Spontaneous Hyperthermia and its Mechanism in the Intraluminal Suture Middle Cerebral Artery Occlusion Model of Rats

Fuhai Li, MD; Tsuyoshi Omae, MD; Marc Fisher, MD

Background and Purpose—The intraluminal suture middle cerebral artery occlusion (MCAO) model is increasingly used in experimental stroke studies. The purposes of this study were to determine whether (1) spontaneous hyperthermia occurs after different periods of MCAO in this model, (2) hypothalamic injury contributes to hyperthermia, and (3) hyperthermia increases infarct volume after permanent MCAO.

Methods—Rats were subjected to 60, 90, and 120 minutes of transient MCAO (n=8 per group), permanent MCAO (n=8 per group, 5 groups), and permanent hypothalamic occlusion, in which an occluder was inserted 15 to 15.5 mm to block only the hypothalamic branch from the internal carotid artery (n=4) with the use of the intraluminal suture MCAO method. In one group undergoing permanent MCAO, the body temperature was maintained at 37°C throughout the experiment. In another group (n=4) undergoing 90 minutes of temporary MCAO, diffusion- and perfusion-weighted imaging were performed to document the in vivo ischemic changes in the hypothalamus. Body temperature was measured hourly for 12 hours. At 24 hours (12 hours in 2 permanent MCAO groups), triphenyltetrazolium chloride staining was used to verify ischemic hypothalamic injury and to calculate corrected infarct volumes.

Results—Spontaneous hyperthermia (>39°C) occurred in the 120-minute group, all permanent MCAO groups, and the hypothalamic occlusion group but not in the 60-minute or the 90-minute groups. Hypothalamic infarction was found in 1 rat each in the 60-minute and 90-minute groups, 6 of the 8 rats in the 120-minute group, 37 of the 40 rats in the permanent occlusion groups, and all 4 rats in the hypothalamic occlusion group. After 90 minutes of transient MCAO, the decreased cerebral blood flow and apparent diffusion coefficient values in the hypothalamic region during occlusion recovered fully 2 hours after reperfusion. The corrected infarct volumes were identical in all permanent occlusion groups.

Conclusions—The intraluminal suture MCAO lasting for ≥2 hours induces spontaneous hyperthermia that is associated with hypothalamic injury, and delayed spontaneous hyperthermia does not increase infarct volume after permanent intraluminal suture MCAO. (Stroke. 1999;30:2464-2471.)

Key Words: cerebral ischemia, focal □ hyperthermia □ middle cerebral artery occlusion □ rats
(1) whether spontaneous hyperthermia occurs after different periods of ischemia and different insertion routes of the suture occluder, (2) the nature of the potential mechanism of spontaneous hyperthermia, and (3) whether spontaneous hyperthermia increases infarct volume after permanent intraluminal suture MCAO.

Materials and Methods

Animal Preparation

All procedures used in this study were in accordance with our institutional guidelines. Seventy-two male Sprague-Dawley rats weighing 300 to 360 g were anesthetized with an intraperitoneal injection of 400 mg/kg chloral hydrate. PE-50 polyethylene tubing weighing 300 to 360 g were anesthetized with an intraperitoneal injection of 400 mg/kg chloral hydrate. PE-50 polyethylene tubing was inserted into the left femoral artery for continuous monitoring of blood samples to measure pH, PaCO₂, and PaO₂ at baseline and 60 minutes after MCAO. During the surgical procedure, temperature was continuously monitored with a rectal probe and maintained at 37°C with a thermostatically controlled heating lamp.

Focal Brain Ischemia

Focal brain ischemia was induced by the intraluminal suture MCAO method as previously described.1,2 Briefly, the right CCA, ICA, and ECA were exposed through a midline incision of the neck. A 4-0 silicone-coated nylon suture was used as an occluder and was inserted via the CCA (CCA route) or ECA (ECA route). For the CCA occlusion route, the proximal portions of the right CCA and the ECA were ligated with 5-0 surgical sutures, and the occluder was inserted through an arteriotomy of the right CCA 3 mm below the carotid bifurcation. For the ECA occlusion route, the occluder was inserted through a stump of the ECA, and the CCA was kept open intact. The occluder was advanced into the ICA 17 to 19 mm above carotid bifurcation to occlude the origin of the MCA. For temporary MCAO, reperfusion was obtained by withdrawing the occluder was properly lodged in the anterior cerebral artery and thus blocked blood flow to the middle cerebral artery (MCA). For temporary MCAO, reperfusion was obtained by withdrawing the suture approximately 10 mm. For hypothalamic occlusion, the suture was inserted through an arteriotomy of the right CCA 3 mm below the carotid bifurcation and advanced into the ICA only 15 to 15.5 mm to occlude the hypothalamic branch originating from the ICA.

Experimental Protocol

Animals were randomly assigned to the 9 experimental groups, as shown in Table 1. To determine whether spontaneous hyperthermia is dependent on the duration of ischemia, rats were subjected to 60 minutes of ischemia, 90 (group B), or 120 (group C) minutes of transient MCAO or permanent MCAO (group D). Group E was designed to determine whether hyperthermia could be avoided when relatively long periods of anesthesia were given. Group F (with controlled normothermia) and group G (without temperature control for 12 hours after permanent MCAO) were used to determine whether spontaneous hyperthermia increases infarct size. Group H was used to determine whether hyperthermia could be avoided when the suture occluder was inserted via the ECA and the CCA remained open and intact. Group I was designed to determine whether occluding the hypothalamic vasculature alone induces spontaneous hyperthermia. The rats’ body temperature was maintained at 37°C for the initial 6 hours in group E and for the entire 12 hours in group G by means of a thermostatically controlled heating lamp with the animals under anesthesia. Animals in the other groups were allowed to recover from anesthesia after surgical procedures that ended at 60 minutes after MCAO. After the surgical procedures, the rats were returned to their cages, where a room temperature of 22°C to 24°C was constantly maintained. Rectal temperature was measured hourly for 12 hours in all groups and at 24 hours in all groups but groups F and G (12 hours of survival). A microprocessor thermometer with 0.1°C resolution (Omega Engineering, Inc) was used to measure rectal temperature by inserting the rectal probe to a depth of 6.5 cm.15 To investigate the in vivo ischemic changes in the hypothalamic regions caused by the intraluminal suture occluder, 4 other rats who were subjected to 90 minutes of temporary MCAO underwent diffusion-weighted (DWI) and perfusion-weighted MRI (PWI). After MCAO, the animals were anesthetized with 1.0% isoflurane delivered in air at 1.0 L/min. Body temperature was continuously monitored with a rectal probe and was maintained at 37°C by means of a thermostatically regulated heated-air flow system. The rats were reperfused by withdrawing the occluder in the magnet bore 90 minutes after MCAO. Animals dying prematurely or having subarachnoid hemorrhage at postmortem examination were excluded and replaced.

MRI Measurements

The MRI studies were performed in a GE CSI-II 2.0-T/45-cm high-field imaging spectrometer (GE NMR Instruments) operating at 85.56 MHz for 1H and equipped with ±20 G/cm self-shielding gradients. Pulsed-field gradient nuclear MR was used to noninvasively measure diffusion rates of brain water.16 Eight contiguous coronal slices of DWI, 2 mm in thickness, were acquired with a spin-echo echo-planar imaging (EPI) sequence (field of view [FOV], 25.6×25.6 mm²; matrix size, 64×64 pixels; repetition time [TR], 5 seconds; echo time [TE], 74 ms; EPI data acquisition time, 65 ms; signal averages, 2). Half-sine-shaped gradients were applied along 1 of 3 orthogonal axes. Nine b values, ranging from 18 to 1553 s/mm², were used to...
measure apparent diffusion coefficient (ADC) of water along each of the 3 orthogonal gradient axes. The average ADC (ADC\textsubscript{a}) was calculated by averaging the ADC values from the 3 orthogonal gradient axes on a pixel-by-pixel basis,\textsuperscript{17} and ADC\textsubscript{av} maps were generated.\textsuperscript{18} CBF\textsubscript{i} maps were generated.\textsuperscript{19} and CBF\textsubscript{i} maps were generated.\textsuperscript{19} The CBF\textsubscript{i} and ADC\textsubscript{av} values were measured minutes after MCAO. The CBF\textsubscript{i} and ADC\textsubscript{av} values were measured minutes of transient MCAO. However, spontaneous hyperthermia (\(\geq 39^\circ\text{C}\)) developed in the groups undergoing 2 hours of transient (group C) or permanent MCAO via the CCA route (groups D, G) or via the ECA route (group H) and in the group undergoing permanent MCAO with the initial 6 hours of controlled normothermia under anesthesia (group E). Hyperthermia occurred when the occluder was intentionally inserted only 15 to 15.5 mm to occlude the hypothalamic branch from the ICA (group I). Temperature in group F was maintained normal for the entire period.

The brain slices were incubated for 30 minutes in a 2% solution of triphenyltetrazolium chloride (TTC) at 37°C and fixed by immersion in a 10% buffered formalin solution.\textsuperscript{20} Then the brain slices were photographed with the use of a charge-coupled device camera. The unstained areas were defined as infarcted. With the use of an image analysis program (Bio Scan OPTIMAS), the corrected infarct volumes were calculated to compensate for brain edema as previously described.\textsuperscript{21,22}

### Determination of Hypothalamic Damage

From the TTC-stained brain slices (usually the fourth slice), one investigator (T.O.), familiar with the anatomic location of the hypothalamus and not aware of the group assignment, determined whether ipsilateral hypothalamic injury occurred. The normal hypothalamus stained dark red. Pink or unstained (white) hypothalamus was judged to indicate ischemic injury.

### Statistical Analysis

Data are presented as mean±SD. Statistical analyses were performed with the use of a t test and 1-factor or 2-factor repeated-measures ANOVA. A 2-tailed value of \(P<0.05\) was considered statistically significant.
The mean body weight of rats did not differ among the groups (P=0.93). Physiological variables such as mean arterial blood pressure, PCO₂, and PO₂ were within the normal ranges and did not show significant difference among the groups at each time point (P>0.15), as shown in Table 2. The premature death rate was 1 in group B, 3 in group C, 1 in group D, 2 in group E, 2 in group F, and 1 in group H. Subarachnoid hemorrhage was detected at postmortem examination in the following numbers of animals: 1 in group A, 1 in group C, 2 in group E, and 1 in group G.

During surgical procedures, temperature in all groups was normal (37°C). The rats usually recovered from anesthesia approximately 2 hours after the surgical procedures terminated. As shown in Figure 1, there was no hyperthermia (<38°C) in group A (60-minute occlusion) and group B (90-minute occlusion). However, as rats recovered from anesthesia, the temperature gradually rose and reached 39°C in group C (120-minute occlusion) at 8 hours and in group D (permanent occlusion via the CCA) at 5 hours after MCAO. In group E, hyperthermia (≥39°C) occurred 4 hours after the initial 6 hours of anesthesia was stopped. The temperature in group F was maintained in the normal range (37°C) throughout the 12-hour observation period. Hyperthermia also occurred in group G (permanent occlusion via the CCA) and group H (permanent occlusion via the ECA) at 4 hours after MCAO. Interestingly, the temperature reached 39°C at 5 hours after MCAO in group I, in which the occluder was intentionally advanced only 15 to 15.5 mm to occlude the hypothalamic branch originating from the ICA.

The identification of hypothalamic injury is shown in Table 3. One of the 8 rats in each group undergoing focal ischemia for 60 and 90 minutes was judged to have hypothalamic infarction. Six of the 8 rats undergoing 120 minutes of temporary MCAO and 37 of the 40 rats undergoing permanent MCAO had hypothalamic infarction. All 4 rats that were subjected to hypothalamic artery occlusion had ischemic injury of the hypothalamus. Representative TTC staining of the hypothalamus is shown in Figure 2.

The mean CBFᵱ values from all 4 rats demonstrated by perfusion imaging decreased significantly in the hypothalamic region (43±8% of contralateral region; P<0.001) as well as the MCA territory during MCAO; values revealed almost full recovery 2 hours after reperfusion (210 minutes after occlusion) in the hypothalamic area (93±13% of contralateral region; P=0.33) but not in the MCA territory. The mean ADCᵱ values from all 4 rats also declined significantly (65±8% of contralateral region; P=0.02) after MCAO and almost completely normalized after reperfusion (95±9% of contralateral region; P=0.52). Postmortem TTC staining at 24 hours after MCAO demonstrated no hypothalamic damage in all 4 rats. Representative CBFᵱ and ADCᵱ maps and TTC staining from one rat undergoing 90 minutes of transient MCAO are shown in Figure 3.

The ischemic infarct volumes in each group are shown in Figure 4. The corrected infarct volume was significantly smaller in the 60-minute group (P=0.026, t test) and the 90-minute group (P=0.024, t test) compared with the permanent occlusion group (group D). There was no significant difference in infarct size between the 120-minute group and the permanent occlusion group (group D) (P=0.65, t test). The corrected infarct volume was almost identical among all permanent occlusion groups (P=0.98, 1-factor ANOVA), despite different occlusion routes (CCA versus ECA), different survival times (12 versus 24 hours), and different body temperatures (controlled normothermia versus spontaneous hyperthermia). The ischemic infarct size was variable in the 60-minute occlusion group (coefficient of variation [SD/mean]=48%), while the infarct sizes in the 90-minute, 120-minute, and permanent occlusion groups were reproducible (coefficient of variation=15% to 25%).

### Discussion

The present study demonstrates that (1) delayed spontaneous hyperthermia (>39°C) occurs in rats undergoing 2 hours of transient and permanent intraluminal suture MCAO, (2) hypothalamic injury caused by the intraluminal suture is

#### Table 3. The Results Assessing Hypothalamic Infarction Determined by TTC Staining

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We tested uncoated 3-0, uncoated 4-0, poly-L-lysine-coated leads to spontaneous hyperthermia. In a preliminary study, demonstrated that MCAO induced by an uncoated 3-0 suture reached 39°C to 39.5°C after 2 hours of temporary or permanent MCAO in Wistar rats. It has not been proven that spontaneous hyperthermia is related to a specific rat strain or a specific type of filament occluder. Using Sprague-Dawley rats, we demonstrated that a gradual rise in body temperature occurred and reached 39°C as the rats recovered from anesthesia after 2 hours of temporary or permanent intraluminal suture MCAO, indicating that spontaneous hyperthermia is not related to the rat strain. Kuluz et al previously demonstrated that MCAO induced by an uncoated 3-0 suture leads to spontaneous hyperthermia. In a preliminary study, we tested uncoated 3-0, uncoated 4-0, poly-L-lysine-coated 3-0, and silicone-coated 6-0 suture occluders and found that these different kinds of sutures also induced hyperthermia after permanent MCAO (data not shown), suggesting that spontaneous hyperthermia is not unique to the occluder types.

In addition, spontaneous hyperthermia occurred when the suture occluder was inserted via either the CCA or the ECA, which indicates that an open and intact CCA does not prevent spontaneous hyperthermia. Interestingly, <90 minutes of temporary MCAO does not give rise to hyperthermia, consistent with a recent report. Our results, along with others, demonstrate that spontaneous hyperthermia is related to the duration of MCAO and is likely a general complication of the intraluminal suture MCAO model, if MCAO lasts for ≥2 hours. It was reported that hyperthermia could be avoided if anesthesia was used to maintain normal temperature during ischemia and the first hour of reperfusion after 1 hour of transient MCAO and if anesthesia plus temperature control was maintained for the initial 3 hours after MCAO or external cooling was performed for the initial 4 hours after 2 hours of transient MCAO. However, the present study demonstrates that spontaneous hyperthermia after permanent MCAO still develops after the rats recovered from anesthesia even though a normal temperature was maintained for 6 hours under anesthesia, suggesting that anesthesia only masks spontaneous hyperthermia and fails to prevent it after permanent MCAO.

What are the possible mechanisms of spontaneous hyperthermia? It is unlikely that hyperthermia is caused by an infection since spontaneous hyperthermia occurred quickly in rats undergoing ≥2 hours of MCAO and did not develop in rats undergoing sham operation, in which the suture occluder was inserted only 2 mm above the carotid bifurcation, and ≤90 minutes of temporary MCAO, as demonstrated by our study and others. One study previously demonstrated that interfering with blood flow to the brain temperature regulatory center in the hypothalamus could change the body temperature. Using autoradiographic technique, Zhao et al demonstrated a reduction of blood flow in the hypothalamus after suture MCAO. The blood supply to the hypothalamus originates from the anterior cerebral artery, the ICA, and the posterior communicating artery. Accordingly, when the suture occluder is inserted to block the blood flow to the MCA, it simultaneously interrupts blood flow to the hypothalamus as well. Hypothalamic damage after insertion of a filament suture into the ICA to occlude the MCA was documented in previous studies. Our results confirm that the ischemic injury in the hypothalamus is likely an important factor for spontaneous hyperthermia seen with the intraluminal suture MCAO model, as suggested by the following observations: first, hyperthermia is...
closely related to hypothalamic damage after intraluminal MCAO. In the groups (60- and 90-minute) without hyperthermia, only 2 of the 16 rats were observed to have hypothalamic damage. In the groups (120-minute and permanent) with hyperthermia, however, 43 of the 48 rats had hypothalamic injury. Second, when the suture occluder was intentionally inserted only 15 to 15.5 mm to occlude the vascular branch from the ICA to the hypothalamus, all 4 rats had hypothalamic damage and hyperthermia. Third, in the rats undergoing 90 minutes of temporary MCAO, the CBF and ADC values demonstrated by in vivo MRI study in the hypothalamic region significantly decreased during MCAO and fully recovered after reperfusion. Consequently, no hypothalamic injury was seen at postmortem TTC staining (Figure 3). This indicates that the hypothalamus is likely to tolerate 90 minutes of temporary ischemia in this model, probably because of its multiple vascular supply. More than 2 hours of ischemia, however, appears to be beyond the critical threshold of hypothalamic neurons, and subsequent ischemic damage in hypothalamus develops. Further studies are needed to address why hypothalamic damage consistently results in hyperthermia rather than hyperthermia and whether hypothalamic damage affects plasma glucose levels, since we did not measure this variable in the present study.

Another interesting finding in this study is that the ischemic infarct volume in the group with controlled normothermia for 12 hours was almost identical to that in the groups with delayed spontaneous hyperthermia with a 12-hour survival or 24-hour survival after permanent MCAO. This indicates that delayed spontaneous hyperthermia does not increase ischemic infarct volume. Many previous studies demonstrated that mild early artificial hyperthermia in brain tissues (39°C) exacerbates both the severity and extent of ischemic damage after global forebrain ischemia.9,10,30 The effect of hyperthermia on ischemic infarct volume after focal brain ischemia is controversial. Using a model of direct MCA clipping or electrocoagulation, Morikawa et al.13 observed that hyperthermia significantly increased infarct volume after 2 hours of transient MCAO but not permanent MCAO when brain temperature was modulated to 39°C. However, when the brain and body temperatures were elevated to 40°C before or immediately after occlusion, the infarct volumes significantly increased compared with the normothermia group.11 With the intraluminal suture MCAO model, a temperature of 39.2°C augmented infarct volumes significantly after 90 minutes of temporary MCAO.22 A recent study demonstrated that a delayed postischemic elevation of 40°C, but not 39°C, worsened pathological outcome after 60 minutes of transient MCAO.32 These findings suggest that the detrimental effects of hyperthermia on histopathological outcomes are likely related to the severity of ischemia, duration of ischemia, and degree of hyperthermia. Although it is not conclusive why the spontaneous hyperthermia observed in this study does not aggravate ischemic outcome, several possible explanations can be drawn. First, the extent of ischemic damage is mainly determined by the severity and duration of ischemia, despite the fact that other factors such as hyperthermia or hyperglycemia13,34 may aggravate it. However, when the degree of ischemia is severe and the duration is prolonged, for example, in intraluminal suture permanent MCAO, the infarct volume may be almost maximal because of the large artery involved and degree of blood flow impairment. Therefore, other adverse factors may fail to increase infarct volume. Second, there may be a temperature threshold for exacerbating pathological outcomes, as discussed previously. The spontaneous hyperthermia (<40°C) documented in this study may not reach the threshold needed to increase ischemic infarct volume. Furthermore, it is not known whether hyperthermia developed in the brain tissue since we did not measure the brain temperature directly because this would have required an invasive procedure for inserting a needle thermistor in awake rats. Although the body temperature was maintained as normal, brain temperature in the ischemic regions may decrease by 1°C to 2°C after focal ischemia without modulation of brain temperature, as a previous study demonstrated.31 Therefore, the brain temperature in the rats with elevated rectal temperature (39°C to 39.5°C) may have increased just slightly. Finally, it is not known whether delayed spontaneous hyperthermia has the same adverse effects on pathological outcomes as artificial early hyperthermia does. In this study we did not determine the infarct volumes at delayed time points (for instance, 2 or 4 weeks). Further studies are needed to address whether spontaneous hyperthermia has delayed effects on ischemic damage. In addition, studies are also needed to determine whether spontaneous hyperthermia aggravates ischemic outcomes in the transient MCAO model, since artificial hyperthermia may worsen ischemic damage in transient ischemia more than in permanent ischemia.31

In conclusion, the present study demonstrated that spontaneous hyperthermia after the intraluminal suture MCAO is related to the duration of ischemia, is apparently associated with ischemic damage of the hypothalamus, and does not increase the ischemic infarct volume in permanently occluded rats with the suture MCAO model.

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References


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**Editorial Comment**

Previous studies have reported spontaneous hyperthermia during transient MCAO using the intraluminal suture model. The present study determined whether spontaneous hyperthermia could be documented with different periods of MCAO, whether hypothalamic damage contributed to the hyperthermic response, and whether the addition of hyperthermia had an effect on infarct volume after permanent MCAO. The authors determined that the duration of occlusion is a critical factor in determining whether spontaneous hyperthermia is observed and that hypothalamic injury appears to be associated with this temperature effect. These factors, in addition to anesthetic protocols, may explain why spontaneous hyperthermia is not always observed after intraluminal MCAO.¹

Hyperthermia during and/or after a cerebral ischemic insult has been reported to worsen outcome after experimental ischemia and clinical stroke.²³ As pointed out in the present study, the consequences of temperature elevations on ischemic outcome depend on multiple factors, including the severity of the insult, the duration of ischemia, and the degree of hyperthermia. In this study spontaneous hyperthermia did not increase infarct volume after permanent ischemia. As indicated by the authors, a reason for this result may be that permanent intraluminal suture MCAO produces an infarct volume that is maximal and therefore not sensitive to secondary injury mechanism, including postschismic hyperthermia. However, it should also be stressed that infarct volume was assessed at a 24-hour survival period. This is a relatively short survival period and may therefore not define the final histopathological outcome. From a clinical perspective, it would be important to assess the affects of spontaneous hyperthermia on chronic histopathological and behavioral outcome.

Evidence was also provided for a role of hypothalamic ischemic damage in the development of spontaneous hyperthermia. Possible mechanisms for spontaneous hyperthermia after ischemic damage may be complex and also involve the synthesis or activation of 1 or more endogenous pyrogens.
For example, interleukin 1β (IL-1β) plays a key role in the regulation of body temperature under normal and pathological conditions. In addition, several studies have documented the upregulation of IL-1β after brain ischemia. Whether treatment with an antibody to the IL-1β receptor subtype IL-1RII would inhibit spontaneous hyperthermia under the present conditions remains to be determined. Novel strategies to prevent periods of hyperthermia after clinical stroke require continued investigation.

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