebral vasospasm is the major complication after SAH with a prevalence measured by angiography approaching 70% during the first 2 weeks, in which 20% to 30% of patients will experience delayed ischemic neurological deficit (DIND) leading to infarction and thus long-term morbidity and mortality.1-3 Thus, patients are usually monitored in an intensive care unit setting with trained stroke nurses and physicians for early detection of vasospasm and initiation of treatment.

To ensure appropriate intravascular volume and cardiac output (CO) for adequate cerebral perfusion and oxygenation delivery capacity in patients with post-SAH vasospasm, optimal hemodynamic monitoring is of high importance. In this regard, many physicians follow thermodilution–CO and/or fluid-filled monitoring systems as a guide for the goal-directed fluid and vasopressor therapy after SAH.2-6 The pulmonary artery catheter (PAC) has been the clinical gold standard for CO measurement, but concerns regarding the...
safety, efficacy, and cost have been raised. Measurements of cardiovascular filling pressures obtained from a PAC (pulmonary capillary wedge pressure [PCWP]) or a central venous catheter (central venous pressure [CVP]) are commonly used for estimation on the quality of circulating volume and prediction of fluid responsiveness but are often found inadequate.9–12

As a less invasive alternative that can provide additional hemodynamic variables without cardiopulmonary catheterization, transpulmonary thermodilution (PiCCO plus; Pulsion Medical Systems, Munich, Germany) have gained increasing acceptance in many European intensive care units and operating rooms.13,14 The system involves injecting saline through any central venous catheter and calculating thermodilution CO at the thermistor-tipped peripheral arterial catheter with a modified Stewart-Hamilton equation, then it allows to calculate continuous CO based on the arterial pressure waveform alone after calibration for the individual vascular impedance by transpulmonary thermodilution, referred to as pulse contour analysis.15 Furthermore, PiCCO allows estimation of global end diastolic volume and intrathoracic blood volume, both of which constitute a reliable indicator of cardiac preload16–18 and of extravascular lung water, which is a sensitive indicator of pulmonary edema.19–21

We have recently introduced a novel approach to goal-directed hemodynamic management with this system in the treatment of hypovolemic, neurogenic pulmonary edema, and cerebral vasospasm after SAH,22–24 providing a testament to the growing interest in less invasive hemodynamic monitoring in the neurocritical care. However, the study was limited in not having a control technique (eg, PAC monitoring), and thus expanded use and reliability of this new hemodynamic monitor have been warrant.25–26 Therefore, this study was undertaken to validate the usefulness of goal-directed hemodynamic management using the PiCCO system compared with the conventional fluid management protocol guided by the pulmonary artery thermodilution and filling pressures in patients after SAH.

Methods
Full details about this section can be accessed in the supplemental data, available online at http://stroke.ahajournals.org.

Patients
One hundred sixteen patients (41 men and 75 women; age, 64 ± 11 years) with aneurysmal SAH were enrolled from April 2005 to August 2008 at 2 sites (Research Institute for Brain and Blood Vessels–Akita, Akita, Japan; and Teine Keijinkai Medical Center, Sapporo, Japan). The study protocol was approved by the Institutional Ethical Committee and informed consent was obtained from each patient or an appropriate designee. Patients entered the study within 24 hours of the onset of symptoms (designated Study Day 0). Exclusion criteria were (1) both good clinical grade (World Federation of Neurological Surgery Grade I) and modest bleeds (Fisher CT grading scale 3) as described previously.22

Procedures
General Management
All patients had a 7-Fr central venous catheter inserted in the subclavian or femoral vein postoperatively and received a baseline crystalloid infusion of 1500 to 3000 mL/d up to Day 14 after the onset of SAH. Hyponatremia was corrected by administering NaCl, fluidrocortisone, or hydrocortisone as necessary.22 They were followed with daily transcranial Doppler (TCD) sonography using standard criteria for TCD vasospasm.27 Clinically, patients who become symptomatic with DIND due to vasospasm were defined as any ≥2-point fall in modified Glasgow Coma Scale or unaccountable new focal neurological deficit lasting ≥2 hours and were placed on a continuous intravenous infusion of dobutamine to the level at which the deficit resolved, or there was a maximal systolic blood pressure of 200 mm Hg, as the standard approach to increase cerebral blood flow medically for the treatment of vasospasm at our institute (hyperdynamic therapy).28 Vasospasm-related ischemic infarct was defined as the development of a new lesion consistent with infarction on CT or MRI in the vascular territory of TCD or angiographic vasospasm.

PiCCO-Guided Management
For transpulmonary thermodilution-based hemodynamic monitoring, a 4-Fr 16-cm thermost catheter (Pulsicath PV2014L16; Pulsion Medical Systems, Munich, Germany) was inserted into the brachial artery at least until Day 4 after onset of SAH. The arterial catheter and central venous catheter were connected to pressure transducers and to the PiCCO monitor for determination of CO, global end diastolic volume, and extravascular lung water intermittently by triplicate central venous injections of 15-mL ice-cold saline (<8°C). In this study, transpulmonary thermodilution-derived cardiac index (TPCI) and calibrated arterial pulse contour continuous cardiac index (PCCI; normal value, 3.0 to 5.0 L/min/m²), global end diastolic volume index (GEDI; 680 to 800 mL/m²), and extravascular lung water index (ELWI; 3 to 7 mL/kg) were measured at least twice daily until Day 14.

Patients monitored with PiCCO were assigned to receive intravascular volume expansion with 6% hydroxyethyl starch (HES; 500 to 1500 mL/d) after Day 4 of SAH onset if the cardiac index fell below the target levels (<3.0 L/min/m²) due to hypovolemia (GEDI <680 mL/m²). If patients had TCD vasospasm and HES was ineffective in raising GEDI above lower targets and the low cardiac index persisted for at least 12 hours, supplemental 25% albumin solution (50 to 100 mL/d) was administered. If the low cardiac index persisted even under hypervolemia (GEDI ≥850 mL/m²) along with the maximum fluid therapy for at least 12 hours, dobutamine at low doses (3 to 5 µg/kg/min) was initiated to maintain the normal cardiac index values. When DIND was diagnosed, the cardiac index target raised (≥3.5 L/min/m²) and managed with hyperdynamic therapy with dobutamine (3 to 20 µg/kg/min).

Conventional Management
For the conventional method, patients were maintained under euvolemia with CVP of 5 to 8 mm Hg by supplemental crystalloids (500 to 1500 mL/d) and if DIND was present, a 7.5-Fr PAC (Swan-Ganz CCO catheter; Edwards Lifesciences, Irvine, Calif) was introduced through the right internal jugular vein for measurement of cardiac index (PACI) and stroke volume index (SVI; normal value, 33 to 47 mL/m²) as previously described29 and their hemodynamic goals were shifted to maintain PCWP of 12 to 16 mm Hg or, if only CVP is available, levels of 8 to 12 mm Hg with hemodynamic augmentation (cardiac index ≥3.5 L/min/m²) initially with HES followed by supplemental 25% albumin and, finally, enhancement of cardiac contractility with dobutamine.34 Because of the cardiopulmonary invasiveness, the PAC monitoring was initiated only when DIND was suspected, measured at least twice daily, and the placement never exceeded 7 days. Daily fluid balance was calculated for a reference by subtracting urinary volume from total oral and intravenous intake and aimed to keep at 500 mL positive by adjusting intravenous fluid administration.

Protocols
Validation Study
In this series, hemodynamic monitoring with PiCCO and PAC was performed simultaneously in 16 post-SAH patients. Direct comparison of CO measurements could only be performed in cases with suspected vasospasm because PAC monitoring being invasive was
only performed in this subgroup. A complete set of hemodynamic measurements at steady state (baseline) as well as those in response to volume expansion with supplemental colloid (500 mL of HES without and with 50 mL of 25% albumin solution) infused at 5 mL/kg/h were recorded. Each measurement was performed after the end of the infusion. The end points for the preload assessment were the prevalence of mild hypervolemia according to GEDI >800 mL/m² or the predictive values of CVP >15 mm Hg and/or PCWP >20 mm Hg.

Clinical Assessment Study
In a subsequent prospective trial of 100 consecutive cases, clinical course (vasospasm, daily fluid intake/output, balance, therapy-related cardiopulmonary complications) and functional outcome (modified Rankin Scale score at 3 months) of this new management were compared with conventional method. Patients were randomly allocated to receive either PiCCO-guided management or institutional standard management using a central venous catheter and PAC.

Statistical Analysis
Statistical analysis was performed using software (GraphPad PRISM Version 5.01; GraphPad Software, San Diego, Calif). Continuous data that were normally distributed using the D’Agostino-Pearson normality test were compared using paired t test or one-way analysis of variance with post hoc Bonferroni-Dunn correction. Nonnormal continuous data were compared with the Mann–Whitney U test. Categorical comparisons were made using the Fisher exact test. For comparisons between absolute cardiac index values determined by 3 different methods (TPCI, PCCI, and PACI) or changes (Δ from baseline) between 3 preload variables (GEDI, CVP, and PCWP) and PAC-derived reference SVI, Pearson or Spearman correlation coefficients were established. Linear regression was calculated by using the least squares method. Bias (mean difference from the reference technique) and precision or limits of agreement (bias±2 SD) were calculated by using the Bland-Altman analysis.30 Percentage error (2 SD of the bias/mean reference cardiac index×100) was calculated for interchangeability of the 2 methods according to the criterion described by Critchley and Critchley.11 A rise of >10% in SVI after volume expansion defined the responders and receiver operating characteristic curves were used to evaluate the predictive value of the preload indices on fluid responsiveness. A probability value <0.05 was considered significant. All values are expressed as means±SD unless otherwise stated.

Results
Validity of Hemodynamic and Volumetric Measurements
A total of 263 measurements were recorded over a mean of 6±1 days in the 16 patients with SAH (4 men and 12 women; age, 64±10 years; World Federation of Neurological Surgery Grade I: 3; II: 3; III: 2; IV: 6; V: 2; Fisher Grade 3: 14; 4: 2) who underwent surgical clipping and were diagnosed with vasospasm. The time-course changes of cardiac index with each method can be accessed in the supplemental data.

Results of analysis of pooled data for cardiac index values showed high correlations and close agreement among 3 methods (Figure 1). Fairly good coefficients of correlation (r) of TPCI or PCCI with PACI (r=0.85, P<0.0001 and r=0.77, P<0.0001, respectively) was achieved with the line of regression falling close to the line of identity. Bias and precision according to the Bland-Altman plot were 0.05 and 0.11 L/min/m² and ±0.25 and ±0.33 L/min/m² with percentage errors of 13.5% and 18.0%, respectively.

With regard to the effects of volume expansion by defined fluid loading on pooled data for preload measures, good relationship was found between ΔGEDI and ΔSVI during volume expansion (r=0.67, P<0.0001), whereas there was poor correlation of ΔPCWP or ΔCVP with ΔSVI (r=0.23, P=0.003 and r=0.04, P=0.64, respectively; Figure 2). Furthermore, it is notable that GEDI before volume expansion still showed a significant correlation with SVI (r=0.66, P<0.0001), whereas the values of PCWP or CVP did not
correlate with SVI ($r=0.14$, $P=0.06$ and $r=0.03$, $P=0.62$, respectively). To assess the ability of GEDI, PCWP, and CVP to discriminate between responders and nonresponders to volume expansion, receiver operating characteristic curves were generated using the values averaged across all of the fluid challenges (Figure 3). A total of 167 volume challenges were administered in this study with a 42% response rate (70 patients with SAH receiving either transpulmonary thermodilution-guided or central venous catheter/PAC-based management (50/each group) is given in the Table. In the transpulmonary thermodilution group, the PiCCO system was inserted for all patients until Day 3±1 after SAH onset and initiated hemodynamic monitoring over a mean of 9±2 days, whereas in the conventional management, patients were generally managed with CVP and fluid balance, and PAC monitoring was performed only when they were diagnosed with DIND (n=24, placed until Day 7±2 after SAH onset and monitored over a mean of 5±1 days). The time to establish the hemodynamic goal (cardiac index ≥3.5 L/min/m²) for patients with vasospasm was faster in the PiCCO group (n=16) than in the PAC-guided standard management group (n=24; 3±1 days versus 4±1 days after the diagnosis of vasospasm; $P=0.03$) with maximum cardiac index values of 4.5 L/min/m² and 4.3 L/min/m² ($P=0.18$), respectively. The maximal dobutamine doses required for hemodynamic augmentation were not different between the groups (9.2±6.0 µg/kg/min [n=12] versus 9.6±4.0 µg/kg/min [n=20]; $P=0.42$).

Transpulmonary thermodilution was associated with less incidences of TCD vasospasm (50% with PiCCO-guided management versus 66% with standard indicator-guided management; $P=0.03$), DIND (32% versus 48%; $P=0.03$), and vasospasm-related cerebral infarction (6% versus 14%; $P=0.049$). Functional outcomes at 3-month follow-up appeared to have trends toward favorable outcomes (modified Rankin Scale score 0 to 3: 56% versus 44%) for patients managed with transpulmonary thermodilution but did not reach statistical significance ($P=0.0598$).

Medical therapy-related cardiopulmonary complications included pulmonary edema (n=4 for standard management),
arrhythmia (n = 2; one per each management), and vasospastic angina (n = 1 for standard management), which was greater for standard management than for transpulmonary thermodilution-guided management (12% versus 2%; \( P < 0.01 \)). None of the patients who were diagnosed with pulmonary edema met criteria for acute lung injury or acute respiratory distress syndrome\textsuperscript{32} as observed previously in some patients with neurogenic pulmonary edema.\textsuperscript{24} All of the cardiovascular complications were observed at higher-dose dobutamine (\( >15 \mu g/kg/min \)) for hyperdynamic therapy of patients with vasospasm, whereas the pulmonary edema occurred during volume loading. With regard to the fluid therapy, standard indicator-guided management required more fluid administration (maximal daily fluid intake, 5756±882 mL for conventional management versus 4935±563 mL for PiCCO-guided management; \( P=0.01 \)) to attain the hemodynamic target than PiCCO-guided management (Figure 4), whereas the differences did not affect fluid output or net water balance (\( P>0.05 \)).

**Discussion**

The principal findings of this study are that (1) PiCCO-derived intermittent and continuous CO exhibit good agreement with reference CO determined by the established PAC technique in patients diagnosed with vasospasm; (2) preload volume measurements of GEDI determined by this system may be a superior predictor of fluid responsiveness to those of conventional filling pressures for the treatment of vasospasm; and (3) the PiCCO-guided early goal-directed hemodynamic paradigm appears to have a therapeutic advantage over conventional methods for a better clinical course with less cardiopulmonary complications.

We used the method described by Critchley and Critchley\textsuperscript{31} to compare CO measurements, because it incorporates not only the error of the method to be tested, but also adjustments for errors in the reference method itself. These authors concluded that a percentage error of 30% between the test and reference method indicates that the test method is no less accurate than the reference method. In this study, we found TPCI and PCCI showed close agreement to the reference PACI with high correlation (\( r=0.85 \) and 0.77) with the slope of each regression line overlapping the identity line and a low percentage error (13.5% and 18.0%). Although validation of transpulmonary thermodilution for measurement of CO has been performed under a variety of experimental and clinical studies,\textsuperscript{13,14} this is, to our knowledge, the first study that evaluated the interchangeability of 2 different devices, the current clinical standard PAC and the less invasive PiCCO system in patients with vasospasm after SAH. Besides our reports so far, this system has not been used for practical purposes of post-SAH hemodynamic management, except in a case report in which the intravascular volume quantification using the PiCCO was required for preventing further pulmonary edema caused by excessive triple-H therapy.\textsuperscript{33}

Good fluid management of cerebral vasospasm involves knowing how much hydration patients will tolerate and optimizing preload by avoiding fluid overload with pulmo-
nary edema to stabilize cardiac performance before trying to optimize cerebral perfusion. Our results demonstrated that GEDI appears to be more reliable for estimating intravascular volume status as “static” and “dynamic” preload measures based on fairly good correlations obtained both between baseline GEDI and SVI and between their changes (Δ) during volume expansion when compared with conventional preload indicators CVP or PCWP. The results are also supported by higher predictive values for GEDI to responsiveness of SVI to defined volume loading (Figure 3).

The PiCCO algorithm allows us to estimate not only “one picture” as cardiac preload (GEDI), but also an effective functional answer (continuous CO monitoring) together with a pulmonary edema quantification (ELWI),20,21 all of which potentially gives us the opportunity of responding rapidly to stress-related hemodynamic consequences early after SAH.22,23 The present data demonstrated a significant impact of PiCCO CO optimization based on our goal-directed hemodynamic paradigm on DIND and vasospasm-related cerebral infarction and significantly less cardiopulmonary complications without any significant functional impact on the clinical outcome at 3 months. It is known that neither PAC nor volumetric monitoring “per se” improves outcome in critically ill patients.18 Furthermore, hypovolemia is often exaggerated from the early stage of SAH without a significant impact on CO22 or on brain tissue perfusion,2,34 suggesting the need for careful fluid management to avoid hypovolemia for reducing the risk of delayed cerebral ischemia. Taken together, the better clinical course of our patients receiving the new management paradigm might be explained by placement of the PiCCO from the early phase is effective for stabilization of cardiac performance under normovolemia safely and appropriately before the onset of cerebral vasospasm without overloading them.

When interpreting the data presented in this study, some methodological aspects and limitations must be considered. First, it was an unblinded study design. Specifically, the diagnostic accuracy of vasospasm depends largely on clinical skills of each faculty member in the neurocritical care unit. Thus, the delay of therapeutic intervention in patients undergoing standard management may have resulted in worse clinical course and functional outcome than the PiCCO-guided hemodynamic management starting from early post-SAH. Second, the target cardiac index values used for goal-directed management before and during vasospasm were arbitrary and supranormal. In the setting of vasospasm, targeting cerebral autoregulation improvement by continuous neuromonitoring of cerebral perfusion and brain tissue oxygenation35–37 to allow individual titration of cardiac index goals may be used to determine the benefit of the treatment in future clinical trials. Third, although the method of fluid challenge we used was standardized, it included different amounts and volume expansion properties of colloids as recommended clinically. By choosing relatively high amount (500 to 550 mL) of colloid solution(s) with standard speed of volume expansion and by setting the definition of fluid responsiveness (SVI >10%) in reference to the pre-existing literature,28 we attempted to prevent the possibility of not identifying responders, and the rate of responders to the volume load (42%) in this study was relevant to the previous data. Finally, the observations made in this study are limited because of the small patient number and the restriction to only our goal-directed paradigm based on PiCCO measurements. Thus, the readers should keep in mind in interpreting our results that we are not answering the question whether PiCCO can be substituted directly for conventional PAC to improve outcome.

**Conclusions**

The present data confirmed the concept of early goal-directed treatment paradigm to optimize CO and volume status using bedside transpulmonary thermodilution monitoring for optimizing the complexity of SAH-induced hemodynamic consequences and prognosis of post-SAH vasospasm over conventional methods.

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**Disclosures**

None.

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