Performance of Third-generation FloTrac/Vigileo system during hyperdynamic therapy for delayed cerebral ischemia after subarachnoid hemorrhage

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Received: 23 May 12 Accepted: 13 July 12 Published: 27 August 12

This article may be cited as:
Mutoh T, Ishikawa T, Kobayashi S, Suzuki A, Yasui N. Performance of Third-generation FloTrac/Vigileo system during hyperdynamic therapy for delayed cerebral ischemia after subarachnoid hemorrhage. Surg Neurol Int 2012;3:99.

Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2012/3/1/99/100195

Abstract

Background: Monitoring of cardiac output (CO) is important for promising safe approach to goal-directed hemodynamic therapy for delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH), but is often precluded by the invasiveness and complexity of ongoing monitoring modalities. We examined the clinical utility of less-invasive management using an uncalibrated arterial pressure waveform-derived cardiac output (APCO) monitor with refined algorithm (Third-generation FloTrac/Vigileo, Edwards, Irvine, CA, USA) during hyperdynamic therapy for post-SAH DCI, compared with transpulmonary thermodilution (PICCO, Pulsion, Munich, Germany) as a reference technique.

Methods: Forty-five patients who underwent surgical clipping within 24 h of SAH onset and subsequently developed clinical deterioration attributable to DCI were investigated. Validation of the APCO-derived cardiac index (CI) during dobutamine-induced hyperdynamic therapy was compared with a reference CI analyzed by transpulmonary thermodilution in 20 patients. In a subsequent trial of 48 cases, the overall clinical results from patients managed with each device were compared.

Results: The APCO underestimated CI with an overall bias ± SD of 0.33 ± 0.26 L/min/m² compared with transpulmonary thermodilution, resulting in an error of 14.9%. The trends of CI for both techniques at each dobutamine dose were similar ($r^2 = 0.77; P < 0.0001$). No statistically significant differences were observed between the device groups for frequencies of neurological improvement, cerebral infarction, cardiopulmonary complications, or functional outcomes at 3 months.

Conclusions: These data suggest that the refined APCO tends to underestimate CI compared with reference transpulmonary thermodilution during hyperdynamic therapy with dobutamine for reversing DCI, but may be acceptable in this select category of patients to obtain comparable clinical results.

Key Words: Cardiac output, hemodynamic monitoring, pulse contour analysis, subarachnoid hemorrhage, transpulmonary thermodilution
INTRODUCTION

Cerebral vasospasm is currently the leading but potentially treatable cause of death and disability after aneurysmal subarachnoid hemorrhage (SAH), in which 40% of patients will progress to clinical deterioration attributable to delayed cerebral ischemia (DCI), and 15–20% will develop a disabling stroke or die.[13] Monitoring of cardiac output (CO) is important for promising safe approach to goal-directed hemodynamic therapy for DCI after SAH,[7,11,19–22,28] but is often precluded by the invasiveness and complexity of ongoing thermodilution technique using a pulmonary artery catheter (PAC).[12,26] Recently, a new CO monitoring technology (FloTrac/Vigileo; Edwards Lifesciences, Irvine, CA, USA) that use the radial arterial pressure waveform and individual patient demographic data without the need for external calibration, has been introduced to various critical care situations. Despite its ease of use and reduced invasiveness, the reliability of tracking continuous CO using early versions of the associated software (currently updated to a third-generation device) in perioperative SAH patients was not enough to satisfy our requirements.[18] Furthermore, clinical data regarding the treatment of patients suffering from post-SAH DCI, where more intensive hemodynamic augmentation (e.g., triple-H or hyperdynamic therapy) is required, are still lacking.

We therefore carried out a pilot clinical trial to (1) investigate the reliability of the refined third-generation FloTrac/Vigileo system during hyperdynamic therapy with dobutamine for reversing DCI following SAH compared with the transpulmonary thermodilution of known accuracy as a reference technique and (2) compare clinical results from patients managed with each device.

MATERIALS AND METHODS

This study was approved by our Institutional Review Board and written informed consent was obtained from the patients or their relatives in all cases. We screened patients with SAH who were admitted to the Research Institute for Brain and Blood Vessels in Akita from January 2008 until June 2011 and who underwent surgical clipping within 24 h of onset (designated study day 0). We recruited those who met the following inclusion criteria: (1) at least 18 years of age; (2) aneurysmal cause of SAH; and (3) clinical deterioration attributable to DCI between days 4 and 14 after hemorrhage. Exclusion criteria were (1) cardiac failure or arrhythmia that can limit correct APCO tracking; (2) contraindications to hyperdynamic therapy with dobutamine (e.g., neurogenic pulmonary edema, Takotsubo cardiomyopathy, and left ventricular outflow tract obstruction); and (3) technical difficulties in establishing safe, stable monitoring due to patient characteristics.

General management

Patients were treated according to the SAH treatment protocol of our institution,[18–21,23] including daily transcranial Doppler as screening for vasospasm. They rested in bed up to day 14 with intravenous fluids of 1,500–4,000 mL/day and oral food intake or nasogastric tube nutrition of 1,200–1,500 kcal/day to keep daily fluid balance at 750 mL positive (compensating for insensible fluid loss) and serum albumin concentration ≥ 3 g/dL. Hyponatremia (defined as a serum sodium level of <135 mEq/L for at least 2 consecutive days) was corrected by adding an ampule(s) of 10% NaCl (20 mL) to the main fluid bag. If hyponatremia persisted, fludrocortisone (0.1 mg/d) was given as necessary.[17] Systolic blood pressures were controlled below 180 mmHg by administering calcium antagonists nicardipine.[11] Nimodipine was not used (this drug is unavailable in Japan). Fasudil hydrochloride was administered three times a day, with a dose of 50 mg at each administration.[29]

DCI was defined clinically as decreased Glasgow Coma Scale of at least 2 points lasting ≥ 2 h or a new focal deficit that had developed between days 4 and 14 after SAH and that could not be explained by other possible causes. Patients were then placed on continuous intravenous infusion of DOB administered initially at a low dose of 3 µg/kg/min and then increased in 3 µg/kg/min increments to induce hemodynamic augmentation (APCO target ≥ 3.5 L/min/m² or ≥ 25% increase from baseline) to a level at which the deficit was fully resolved or there was a maximal systolic blood pressure of 180 mmHg or heart rate of 130 beats/min as the standard approach to increase cerebral blood flow medically for the treatment of DCI.[17] Cerebral infarction due to DCI was defined on magnetic resonance imaging (MRI) as the presence of acute ischemic lesion (i.e., hyperintense on diffusion-weighted images without T2-weighted signal intensities) obtained immediately after clinical deterioration as well as on day 14 for routine follow-up. If the patient’s clinical symptoms did not progress for at least 48 h and no new evidence of DCI-related infarction could be found on follow-up MRI on day 14, dobutamine was gradually decreased every 12 h in 3- to 5-µg/kg/min increments.

Hemodynamic monitoring

FloTrac/Vigileo system

Radial artery access was established with a 20- or 22-gauge catheter connected to a FloTrac sensor kit (MHD8S, Edwards Lifesciences). The APCO indexed to body surface area (APCI) by means of the DuBois formula (BSA = body weight [kg] × body length [cm]1/25 × 71.84) was determined from the arterial pressure waveform using the algorithm of the Vigileo monitor (MHM1, Edwards Lifesciences) utilizing the relationship between pulse pressure and stroke volume and the inverse relationship of pulse pressure with aortic compliance,
with a calculation performed every 20 s on the basis of the preceding 20-s interval of arterial waveform analysis. A conversion factor (±) was used to account for dynamic changes in vascular tone, and was calculated from pressure waveform characteristics along with patient demographic data (age, gender, height, weight, and body surface area) 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 third-generation software (version 3.02; Edwards Lifesciences) in combination with a reduction of pulse wave detection noise.[8]

PiCCO system
A 7-Fr central venous catheter was inserted in the subclavian or femoral vein. A 4-Fr 16 cm thermistor catheter (Pulsocath PV2014L16, Pulsion Medical Systems, Munich, Germany) was then inserted into the brachial artery and connected to an integrated bedside monitoring system (PiCCO, Pulsion Medical Systems). Reference transpulmonary thermodilution cardiac output (TPCO) was determined by triplicate central venous injections of 15-mL ice-cold saline (< 8°C). The thermodilution curve was analyzed using the Stewart–Hamilton algorithm followed by the pulse contour analysis for continuous measurements. Global end-diastolic volume (GEDV) that constitutes a reliable volumetric indicator of cardiac preload was calculated from the difference between intrathoracic and pulmonary thermal volume, according to the PiCCO-technology.[24] TPCO and GEDV were indexed to body surface area, yielding cardiac index (TPCI, normal value: 3.0–5.0 L/min/m²) and GEDV index (GEDI, normal value: 680–800 mL/m²), respectively. In patients managed with PiCCO, values of GEDI, rather than fluid balance, were considered a more robust parameter of intravascular volume status to titrate fluids to prevent hypervolemia (GEDI <680 mL/m²) during the therapy.[20,21]

Study protocol
Validation study
Measurements of CI were performed during hyperdynamic therapy with dobutamine before and 60 min after dobutamine infusion at each dose increment (D0, before administration; D1, 3 µg/kg/min; D2, 6 µg/kg/min; D3, 9 µg/kg/min; D4, 12 µg/kg/min; and D5, 15 µg/kg/min) in 20 patients. TPCI measurements were performed simultaneously for comparison with APCI for each period and are referred to as reference-CI. At each data point, values of APCI were averaged over the 30-s period immediately before the central venous bolus injection procedures for TPCI.

Clinical performance study
In a subsequent trial of 48 consecutive patients (n = 24/ group), clinical courses (responsiveness to dobutamine [defined as a reversal of at least one clinical symptom attributable to DCI], cerebral infarction on MRI, and cardiopulmonary complications [e.g., pulmonary edema, congestive heart failure, and arrhythmia/tachycardia that may limit DOB dose increments]) and functional outcomes (modified Rankin scale [mRS] score at 3-months) from patients managed with each device were compared. Time setup for operating each monitoring system (T.M. performed all of the procedures assisted by one member of the nursing staff), maximal dobutamine dose, duration of hyperdynamic therapy (i.e., entire period of dobutamine administration), and daily fluid intake, output, and balance during the study period were also compared.

Data analysis
Statistical analysis was performed using GraphPad Prism and StatMate (GraphPad software, San Diego, CA, USA). The sample size had been determined by a power analysis. To obtain a power>90% with an estimated difference between groups of 10% using CI, a total sample size of 20 patients had been determined with a type I error of 0.025. To detect a 20% decrease in DCI-related infarction, 24 patients per group had been required with an assumed α error of 0.05 (two-sided) and type II error of 0.2.

Continuous data that were normally distributed using the D’Agostino-Pearson normality test were compared using a t-test or analysis of variance (ANOVA) with post hoc Bonferroni–Dunn correction, where appropriate. Categorical comparisons were made using the Fisher’s exact test. For comparisons between data determined by two methods, Pearson or Spearman correlation coefficients were established. Linear regression was calculated using the least-squares method. Bias (mean difference from the reference technique) and precision or limits of agreement (bias ± 2 SD) were calculated using the Bland–Altman analysis.[5] The percent error (2 SD of the bias/mean reference CI × 100) was calculated for the interchangeability of the two methods according to the criterion described by Critchley and Critchley.[5] A P value <0.05 was considered statistically significant. All values are expressed as means ± SD, unless otherwise stated.

RESULTS
Of 81 patients with SAH admitted in the period of interest, 15 patients were excluded on the basis of delayed admission (> 24 h) (n = 3), cardiac failure or arrhythmia on admission (n = 2), contraindications to hyperdynamic therapy due to Tako-tsubo cardiomyopathy with (n = 3) or without neurogenic pulmonary edema (n = 1), and left ventricular outflow tract obstruction (n = 2), and technical difficulties in establishing monitoring (n = 2). Sixty-eight patients were eligible for further analysis.
A total of 95 measurements were recorded during hyperdynamic therapy with dobutamine in 20 post-SAH patients (13 females and 7 males; 67 ± 11 years-old) over a mean of 5 ± 1 days (range, 2–7 days). Overall, the CI was 3.4 ± 0.5 (range: 2.2–4.5) L/min/m² for APCI, 3.7 ± 0.5 (2.5–5.0) L/min/m² for TPCI. Results of the analysis of pooled data for CI showed high correlations and moderate agreement between the FloTrac and reference techniques [Figure 1a]. Good coefficients of correlation of APCI with TPCI ($r^2 = 0.77; P < 0.0001$) were achieved, and its bias and precision according to the Bland–Altman plot were 0.33 L/min/m² and ± 0.26 L/min/m² with percentage errors of 14.9%.

Subgroup analysis between APCI and reference TPCI measured at different dobutamine infusion doses are shown in Figure 2. Hemodynamic variables measured at each point are listed in Table 1. Although both devices demonstrated parallel dose-dependent elevation of CI during the therapeutic range of dobutamine ($P < 0.01$, dose effect; $P = 0.84$, treatment effect) [Figure 1a], APCI tended to underestimate reference TPCI by approximately 0.3 L/min/m², with similar levels of bias, precision, and percentage error during the therapy [Figure 1b]. With regard to other hemodynamic parameters, no statistically significant differences were observed among the data, with the exception of slightly lower BP values at baseline derived from the radial FloTrac/Vigileo system than those from the femoral transpulmonary thermodilution [Table 1].

A summary of clinical data for 48 post-SAH patients is given in Table 2. Baseline characteristics including patient age, sex, SAH grades, aneurysm location, onset of clinical DCI were not different between the two management groups. Setup time for hemodynamic monitoring was faster in patients receiving the uncalibrated FloTrac/Vigileo system than those requiring the transpulmonary thermodilution method ($P < 0.01$). Patients managed with the FloTrac/Vigileo system tended to have a greater daily fluid intake during the therapy than those guided with transpulmonary thermodilution ($P = 0.0001$). No statistically significant differences were detected between the device groups for frequencies of clinical response to dobutamine, cerebral infarction, cardiopulmonary complications (atrial tachycardia or atrial fibrillation of ≥130 beat/min in all of the cases), maximal dobutamine dose, duration of hyperdynamic therapy or favorable functional outcome at 3 months.

DISCUSSION

Our clinical experience suggests that the third-generation FloTrac/Vigileo system with a refined algorithm still underestimates CI compared with reference transpulmonary thermodilution during hyperdynamic therapy with dobutamine in patients suffering from post-SAH DCI. However, the reliability of this more user-friendly system to track CI properly may be acceptable as a trend device in this select category of patients to obtain comparable clinical results.

In this study, we used transpulmonary thermodilution as a reference technique for comparison of CI values with the FloTrac/Vigileo system, which has been extensively compared with classic pulmonary artery

![Figure 1: Relationship between cardiac index (CI) determined by the FloTrac/Vigileo system and reference transpulmonary thermodilution for 20 SAH patients. APCI, arterial pressure-based pulse contour CI analyzed by the FloTrac/Vigileo system; TPCI, transpulmonary thermodilution CI determined by the PiCCO system. (a) Least-squares regression line (solid line) and the line of identity (dotted line); (b) Bland–Altman plot of bias (solid line) and precision (dotted lines).](#)

![Figure 2: Subgroup analyses of cardiac index (CI) determined by the FloTrac/Vigileo system and reference transpulmonary thermodilution at different doses of dobutamine during hyperdynamic therapy in 20 SAH patients. (a) Changes of CI in response to dobutamine dose increments. Values (mean ± SD) measured before (D0) and 60 min after dobutamine infusion at each increment of dose (D1, 3 µg/kg/min; D2, 6 µg/kg/min; D3, 9 µg/kg/min; D4, 12 µg/kg/min; and D5, 15 µg/kg/min). (b) Bland–Altman plot of bias and precision analyzed between FloTrac/Vigileo system and reference transpulmonary thermodilution.](#)
thermolaminectomy and now becomes a standard for validation studies.\textsuperscript{[6,9,18,25,27]} With regard to the reliability of the transpulmonary thermodilution system, we have previously found that in postoperative SAH patients suffering from cerebral vasospasm, TPCI exhibited excellent correlation ($r = 0.85$) and small bias (0.25 L/min/m$^2$) with an overall low percentage error (13.5%) compared to PAC-derived thermodilution CI.\textsuperscript{[21]}

According to the method described by Critchley and Critchley,\textsuperscript{[9]} 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 light of recent results from validation studies regarding the third-generation FloTrac/Vigileo system, overall agreement errors with thermodilution have still varied from 20% to 54\%,$^{[1,13,16,32]}$ implying that the uncalibrated system is no better and even worse than thermodilution using the current benchmark of 30%. In this study, the third-generation FloTrac system demonstrated an overall percentage error of 14.9\% for all data pairs during hyperdynamic therapy with dobutamine for the treatment of post-SAH DCI, although the values tended to underestimate the reference CI (<0.3 L/min/m$^2$) [Figure 2a]. Even an absolute error of 13.5\% for the TPCI method from the ‘clinical gold standard’ pulmonary artery thermodilution-derived CI\textsuperscript{[21]} was considered, the APCI readings throughout the hyperdynamic therapy [Figure 2b] still allow for the upper-limits of estimated error (up to 16.5\%).

In this study, we used dobutamine to reverse neurologic symptoms attributable to DCI. Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the $\beta$-receptors of the heart while producing less marked chronotropic, hypertensive, arrhythmogenic or vasodilatory effects. Our results suggest that intensive hyperdynamic therapy with dobutamine by step-up dose increments within a therapeutic range (3–15 $\mu$g/kg/min) produces less increase in heart rate and less decrease in peripheral vascular resistance [Table 1]. Since the peripheral arterial pulse wave results from the interaction between left ventricular output and the capacitance of the vascular tree,$^{[30,34]}$ the use of vasoactive

Table 1: Hemodynamic data for 20 subarachnoid hemorrhage patients obtained simultaneously from two hemodynamic devices during hyperdynamic therapy

| Characteristics       | D0          | D1          | D2          | D3          | D4          | D5          |
|-----------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| HR, beats/min         | 77 ± 12     | 83 ± 12     | 85 ± 15     | 87 ± 14     | 93 ± 11*    | 96 ± 10*    |
| MAP-F, mmHg           | 91 ± 6      | 91 ± 10     | 92 ± 12     | 95 ± 10     | 95 ± 12     | 91 ± 9      |
| MAP-R, mmHg           | 86 ± 7\*    | 87 ± 11     | 88 ± 11     | 91 ± 12     | 90 ± 13     | 87 ± 7      |
| CVP, mmHg             | 7 ± 2       | 8 ± 2       | 7 ± 1       | 7 ± 2       | 8 ± 2       | 8 ± 2       |
| GEDI, mL/m$^2$        | 715 ± 50    | 723 ± 64    | 728 ± 70    | 729 ± 66    | 751 ± 57    | 753 ± 61    |
| ELWI, mL/kg           | 7 ± 1       | 7 ± 2       | 7 ± 2       | 8 ± 2       | 8 ± 2       | 9 ± 2       |
| SVRI, dym/s/cm$^5$/m$^2$ | 1,827 ± 188 | 1,850 ± 205 | 1,852 ± 211 | 1,853 ± 248 | 1,786 ± 210* | 1,645 ± 263* |

Values (mean ± SD) measured before (D0) and 60 min after dobutamine infusion at each increment of dose (D1: 3 $\mu$g/kg/min; D2: 6 $\mu$g/kg/min; D3: 9 $\mu$g/kg/min; D4: 12 $\mu$g/kg/min; and D5: 15 $\mu$g/kg/min). HR: Heart rate; MAP-F: Mean femoral arterial pressure; MAP-R: Mean radial arterial pressure; CVP: Central venous pressure; GEDI: Global end-diastolic volume index; ELWI: Extravascular lung water index; SVRI: Systemic vascular resistance index. \*P < 0.05 vs. D0; \*P < 0.05 vs. MAP-F

Table 2: Clinical data for 48 SAH patients undergoing hemodynamic management assisted with two devices

| Characteristics       | Third-generation FloTrac/Vigileo (n = 24) | Transpulmonary thermodilution (n = 24) |
|-----------------------|------------------------------------------|---------------------------------------|
| Sex, M/F              | 9/15                                     | 7/17                                  |
| Age (years)           | 67 ± 10                                  | 66 ± 11                               |
| WFNS grade            | I–III (good) 17                           | 15                                    |
|                       | IV, V (poor) 7                            | 9                                     |
| Aneurysm location     | ACoA/ACA 7                               | 8                                      |
|                       | MCA 9                                    | 9                                      |
|                       | ICA 8                                    | 7                                      |
| Fisher CT grade       | III 21                                   | 22                                     |
|                       | IV 3                                     | 2                                      |
| Onset of clinical DCI | 7 ± 2                                    | 8 ± 2                                  |
| (day)                 | 19 ± 6*                                  | 32 ± 7                                 |
| Setup time for        | 17 (71%)                                 | 18 (73%)                               |
| monitoring (min)      | 6 (25%)                                  | 4 (17%)                                |
|                       | 2 (8%)                                   | 2 (8%)                                 |
| Clinical response to  | 10.1 ± 4.4                               | 9.3 ± 3.3                              |
| DOB (mmHg)            | 5,470 ± 669\*                            | 4,490 ± 663                           |
| Fluid intake (mL/day) | 4,677 ± 704                              | 3,964 ± 709                           |
| Fluid output (mL/day) | 794 ± 377                                | 526 ± 463                             |
| Fluid balance (mL/day)| 0.2–5 (favorable) 15                      | 14                                     |
| mRS at 3-month        | 2–5 (poor) 9                              | 10                                     |

WFNS: World Federation of Neurosurgical Societies, ACA: Anterior cerebral artery, ACoA: Anterior communicating artery, MCA: Middle cerebral artery, ICA: Internal carotid artery, DCI: Delayed cerebral ischemia, DOB: Dobutamine, MRI: Magnetic resonance imaging, mRS: modified rankin scale. Transpulmonary thermodilution was used as a reference monitoring technique. Values are expressed as mean ± SD or number of patients. \*P < 0.05 vs. reference group.
drugs to establish hemodynamic targets or adverse physical/psychological conditions activating sympathetic nervous function may have caused changes in the arterial vascular compliance and resistance to increase bias in CI. This is a beneficial aspect of dobutamine use because high-dose norepinephrine for treating post-SAH DCI yielded insufficient precision (27.9%) of APCO-derived measurements compared with transpulmonary thermodilution, even when it was analyzed with the third-generation FloTrac/Vigileo system.\[15\]

In this study, both the FloTrac/Vigileo and transpulmonary thermodilution devices demonstrated a similar clinical course and functional outcome when used for a short period of time (approximately 1 week) receiving intravenous dobutamine infusion. It is interesting to note that transpulmonary thermodilution resulted in less fluid intake during the hemodynamic therapy. This may be due to differences in fluid indicators employed for each because GEDI, a volumetric preload variable derived from transpulmonary thermodilution, more adequately predicts preload ventricular response to fluid loading than conventional fluid balance or central venous pressure.\[10,20,21\] In this context, transpulmonary thermodilution may be more suitable for managing patients with severe systemic complications requiring more intensive goal-directed fluid therapy such as pulmonary edema and Takotsubo cardiomyopathy.\[15,22\]

When interpreting the data presented in this study, some methodological aspects and limitations must be considered. First, we compared APCI analysis with an imprecise reference technique (transpulmonary thermodilution) having an inherent bias of approximately 10%, compared with the ‘clinical gold standard’ for CI monitoring using a PAC. However, PAC is not a highly reliable reference standard and is susceptible to variation between measurements due to a variety of factors such as cold-induced reduction in heart rate, loss of thermal indicators, and incorrect catheter placement.\[15,9\] A more robust technique for CI measurement such as ultrasonic and electromagnetic flow meters applied directly to the aorta might yield different results. However, this type of study can only be performed using laboratory animal models. Second, the observations made in this study are limited by the small number of SAH patients tested. The study population enrolled may be highly selective and thus not be directly applicable to other situations, including hemodynamically unstable patients as excluded in this study. Although it was determined by power analysis, smallest sample size used in this study might not be compensated for possible dropouts. Nevertheless, the advantage of the less-invasive, easy-to-setup system on being ready for CI monitoring is still attractive for treating acute neurologic deterioration with inotropes. Further studies examining whether management using this bedside monitoring device is possible in other clinical settings in larger populations and whether the outcome is generally better than other methods are warranted.

ACKNOWLEDGEMENTS
This study was presented in part at the American Heart Association’s International Stroke Conference 2009, San Diego, CA, February 18–20, 2009. This work was supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (G22592026) and Project Research Grant from Akita Prefecture (H221001, H231105).

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