Effects of Induced Hypertension on Intracranial Pressure and Flow Velocities of the Middle Cerebral Arteries in Patients With Large Hemispheric Stroke

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Background and Purpose—Our aim was to prospectively evaluate the effects of induced arterial hypertension in patients with large ischemic stroke.

Methods—A total of 47 monitoring sessions in 19 patients with acute, complete, or subtotal middle cerebral artery (MCA) territory stroke were performed. Intracranial pressure (ICP) was monitored using a parenchymal catheter. Mean arterial blood pressure (MAP), ICP, and peak mean flow velocity of the middle cerebral arteries (V_m MCA) were continuously recorded. Patients with acute ICP crises were excluded. After obtaining baseline values, MAP was raised by an infusion of norepinephrine to reach an MAP increase of at least 10 mm Hg. After MAP had reached a peak plateau level, the norepinephrine infusion was stopped.

Results—Baseline MAP was 83.6±1.6 mm Hg and rose to 108.9±2.0 mm Hg after infusion of norepinephrine. ICP slightly increased from 11.6±0.9 mm Hg to 11.8±0.9 mm Hg (P<0.05). Cerebral perfusion pressure rose from baseline 72.2±2 mm Hg to 97±1 mm Hg (P<0.0001). V_m MCA was already higher on the affected side during baseline measurements. At maximum MAP levels, V_m MCA rose by 25.5±5.5 cm/s on the affected side and by 8.6±1.6 cm/s on the contralateral side.

Conclusions—In patients with large hemispheric stroke without an acute ICP crisis, induced hypertension enhances cerebral perfusion pressure and augments the V_m MCA(s), more so on the affected side. The ICP slightly increases; however, this is probably not clinically significant. (Stroke. 2002;33:998-1004.)

Key Words: blood flow velocity ■ cerebral perfusion pressure ■ hypertension ■ intracranial pressure ■ norepinephrine ■ stroke

After acute stroke, arterial blood pressure (BP) is elevated in most patients during the acute phase and usually falls after a few days regardless of whether the patient has a history of arterial hypertension.1 It has been hypothesized that the arterial hypertension that develops immediately after stroke represents a pathophysiological response to maintain or enhance perfusion of reversibly damaged tissue in the penumbra of the infarction, where normal autoregulatory mechanisms are impaired and the perfusion passively follows the variations in the BP.2 The impact of arterial hypertension on patient outcome has not been fully elucidated yet. Jorgensen et al3 demonstrated an inverse ratio of mean arterial blood pressure (MAP) to progression of stroke after arrival at the hospital. In contrast, Davalos et al4 found that high systolic BP increased the risk of stroke progression. On the other hand, Britton and Röden5 found no relation at all between BP and progression of stroke. In a recent study, Ahmed and Wahlgren6 reported that an initial high BP after acute stroke is associated with poor functional outcome.

Theoretically, lowering BP could result in further neuronal damage by directly reducing perfusion to the compromised but still viable brain tissue in the ischemic penumbra surrounding the infarct core. Although there is no firm evidence from controlled studies on the optimum mode of BP management after acute stroke,7 current treatment guidelines recommend waiting to lower raised BP values after acute ischemic stroke for several days or even weeks.8 This recommendation is based on an inhomogeneous collection of circumstantial evidence, various animal experiments, single case reports, case series, and pathophysiological considerations.

Whether BP should even be increased to improve cerebral perfusion in patients with acute ischemic stroke is not known. Hypertension could reduce focal cerebral injury by increasing intraluminal hydrostatic pressure, which serves to open collateral channels and improve perfusion to ischemic tissue in the ischemic penumbra.9,10 Although hypertensive therapy has an appealing logic, there are few experimental data and almost no human data to support the practice.

The question of optimal BP can ultimately only be answered by appropriate prospective randomized intervention.
trials. These trials, though, will be difficult to conduct because the current treatment guidelines already advocate high BP or cerebral perfusion pressure (CPP) in these patients. Furthermore, the BP levels may not play the same role for all patterns of ischemic stroke. While in some patients, high BP might be desirable, in others, arterial hypertension could have detrimental effects. Arterial hypertension has been suggested to have a particular benefit in patients with large territorial infarctions, in contrast to patients with lacunar stroke caused by local arteriosclerosis of small vessels. We investigated the effects of a brief episode of induced arterial hypertension on intracranial pressure (ICP) and CPP and peak mean flow velocity of the middle cerebral arteries (Vm MCA) as a surrogate marker of the cerebral perfusion in patients with large hemispheric stroke.

Subjects and Methods

From February to August 2001, 19 consecutive patients with acute, complete, or subtotal (>2/3) middle cerebral artery (MCA) territory stroke were included in this study. All patients were intubated, ventilated, and anesthetized with analgesics and sedatives. The patients were routinely nursed in a 30° upright position. Ventilation parameters were adjusted to achieve normocapnia and a PaO2 >90 mm Hg. The ICP was continuously monitored with an intraventricular ICP device (Spiegelberg), inserted on the affected hemisphere. ICP, pulse oxygenation, heart rate, and MAP via a catheter in the radial or femoral artery were continuously monitored. The arterial BP transducer was kept at the level of the foramen of Monro. Crystalline fluids and hydroxyethyl starch solutions were administered to achieve a central venous pressure of between 12 and 16 cm H2O. If volume substitution was not sufficient to reach a CPP of at least 70 mm Hg, norepinephrine was administered as a continuous infusion via a central line. Some of the patients were treated with decompressive surgery or hypothermia (33°C for 72 hours) as previously described. Other specific therapeutic measures such as osmotherapy or hyperventilation were not used until the ICP reached 20 mm Hg or clinical signs of markedly increased ICP such as papillary abnormalities had developed.

During a single monitoring session, ventilation parameters, concomitant medication, and volume replacement remained unchanged, and nursing procedures such as turning or endotracheal suction were restricted to a minimum. Administration of vasopressor drugs before start of the study did not constitute an exclusion criterion. Monitoring was initiated at least 2 hours after specific therapy for increased ICP. Because induced arterial hypertension could, in theory, critically increase an already raised ICP, we excluded any patients with an acute ICP crisis (ICP >20 mm Hg or pupillary abnormalities). We also excluded patients with severe cardiac insufficiency, acute coronary syndrome, bradycardia, pulmonary edema, shock, and renal failure in whom the administration of a vasopressor drug could be hazardous.

Patients without a transtemporal bone window adequate (at least unilaterally) for transcranial ultrasound study were not included in this study. The MCA(s) were identified at a depth of 50 to 58 mm and continuously insonated with a 2-MHz transducer of a pulsed-wave ultrasound machine (Multi-Dop-X4, DWL), which was mounted in a custom-designed frame. In some patients, only unilateral monitoring was feasible because of permanent MCA occlusion on the affected side. Vm MCA was registered online. MAP, ECG, and ICP data were exported to the ultrasound machine as analog data. The CPP was calculated as the difference between MAP and ICP. According to the study protocol, repeated measurements could be performed in the same patient on a daily basis with an interval of at least 18 hours between 2 measurements. A single monitoring session consisted of 4 steps: (1) Baseline values for MAP, ICP, and Vm MCA(s) were obtained during the course of 5 minutes. (2) BP was raised using a continuous infusion of norepinephrine. In patients who had not already been treated with norepinephrine, we chose an initial infusion rate of 2 mg/hour. In patients who already received norepinephrine, the baseline dose was increased by 10%. The initial infusion rate of norepinephrine was adjusted to achieve an MAP increase of at least 10 mm Hg. The infusion rate was reduced if MAP increased above an upper limit of 130 mm Hg. (3) After MAP had reached a plateau level, peak values were recorded for the period of time required for the MAP to stabilize (±10%), which was a minimum of 5 minutes. The norepinephrine infusion was then abruptly stopped or—in patients who were pretreated with norepinephrine—reduced to the previous infusion rate. (4) After MAP had declined, baseline values were recorded again (baseline'). An example of a single monitoring session is depicted in Figure 1.

A monitoring session was only further evaluated if the BP values acquired before and after the end of infusion of norepinephrine when the BP values had declined (baseline') did not differ by more than...
10%. It was otherwise assumed that the observed changes were not exclusively related to the norepinephrine infusion. We did not consider this as an adverse event because spontaneous variations of the BP frequently occur in these patients. All parameters monitored were calculated by averaging the values recorded during the last minute before the start of norepinephrine infusion and before norepinephrine was stopped, and during the 1 minute after the BP values had reached baseline values again. Thus, only 1 value for each parameter and level was used for further statistical analysis. In addition, all parameters monitored were documented each time the MAP increased by 5 mm Hg.

The presence of bleeding complications was evaluated on the next cranial CT, which was performed at least every other day according to our institutional protocol for patients with large MCA infarctions. Outcome was assessed at discharge according to the Glasgow outcome scale.14

This study was conducted according to the local ethics committee standards. Informed consent was obtained from the patients’ relatives. All data were analyzed without identifying the patient.

Statistical analysis was performed using the Wilcoxon signed-rank test to detect differences between each time point and baseline values. Differences were considered significant at values of $P<0.05$. Data are presented as mean±SEM.

Results

In all, 47 monitoring sessions were analyzed in 19 patients (8 women, 11 men; mean age 59.1±2.4 years). According to our inclusion criteria, 7 episodes were not analyzed because the BP values acquired before and after infusion of norepinephrine did not differ by more than 10%. In all episodes, ventilation parameters, fluid therapy, and medication could be maintained during the observation period. Eight patients with right MCA territory stroke underwent decompressive hemicraniectomy, and 10 patients with left MCA territory stroke were treated with therapeutic hypothermia (33°C for 72 hours). One patient with left-sided subtotal MCA territory ischemia was medically treated under normothermic conditions. Sixteen measurements were performed in patients after decompressive surgery. In 10 patients (28 episodes), only unilateral monitoring of the $V_m$MCA could be performed because of permanent occlusion of the vessel on the affected side. In the remaining 9 patients (19 episodes), bilateral monitoring of the $V_m$MCA could be performed. The mean interval between stroke onset and the first monitoring session was 58 (range, 6 to 143) hours. Four patients died of uncontrollable intracranial hypertension, 28 to 84 hours after the last monitoring session. The increase in ICP during the monitoring period did not exceed 1 mm Hg in any of the patients who died, and the ICP returned to baseline values in all 4 patients. The remaining patients remained severely disabled at discharge (Glasgow outcome scale 3). Negative cardiovascular or pulmonary side effects of the norepinephrine infusion were not noted. A follow-up CT was performed in all patients after the monitoring episode, and no hemorrhagic complication was observed. No single monitoring episode lasted longer than 1 hour, and concomitant medication and ventilation parameters could be kept stable during that time in all episodes.

MAP, ICP, CPP, and $V_m$MCA values at baseline, during the plateau of maximum MAP increase, and after return to baseline values are depicted in Figure 2. MAP was raised by 25.3 mm Hg from a mean baseline of 83.6±1.6 mm Hg to 108.9±2.0 mm Hg and returned to baseline values of 83.3±1.4 mm Hg after norepinephrine infusion was discontinued. ICP increased slightly from 11.6±0.9 to 11.8±0 to 9 mm Hg ($P<0.05$) and remained elevated even after MAP had returned to baseline levels (11.8±0.9 mm Hg, $P<0.05$). However, the change in the ICP in absolute numbers was quite small (0.19±0.08 mm Hg). The maximum increase in the ICP observed during induced hypertension was 2 mm Hg. As a result of the changes in the MAP and ICP, CPP increased from baseline 72±2 mm Hg to 97±2 mm Hg ($P<0.0001$) and returned to baseline values again (75±2 mm Hg) after the norepinephrine infusion was stopped. $V_m$MCA was already higher on the affected side at baseline measurements (72.4±11.4 cm/s compared with 48.5±4.8 cm/s in the hemisphere contralateral to the infarct). At maximum MAP levels, $V_m$MCA rose by 25.5±5.5 cm/s (35.5%) on the affected ipsilateral, and by 8.6±1.6 (17.5%) on the contralateral side, and returned to baseline values after discontinuation of the norepinephrine infusion. Bilateral measurements could only be performed during 19 monitoring sessions because of permanent occlusion of the MCA ipsilateral to the lesion. However, separate analysis of the 19 episodes in which only bilateral measurement was possible showed that the increase in the $V_m$MCA was more pronounced on the affected side ($P<0.01$).

Figure 3 shows the changes in the CPP and $V_m$MCA for each 5-mm Hg increase in the MAP from baseline values after the start of norepinephrine infusion. As a result of the minute changes in the ICP, CPP values increased in an almost...
linear fashion in conjunction with the MAP increase. The increase in the $V_m$ MCA was more pronounced on the affected side for all levels ($P < 0.05$). On the unaffected side, the increase in the $V_m$ MCA was small overall; however, there was no decrease in the $V_m$ MCA in any patient.

Comparison of the patients who underwent decompressive surgery with the medically treated patient group showed a higher $V_m$ MCA on both sides in the patients in whom decompressive surgery was performed ($P < 0.001$); however, the CPP was not different between the 2 groups (Figure 4). Of the patients who were treated medically, 20 monitoring sessions were measured under hypothermic (33°C) conditions and 11 monitoring sessions under normothermic conditions. Comparison of these 2 groups did not reveal any differences.

**Discussion**

In this study, we systematically examined for the first time the effects of pharmacologically induced arterial hypertension on physiological variables in patients with ischemic stroke. Although there is no full consensus about this treatment method, induced hypertension is in wide clinical use in patients with cerebral vasospasms after subarachnoid hemorrhage.15,16 In patients with head trauma, the potential benefits of induced arterial hypertension have not been ascertained yet. Mascia et al17 concluded from their findings in a recent study with 12 patients with head trauma that induced hypertension with norepinephrine can only be used to increase MAP and stabilize CPP without aggravating cerebral hyperemia if the autoregulation capacity is preserved. In patients with loss of autoregulation, norepinephrine-induced hyperemia caused a possibly detrimental increase in the cerebral blood flow (CBF). Lang and Chesnut18 tested the relationship between CPP and ICP in patients with head trauma by increasing the MAP to detect changes in ICP. They identified patients with impaired autoregulation in whom MAP elevation caused an increase in ICP, lowered ICP, or had no effect on ICP at all. In our patients with ischemic stroke, increase of MAP did not result in a decrease of ICP in any monitoring session; the observed ICP increases were small and probably clinically irrelevant.

For neurosurgical patient collectives, the impact of induced hypertension and CPP and ICP management on physiological variables and outcome has only been insufficiently evaluated. However, for stroke patients, relevant data are almost nonexistent. Because of the different pathophysiology, the results from patients with head trauma can hardly be used to guide the management of stroke patients.

In theory, the rationale for inducing hypertension is that the ischemic infarct core may be surrounded by areas perfused by collateral vessels where the blood flow is pressure dependent because of impaired autoregulation, constituting a “chronic penumbra.”19 If a chronic penumbra exists, the extent of reversible tissue damage can be reduced by increasing the blood flow in the penumbra. It has been shown in positron emission tomography and MRI studies that the penumbra is unstable over time and space; substantial volumes of potentially viable brain tissue have been demonstrated up to 17 hours after stroke, giving justification for a prolonged treatment with induced arterial hypertension.20

There are no recommendations available regarding the levels to which the BP should be increased. It seems to be obvious that the optimal BP depends heavily on the underlying pathophysiology and individual factors. In chronically hypertensive patients, the plot of CBF versus MAP is shifted toward higher BP.21 The same is true for patients with diabetes.22 In hypertensive patients, cerebral autoregulation may therefore be impaired at “normotensive” levels of MAP. In persons with chronic, inadequately managed arterial hypertension, CBF may therefore passively change with the

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**Figure 3.** Changes in the cerebral perfusion pressure ($\Delta$ CPP) and peak mean flow velocity of the middle cerebral arteries ($\Delta V_m$ MCA) from baseline on both sides for each step of 5-mm Hg mean arterial blood pressure (MAP) increase from baseline values after start of norepinephrine infusion. In all 47 episodes, MAP was increased at least by 10 mm Hg.

**Figure 4.** Cerebral perfusion pressure (CPP) and peak mean flow velocity of the middle cerebral arteries ($V_m$ MCA) on both sides in 8 patients who underwent decompressive surgery (16 episodes) and in 11 patients who were treated medically (31 episodes). $V_m$ MCA on both sides are higher in the patients after decompressive surgery ($P < 0.001$), whereas the CPP is not different between the 2 groups.
MAP at normotensive levels and decrease rapidly as the MAP decreases to even lower levels.

Induced hypertension may also carry some risks for the patient. If an occluded vessel is reperfused, the ischemic infarct changes into a hypemic infarct where blood flow is severely increased, because in the area of severe focal ischemia, maximum arteriolar vasodilatation occurs and the capacity for vasoconstriction is lost. In patients treated with fibrinolysis, arterial hypertension represents a strong risk for bleeding complications. In healthy subjects, systemic hypertension would not be expected to increase CBF. However, in areas of ischemia, if autoregulation of the CBF is lost, arterial hypertension would severely augment CBF, potentially increasing the likelihood of blood-brain barrier disruption and the risk of worsening edema formation or hemorrhage. Thus, induced hypertension could exert opposite effects, depending on the underlying pathophysiology and time point: it could be beneficial in the very early phase of stroke before recanalization has occurred and a large penumbra exists, but it could also be hazardous when applied during longer periods or when initiated after too much time has elapsed.

Surprisingly, the cerebral effects of catecholamines after head trauma have only been studied anecdotaly, and there is almost no data on the effects of catecholamines in patients with stroke. In normal subjects, intravenous infusion of alpha- or beta-adrenoreceptor agonists does not affect the CBF. When the blood-brain barrier is disrupted, norepinephrine can cause an increase in the CBF through a higher cerebral metabolism. In an recent animal experiment after head trauma, phenylephrine augmented the CBF by increasing the CPP. In an experiment with healthy subjects, infusion of norepinephrine into the carotid artery increased the BP, but the CBF remained unchanged. Compared to dopamine and norepinephrine in head trauma patients and found that the increase in ICP was smaller with norepinephrine than with dopamine to achieve the same MAP. We chose norepinephrine, a predominantly alpha-adrenergic drug, because cerebral vessels have a low density of alpha-1 receptors so that norepinephrine would not be expected to produce significant, direct cerebral vasoconstriction. Another advantage of norepinephrine is that it only infrequently causes tachycardia or tachyarrhythmia. Compared with phenylephrine, norepinephrine may cause less direct vasoconstriction in the coronary arteries because of its alpha-adrenergic action. However, norepinephrine increases the cardiac afterload and may contribute to heart failure, bradyarrhythmia, cardiac ischemia due to coronary vasoconstriction, renal failure, and gastrointestinal ischemia. This is of particular importance in stroke patients in whom relevant cardiovascular comorbidity is frequently found.

Animal experiments investigating induced hypertension after experimental stroke produced conflicting results as a result of the different paradigms and techniques. Some studies indicated that induced hypertension ameliorates cerebral perfusion and reduces infarction and edema after experimental focal ischemia in various animal models when applied shortly after ischemia. On the other hand, a high CPP has been shown to enhance edema formation in a rabbit model with induced blood-brain barrier disruption. Induced hypertension used during a prolonged time or initiated after a time delay following experimental stroke could be compared better with the clinical situation but has not yet been sufficiently studied in animal models. In rabbits with temporary ischemia, induced hypertension restored the diminished regional CBF to nearly previous levels and caused a 97% reduction in infarct size; however, the hypertension-induced reduction in infarct size diminished with time, and there was no protective effect when hypertension was maintained during occlusions of greater than 1 hour. The authors concluded that hypertension is protective only in the early phase of ischemia.

There are only sparse data on induced hypertension in humans with ischemic stroke. In 1970, Wise reported on 2 patients in whom neurological symptoms after acute ischemia that were complications of cerebral arteriography, could be quickly reversed by vasopressor therapy and returned whenever vasopressor therapy was discontinued during a period of 2 days. In a later study, he treated 13 normotensive patients with acute ischemic stroke with vasopressor drugs to induce arterial hypertension; again, in 5 of these patients neurological deficits improved. Rordorf et al found in a retrospective analysis of stroke patients treated in an intensive care unit that phenylephrine-induced hypertension was not associated with an increase in morbidity or mortality in acute stroke. In selected patients, frequently with arteriosclerosis and stenotic vessels, raising the BP seemed to be associated with rapid improvement in neurological deficits. In a small, prospective patient series, induced hypertension with phenylephrine improved neurological deficits in 7 of 13 patients with acute stroke, and no side effects were noted. There is only 1 case report on a patient with stroke in whom an attempt was made to monitor the effects of induced hypertension on the cerebral perfusion. In this patient, increasing the BP led to an improvement of the clinical symptoms accompanied by an improved perfusion as demonstrated with perfusion-weighted MR.

In our patients with massive stroke requiring mechanical ventilation, we used physiological parameters as surrogate markers for the intended therapeutic benefit from induced hypertension, because clinical examination is of limited value in these patients. In addition, a clinical benefit could not have been expected from a single, short episode of induced hypertension.

Increased CPP is hardly surprising when the MAP is aggressively raised with vasopressor drugs. It is remarkable that the $V_{\text{m}}$MCA as a marker of the CBF not only increased on the affected side, where it passively changed in conjunction with the changes in the BP, demonstrating complete loss of autoregulation, but also, though to a lesser extent, in the MCA of the unaffected hemisphere. As a consequence of the increased CBF in both hemispheres, the ICP increased slightly as a result of the obvious increase in the cerebral blood volume. In our patients without acute ICP crises, this rather small ICP increase was probably of no clinical relevance. However, in patients with markedly increased ICP and nearly exhausted compensation mechanisms, even a small increase in the ICP may cause acute decompensation. We,
therefore, suggest that induced hypertension should only be used in patients with elevated ICP with great care and under continuous ICP monitoring. Although we had no hint of increasing ICP levels at the end of our MAP peak plateau phase, a long-lasting induced hypertension might eventually lead to increased brain edema and raised ICP, which is not the case if induced hypertension is only applied during a short period of time.

It has to be underlined that \( V_{\text{m}} \),MCA is not identical to CBF. Transcranial Doppler (TCD) ultrasound provides only indirect information about CBF, measuring the flow velocity and not the flow volume; therefore, the changes in \( V_{\text{m}} \),MCA correspond accurately to changes in CBF only if the vessel diameter is constant (which cannot be assumed a priori). Moreover, even very small changes in the position of the TCD probe can alter the readings. In patients with stroke, rapid arteriovenous shunting of blood that bypasses the tissue may occur; therefore, TCD recordings could overestimate the actual tissue perfusion. Despite these various limitations, TCD monitoring is the only available method of noninvasively monitoring CBF changes continuously, and it is generally accepted that the dynamic changes in CBF are closely reflected to the TCD readings.43,44 Single-photon emission computed tomography and perfusion-weighted MR examination techniques would have provided better information on the actual tissue perfusion; however, these methods would have required repeated transport from the intensive care unit, which is problematic in critically ill patients for study purposes only. Measurement of the CBF with a thermal diffusion microprobe, which has been used in neurosurgical patients,45 would have provided direct information on the regional blood flow. Unfortunately, this new and experimental method has not been systematically used in patients with stroke, and it is not yet standardized for clinical purposes. Using TCD, we were not able to estimate CBF on the affected side if the vessel was permanently occluded. Therefore, all information on the perfusion of the affected side is derived from those patients in whom the MCA had recanalized, although it can be assumed that the patients with a permanently occluded vessel may benefit much more from an increased perfusion than patients with an already hyperemic infarction in whom an additional increase in the CBF could even worsen brain edema or cause hemorrhage.

Another critical point is the mode and site of ICP monitoring. In patients with focal cerebral lesions, clinically important ICP gradients of up to 20 mm Hg can be found between the intracranial compartments.46 We chose to monitor ICP over the affected hemisphere; therefore, it can be assumed that the ICP in the contralateral hemisphere or other distant compartments is probably below those levels found in the affected hemisphere.

Conclusions

Our results indicate that norepinephrine-induced hypertension during a short period of time improves CPP, augments \( V_{\text{m}} \),MCA, and slightly raises ICP in patients with large MCA stroke in the absence of acute ICP crises. Our results are, therefore, consistent with a potential benefit of induced hypertension. Safety and efficacy of prolonged phases of arterial hypertension and the potential hazards if used in patients with markedly raised ICP have yet to be evaluated. Although the results of this study seem to encourage the use of induced hypertension for patients with acute large hemispheric stroke, there is not enough evidence from our results and the previously published evidence to recommend induced hypertension as a standard treatment for this patient group.

References


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*Stroke*. 2002;33:998-1004
doi: 10.1161/01.STR.000014584.17714.2E

*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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