Background and Purpose—Systemic circulation management has not been established for patients with poor grade aneurysmal subarachnoid hemorrhage (SAH) or delayed cerebral ischemia (DCI) after SAH. The aims of the study were to examine hemodynamic variables in these patients and to establish treatment strategies.

Methods—A multicenter prospective cohort study of hemodynamic variables from days 1 to 14 was performed using a transpulmonary thermodilution system (PiCCO Plus). Parameters were analyzed by Mann–Whitney test. Multivariate analysis was performed to identify parameters involved in onset of DCI.

Results—The subjects were 204 patients, including 138 with poor grade SAH (World Federation of Neurological Surgeons grades IV and V) and 52 who developed DCI. The extravascular lung water index, pulmonary vascular permeability index, and systemic vascular resistance index were significantly greater in patients with poor grade SAH compared with those with good grade SAH (World Federation of Neurological Surgeons I–III) on day 2 (P=0.049, P=0.039, and P=0.038). Cardiac index was significantly lower in patients with poor grade SAH on days 1 and 2 (P=0.027 and P=0.011). In patients with DCI, the global end-diastolic volume index was significantly lower than in those without DCI on days 3 to 5 (P=0.0053; P=0.048; and P=0.048). In multivariate analysis, median global end-diastolic volume index, cardiac index, and systemic vascular resistance index at an early stage of SAH (days 3–6) were independently related to onset of DCI (P=0.023, P=0.013, and P=0.003).

Conclusions—Patients with poor grade SAH developed heart failure–like afterload mismatch at an early stage, and those with DCI had decreased global end-diastolic volume index (hypovolemia) in the early stage of SAH.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: UMIN000003794. (Stroke. 2013;44:00-00.)

Key Words: delayed cerebral ischemia ■ poor grade subarachnoid hemorrhage ■ transpulmonary thermodilution system

Significant factors influencing the prognosis of aneurysmal subarachnoid hemorrhage (SAH) include the severity at presentation of the disease and delayed cerebral ischemia (DCI).1–3 Approximately 40% of patients with SAH have poor grade SAH,4,5 and these patients often develop pulmonary edema, cardiac dysfunction, and other comorbidities at onset, which also lead to a poor prognosis.6,7 Thus, pre- and postoperative systemic circulation management is the most important factor influencing the prognosis of poor grade SAH. Treatment for DCI has recently advanced, but use of hypervolemia, hypertension, hemodilution (triple-H) therapy and hypervolemic therapy is still controversial in terms of systemic circulation management.8–12 Autoregulation of cerebral vessel is also dysfunctional in patients with SAH, and systemic arterial pressure, intracranial pressure, and cerebral perfusion pressure directly influence the regional cerebral blood flow in these patients.

A transpulmonary thermodilution system (PiCCO, Pulsion Medical Systems, Munich, Germany) for bedside noninvasive monitoring of hemodynamic variables without using cardiopulmonary catheterization is now widely used for patients with SAH,13 and this equipment has been reported to be effective for circulation in management in these patients.14 However, hemodynamic changes have not been examined in terms of the severity of SAH and the presence or absence of DCI. Therefore, this multicenter, prospective, cohort study was performed to examine the dynamics of time-dependent hemodynamic variables on the basis of severity of SAH.
according to World Federation of Neurological Surgeons grade, with the goal of establishing effective treatment on the basis of systemic circulation management.

Materials and Methods

The SAH PiCCO Study was performed as a multicenter, prospective, cohort study. The protocol was approved by the ethics committee of each participating institution and followed the principles of the Declaration of Helsinki. All patient information was anonymized and protected. Informed consent was obtained from all patients or their family members. This study is registered at http://www.clinicaltrials.gov.

Patients

A total of 204 patients from 9 institutions were enrolled in the study between October 2008 and August 2013. On admission, all patients were examined using computed tomography (CT), and their conditions were classified according to the World Federation of Neurological Surveys scale for severity and Fisher group criteria for CT findings. Patients were included if they had a ruptured cerebral aneurysm documented by cerebral angiography or 3-dimensional (3D) angiography. The exclusion criteria were (1) <15 years of age, (2) disappearance of brain stem reflexes, (3) pregnancy, and (4) severe cardiopulmonary dysfunction requiring percutaneous cardiopulmonary support.

PiCCO Monitoring

Systemic hemodynamics were monitored from days 1 to 14 using a single indicator transpulmonary thermodilution system (PiCCO Plus). A PiCCO catheter (Pulsion Medical Systems) was inserted into the brachial or femoral artery, and a central venous line was inserted into the superior vena cava. Both catheters were connected to the PiCCO Plus for continuous monitoring of cardiac output, contractility, and afterload. Transpulmonary thermodilution was performed 3× a day to monitor volume management and lung water, with averages used as daily values. Measurements were obtained by injecting 15 mL of an ice-cold saline (<3°C) bolus into the superior vena cava, with subsequent detection by the thermistor of the PiCCO catheter in the brachial or femoral artery. Thermodilution curves according to the Stewart–Hamilton principle were recorded from the PiCCO catheter to allow estimations of cardiac output, global end-diastolic volume index (GEDI; normal range, 680–800 mL/m²), extravascular lung water index (3.0–10.0 mL/kg), pulmonary vascular permeability index (PVPI, 1.0–3.0), and systemic vascular resistance index (SVRI; 1700–2400 dyn·s/cm⁵ per square meter). Cardiac function was evaluated on the basis of cardiac index (CI; 3.0–5.0 L/min per square meter). Pulmonary edema was defined as a PaO2/FiO2 ratio ≤300 and bilateral infiltrative shadows observed on chest radiography.

Management

After surgical treatment, patients were admitted to the stroke intensive care unit. Postoperative treatment was performed using the standardized protocol for SAH in American Heart Association guidelines. Intracranial pressure was controlled with cisternal or spinal drainage. Euvolemia was maintained for fluid management and fasudil hydrochloride, or a Ca2+ blocker (nicardipine) was administered to prevent onset of DCI. Symptomatic cerebral vasospasm was defined as a new neurological deterioration, either transient or permanent, in the absence of any other identifiable cause of neurological deterioration, including surgical complications, hydrocephalus, intracranial rebleeding, seizure, infection, or metabolic disturbances. The presence of arterial vasospasm was diagnosed by transcranial Doppler ultrasonography. Mean arterial velocities >120 cm/s in the middle or anterior cerebral arteries or >90 cm/s in the basilar arteries, as measured using transcranial Doppler ultrasonography, were considered to suggest development of arterial vasospasm. Patients with these findings typically underwent cerebral angiography and xenon-enhanced CT, single photon emission CT, or 3D CT angiography to confirm the presence of vasospasm. DCI was also defined as symptomatic cerebral vasospasm and cerebral infarction caused by cerebral vasospasm.

Cerebral infarction was defined as a newly detected, low-density area identified by CT when all other causes of formation of low-density areas (eg, low-density areas around the hematoma) were excluded. No treatment restrictions were imposed if a patient developed DCI.

Statistical Analysis

Mean value comparison was used as the sample estimation method. On the basis of data obtained from 10 cases for ~2 months after starting the study, CI was compared between DCI and non-DCI groups. The result indicated that there was a statistically significant difference in CI with the data in the non-DCI and DCI groups set at 5.9±2.5 and 3.8±1.8 L/min per square meter, respectively, and the power of this study and significance level at 90% and 0.05, respectively. Kirkwood formula was used. Furthermore, we estimated that the incidence rate of DCI was 40% and that of poor SAH was 40%. To obtain the difference in confidence interval (CI), one of the hemodynamic indices, on the basis of above assumption, we estimated that the required number of samples was 120 and 50, respectively, and (130 and 55, respectively, allowing for dropouts), which was 10% greater than the number of samples used in the study design.

Comparisons between groups were performed by Mann–Whitney test for continuous variables and by χ² test for class variables. Multivariate analysis was used to identify factors related to onset of DCI, using the median of each hemodynamic parameter at the early stage of onset (days 3–6). P<0.05 was considered significant in all analyses.

Results

Clinical and Demographic Data

The clinical characteristics of the 204 patients in the study are shown in Table 1. The patients included 138 with poor grade SAH (World Federation of Neurological Surgeons IV and V) and 66 with good grade SAH (World Federation of Neurological Surgeons I–III). There was no significant difference in age, sex, incidence of DCI, or surgical treatment between the two groups (Table 2). No significant difference was found between the groups in Fisher grading, sex, age, or GCS. The Fisher grading V group included more women and a higher proportion of patients in the 19–35 year age group than the Fisher grading I and II groups.

Table 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Item</th>
<th>WFNS I to III (n=66)</th>
<th>WFNS IV, V (n=138)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean (range)</td>
<td>64 (25–89)</td>
<td>63 (22–89)</td>
</tr>
<tr>
<td>Sex (women)</td>
<td>48 (72.7%)</td>
<td>91 (65.9%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Fisher group on CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>8 (12.1%)</td>
<td>3 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>51 (77.3%)</td>
<td>68 (49.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 (7.6%)</td>
<td>67 (48.6%)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical clipping</td>
<td>57 (86.4%)</td>
<td>104 (75.4%)</td>
<td>0.085</td>
</tr>
<tr>
<td>DCI</td>
<td>18 (27.3%)</td>
<td>34 (24.6%)</td>
<td>0.69</td>
</tr>
<tr>
<td>SVS</td>
<td>18 (27.3%)</td>
<td>21 (15.2%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Infarction</td>
<td>6 (9.1%)</td>
<td>26 (18.8%)</td>
<td>0.073</td>
</tr>
<tr>
<td>Systemic complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5 (7.6%)</td>
<td>35 (25.3%)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (12.1%)</td>
<td>26 (18.9%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; DCS, delayed cerebral ischemia; SVS, symptomatic cerebral vasospasm; and WFNS, World Federation of Neurological Surgeons.
methods between the groups. However, the incidence of symptomatic cerebral vasospasm was significantly lower in the poor grade SAH group (15.2% versus 27.3%; \( P = 0.041 \)), and the number of patients in Fisher group was significantly higher in the poor grade group (\( P<0.0001 \)). Regarding systemic complications, pulmonary edema developed in 25.3% of patients in the poor grade group, which was significantly higher than the rate in the good grade group (\( P=0.0028 \)).

**Hemodynamic Parameters in Good Grade and Poor Grade SAH Groups**

Changes in hemodynamic parameters obtained with PiCCO are shown in Figures 1 and 2. GEDI, a preload index from days 1 to 14, was slightly above the normal limit in the good grade and poor grade SAH groups, with no significant difference between the groups (Figure 1A). Extravascular lung water index was close to the upper limit of the normal range in both groups, but was significantly greater in the poor grade group on day 2 (\( P=0.049 \)). PVPI was within the normal range in both groups from days 1 to 12, and increased pulmonary capillary permeability did not develop regardless of the severity of SAH (Figure 1C). However, PVPI was significantly greater in the poor grade group on day 2 (\( P=0.039 \)). Cardiac function evaluated based on CI was within the normal range in both groups but was significantly higher in the poor grade group (\( P<0.0001 \)).

**Figure 1.** Changes in global end-diastolic volume index (GEDI; A), extravascular lung water index (ELWI; B), and pulmonary vascular permeability index (PVPI; C) in World Federation of Neurological Surgeons (WFNS) I to III (open bars) and WFNS IV, V (closed bars) cases >14 days after subarachnoid hemorrhage. *\( P<0.05 \) by Mann–Whitney test (2-tailed value).

**Figure 2.** Changes in cardiac index (CI; A) and systemic vascular resistance index (SVRI; B) in World Federation of Neurological Surgeons (WFNS) I to III (open bars) and WFNS IV, V (closed bars) cases >14 days after subarachnoid hemorrhage. *\( P<0.05 \) by Mann–Whitney test (2-tailed value).
lower in the poor grade group on days 1 and 2 (Figure 2A; \(P=0.027\) and \(P=0.011\)). SVRI, an afterload index, was close to the lower limit of the normal range in both groups (Figure 2B) and was significantly greater in the poor grade group on day 2 (\(P=0.038\)). There was no significant difference in the median of the mean arterial pressure from days 1 to 14 between the groups with good grade and poor grade SAH.

Hemodynamic Parameters in DCI and Non-DCI Groups

Changes in hemodynamic parameters in the DCI and non-DCI groups obtained by PiCCO are shown in Figures 3 and 4. The mean onset day of DCI was day 8.0±3.3. GEDI from days 1 to 14 was slightly above the normal limit in the non-DCI group and was significantly lower in the DCI group on days 3, 4, and 5 compared with the non-DCI group (Figure 3A; \(P=0.0053\), \(P=0.048\), and \(P=0.048\)). Extravascular lung water index was within the normal range in both groups (Figure 3B). PVPI was within the normal range from days 1 to 12, and increased pulmonary capillary permeability after SAH did not develop regardless of the presence or absence of DCI (Figure 3C). CI was within the normal range in both groups but was significantly lower in the DCI group on days 3, 4, and 6 (Figure 4A; \(P=0.020\), \(P=0.042\), and \(P=0.0026\)). SVRI was close to the lower limit of the normal range in both groups (Figure 4B) and was significantly greater in the DCI group on days 3 to 7 and day 9 (\(P=0.049\), \(P=0.029\), \(P=0.036\), \(P=0.00031\), \(P=0.0093\), and \(P=0.028\)). Multivariate analysis showed that the medians of GEDI (odds ratio, 0.997;
DCI.10 Patients with poor grade SAH are also likely to develop cardiomyopathy associated with catecholamine surge,7 which
may have been influenced by the small number of patients with poor grade SAH (n=23) and the different study design
compared with the current study.

The characteristic hemodynamics of patients with SAH associated with DCI were equivalent to hypovolemia through a
combination of hemodynamics specific to afterload mismatch before onset of DCI, with a significantly lower CI compared
with the non-DCI group (Figure 4A), a significantly greater SVRI (Figure 4B), and a significantly lower GEDI than that in the
non-DCI group (Figure 3A). In multivariate analysis, low median values of GEDI and CI and a high median SVRI at an early stage of SAH (days 3–6) were independent factors related to onset of DCI (Table 2). A decrease in GEDI occurs immediately before onset of DCI.29 Therefore, it is important for PiCCO to be incorporated into treatment of SAH at an early stage, at least to detect a decrease in GEDI in the premorbid phase of DCI.

The appropriate treatment for DCI in patients with hypovolemia and hemodynamics specific to afterload mismatch is uncertain. Primarily, cerebral perfusion pressure should be maintained by intracranial pressure control, and then systemic blood pressure is lowered to decrease peripheral vascular resistance; inotropic action is increased using dobutamine and other agents; and preload such as volume expansion is increased, for example, by loading the appropriate amount of albumin.30 In this study, the incidence of DCI did not differ significantly between the good grade and poor grade groups, but the incidence of symptomatic cerebral vasospasm was significantly lower in the poor grade group (Table 1). This was because many patients in the poor grade group could not be neurologically evaluated because of impaired consciousness. In light of this finding, the hemodynamics of these patients should be evaluated using PiCCO at the early stage of onset.

There are contrasting opinions on the efficacy of therapy for hypervolemia, hypertension, and hyperdynamics after onset of SAH, and an index for volume management after onset of SAH has not been established.4,11,12,31,32 This lack of clarity may have arisen because the hemodynamics of each patient have been unclear in previous studies. Recently, goal-directed fluid management using a transpulmonary thermodilution system has given good results in treatment of SAH.26 The introduction of PiCCO at the early stage of SAH enables evaluation of indexes of hemodynamics, such as GEDI, CI, and SVRI in real time, which may allow establishment of tailor-made fluid management to inhibit DCI and improve the prognosis of patients with SAH.

Table 2. ORs for Risk Factors for DCI

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% Confidence Interval for OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.01</td>
<td>0.98–1.04</td>
<td>0.59</td>
</tr>
<tr>
<td>Sex (women)</td>
<td>2.11</td>
<td>0.87–5.15</td>
<td>0.10</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1.02</td>
<td>0.41–2.50</td>
<td>0.97</td>
</tr>
<tr>
<td>Treatment, surgical clipping</td>
<td>0.900</td>
<td>0.42–1.93</td>
<td>0.78</td>
</tr>
<tr>
<td>Poor grade SAH</td>
<td>1.23</td>
<td>0.56–2.67</td>
<td>0.61</td>
</tr>
<tr>
<td>GEDI</td>
<td>0.997</td>
<td>0.995–1.000</td>
<td>0.023</td>
</tr>
<tr>
<td>ELWI</td>
<td>0.93</td>
<td>0.83–1.04</td>
<td>0.20</td>
</tr>
<tr>
<td>PVPI</td>
<td>0.898</td>
<td>0.43–1.89</td>
<td>0.78</td>
</tr>
<tr>
<td>SVRI</td>
<td>1.001</td>
<td>1.000–1.002</td>
<td>0.003</td>
</tr>
<tr>
<td>CI</td>
<td>0.60</td>
<td>0.40–0.90</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Data were obtained from a multiple logistic model, including age, sex, pulmonary edema, treatment, poor grade SAH, and the median value of GEDI, ELWI, PVPI, SVRI, or CI obtained from PiCCO Plus at an early stage of onset (days 3–6). CI indicates cardiac index; ELWI, extravascular lung water index; GEDI, global end-diastolic volume index; PVPI, pulmonary vascular permeability index; OR, odds ratio; SAH, subarachnoid hemorrhage; and SVRI, systemic vascular resistance index.

95% CI, 0.995–1.000; P=0.023), CI (odds ratio, 0.602; 95% CI, 0.404–0.897; P=0.013), and SVRI (odds ratio, 1.001; 95% CI, 1.000–1.002; P=0.003) at an early stage of SAH (days 3–6) were independent factors related to onset of DCI (Table 2).

Complications

There were no major complications, such as massive bleeding (≥50 mL), caused by PiCCO catheterization in this study. The incidences of minor bleeding at the catheter insertion site and catheterization-induced focal infection in a subset of all cases were 4% and 0.98%, respectively.

Discussion

DCI after SAH and poor grade SAH are major factors in an unfavorable outcome in patients with SAH.1–3 The therapeutic goal of DCI after SAH is to improve cerebral blood flow and reduce ischemic neuronal damage by intracranial pressure control and a decrease in the metabolic rate of oxygen consumption. However, cerebrovascular autoregulation is damaged in patients with SAH, which induces DCI and a poor outcome.24,25 Hypotension and hypovolemia also decrease local cerebral blood flow, which results in increased development of DCI.10 Patients with poor grade SAH are also likely to develop cardiomyopathy associated with catecholamine surge,7 which decreases cardiac output and systemic arterial pressure and reduces the oxygen supply to the brain. This suggests that maintenance of systemic arterial pressure and cardiac output is important in patients with severe SAH and in those with associated DCI to improve the outcome of SAH and inhibit DCI.26,27

GEDI, a measure of preload, was within the upper limit of the normal range and hypovolemia was not observed in patients with SAH, regardless of the SAH grade (Figure 1A). However, extravascular lung water index and PVPI (Figure 1B and 1C), and SVRI, a measure of afterload (Figure 2B), were significantly greater in the early stage of SAH in patients with poor grade SAH, and CI was significantly lower in the poor grade group (Figure 2A). This result indicates that patients with poor grade SAH are likely to have heart failure because of afterload mismatch in the early stage of SAH. The number of patients with pulmonary edema secondary to increased pulmonary capillary permeability was also greater in the poor grade group (Table 1). Mutoh et al28 reported that CI was already increased at the early stage of onset in patients with poor grade SAH. However, this result might have been influenced by the small number of patients with poor grade SAH (n=23) and the different study design compared with the current study.

The characteristic hemodynamics of patients with SAH associated with DCI were equivalent to hypovolemia through a combination of hemodynamics specific to afterload mismatch before onset of DCI, with a significantly lower CI compared with the non-DCI group (Figure 4A), a significantly greater SVRI (Figure 4B), and a significantly lower GEDI than that in the non-DCI group (Figure 3A). In multivariate analysis, low median values of GEDI and CI and a high median SVRI at an early stage of SAH (days 3–6) were independent factors related to onset of DCI (Table 2). A decrease in GEDI occurs immediately before onset of DCI.29 Therefore, it is important for PiCCO to be incorporated into treatment of SAH at an early stage, at least to detect a decrease in GEDI in the premorbid phase of DCI.

The appropriate treatment for DCI in patients with hypovolemia and hemodynamics specific to afterload mismatch is uncertain. Primarily, cerebral perfusion pressure should be maintained by intracranial pressure control, and then systemic blood pressure is lowered to decrease peripheral vascular resistance; inotropic action is increased using dobutamine and other agents; and preload such as volume expansion is increased, for example, by loading the appropriate amount of albumin.30 In this study, the incidence of DCI did not differ significantly between the good grade and poor grade groups, but the incidence of symptomatic cerebral vasospasm was significantly lower in the poor grade group (Table 1). This was because many patients in the poor grade group could not be neurologically evaluated because of impaired consciousness. In light of this finding, the hemodynamics of these patients should be evaluated using PiCCO at the early stage of onset.

There are contrasting opinions on the efficacy of therapy for hypervolemia, hypertension, and hyperdynamics after onset of SAH, and an index for volume management after onset of SAH has not been established.4,11,12,31,32 This lack of clarity may have arisen because the hemodynamics of each patient have been unclear in previous studies. Recently, goal-directed fluid management using a transpulmonary thermodilution system has given good results in treatment of SAH.26 The introduction of PiCCO at the early stage of SAH enables evaluation of indexes of hemodynamics, such as GEDI, CI, and SVRI in real time, which may allow establishment of tailor-made fluid management to inhibit DCI and improve the prognosis of patients with SAH.
Conclusions

Patients with poor grade SAH have early heart failure-like afterload mismatch, which indicates that they are likely to develop DCI unless adequate preload is established immediately after onset. DCI is more than just an entity with hemodynamic compromise. PiCCO monitoring enabled an understanding of real-time hemodynamic parameters, such as GEDI, CI, and SVRI, which suggests that volume dynamics should be obtained using PiCCO to facilitate an integrated approach to the management of patients with SAH.

Appendix

Participating Centers

Department of Emergency and Critical Care Medicine, Nippon Medical School Hospital; Department of Neurosurgery, Kansai Medical University Hirakata Hospital; Department of Neurosurgery, Tokyo Medical and Dental University, University Hospital of Medicine; Department of Neurosurgery, Fukuoka University Hospital; Department of Neurosurgery, Nagasaki University Hospital; Department of Neurosurgery and Clinical Neuroscience, Yamaguchi University School of Medicine, Yamaguchi, Japan; Department of Emergency and Critical Care Medicine, Nippon Medical School Tama Nagayama Hospital; Department of Neurosurgery, Saitama Medical University General Medical Center; and Department of Neurosurgery, Saitama Medical University International Medical Center.

Acknowledgments

We thank Ichiro Kunitsugu, MD, PhD, Department of Public Health, Yamaguchi University School of Medicine, for advice on statistical analysis.

Disclosures

None.

References


Multicenter Prospective Cohort Study on Volume Management After Subarachnoid Hemorrhage: Hemodynamic Changes According to Severity of Subarachnoid Hemorrhage and Cerebral Vasospasm
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Stroke. published online June 4, 2013; 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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