Combating Hyperthermia in Acute Stroke
A Significant Clinical Concern

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**Background**—Moderate elevations of brain temperature, when present during or after ischemia or trauma, may markedly worsen the resulting injury. We review these provocative findings, which form the rationale for our recommendation that physicians treating acute cerebral ischemia or traumatic brain injury diligently monitor their patients for incipient fever and take prompt measures to maintain core-body temperature at normothermic levels.

**Summary of Review**—In standardized models of transient forebrain ischemia, intraischemic brain temperature elevations to 39°C enhance and accelerate severe neuropathological alterations in vulnerable brain regions and induce damage to structures not ordinarily affected. Conversely, the blunting of even mild spontaneous postischemic hyperthermia confers neuroprotection. Mild hyperthermia is also deleterious in focal ischemia, particularly in reversible vascular occlusion. The action of otherwise neuroprotective drugs in ischemia may be nullified by mild hyperthermia. Even when delayed by 24 hours after an acute insult, moderate hyperthermia can still worsen the pathological and neurobehavioral outcome. Hyperthermia acts through several mechanisms to worsen cerebral ischemia. These include (1) enhanced release of neurotransmitters; (2) exaggerated oxygen radical production; (3) more extensive blood-brain barrier breakdown; (4) increased numbers of potentially damaging ischemic depolarizations in the focal ischemic penumbra; (5) impaired recovery of energy metabolism and enhanced inhibition of protein kinases; and (6) worsening of cytoskeletal proteolysis. Recent studies demonstrate the feasibility of direct brain temperature monitoring in patients with traumatic and ischemic injury. Moderate to severe brain temperature elevations, exceeding core-body temperature, may occur in the injured brain. Cerebral hyperthermia also occurs during rewarming after hypothermic cardiopulmonary bypass procedures. Several studies have now shown that elevated temperature is associated with poor outcome in patients with acute stroke. Finally, recent clinical trials in severe closed head injury have shown a beneficial effect of moderate therapeutic hypothermia.

**Conclusions**—The acutely ischemic or traumatized brain is inordinately susceptible to the damaging influence of even modest brain temperature elevations. While controlled clinical investigations will be required to establish the therapeutic efficacy and safety of frank hypothermia in patients with acute stroke, the available evidence is sufficiently compelling to justify the recommendation, at this time, that fever be combated assiduously in acute stroke and trauma patients, even if “minor” in degree and even when delayed in onset. We suggest that body temperature be maintained in a safe normothermic range (eg, 36.7°C to 37.0°C [98.5°F to 98.6°F]) for at least the first several days after acute stroke or head injury. *(Stroke. 1998;29:529-534.)*

**Key Words:** fever ■ ischemia ■ hypothermia ■ neuroprotection

**The Evidence**

**Hyperthermia Worsens Outcome in Studies of Global and Focal Cerebral Ischemia**

**Global Ischemia**

In a standardized rat model of transient (20-minute) forebrain ischemia produced by temporary bilateral carotid artery occlu-
sions with prior bilateral vertebral artery coagulation,\textsuperscript{7} we showed that ischemic elevations of brain temperature to 39°C enhanced and accelerated the appearance of severe neuropathological alterations in the hippocampus and striatum. In contrast to normothermic ischemia, hyperthermic ischemia also led to marked damage to the superficial layers of neocortex and to foci of frank infarction in cortex, thalamus, cerebellum, and substantia nigra.\textsuperscript{8,9} Hyperthermic ischemic rats tended to remain unresponsive and to die soon after ischemia.\textsuperscript{9} Transient hyperthermia in the absence of ischemia produced no pathological changes.

These findings have been strongly supported and extended by other laboratories in rodent and canine models of transient forebrain ischemia.\textsuperscript{10–15} In one study, the marked loss of hippocampal CA1 pyramidal neurons produced by 5 minutes of high-grade forebrain ischemia in gerbils was dramatically attenuated merely by counteracting the mild core-temperature elevation (approximately 1.5°C) that tended otherwise to occur during the first 90 minutes of postischemic recirculation.\textsuperscript{11} Other workers\textsuperscript{14,15} have called attention to a prolonged period of spontaneous hyperthermia after a 10-minute forebrain ischemic insult in rats, which could be abolished by the administration of dipyrone, an anti-inflammatory/antipyretic drug, resulting in partial neuroprotection. In dogs subjected to 12.5 minutes of complete cerebral ischemia (by arterial hypotension plus intracranial hypertension) with central-arterial and cranial temperature monitoring, those animals maintained at 37°C were behaviorally normal or near normal, while dogs maintained at 39°C either remained comatose or died, and animals held at 38°C had an intermediate outcome.\textsuperscript{13}

### Focal Ischemia

Studies in focal ischemia are also unequivocal in showing a deleterious effect of mild hyperthermia. In a model of reversible proximal middle cerebral artery (MCA) occlusion in rats, the elevation of brain temperature from 36°C to 39°C during a 2-hour period of MCA occlusion resulted in a 3-fold increase in infarction volume as measured histologically.\textsuperscript{16} (In the same study, lowering the brain temperature to 30°C reduced infarct volume by approximately 70% compared with normothermia.) By contrast, the infarct resulting from permanent MCA occlusion in that study was not significantly affected by hyperthermia.\textsuperscript{16} Other investigators, however, using a rat model of permanent MCA and ipsilateral carotid artery occlusions, reported that moderate hyperthermia (39.9°C) for 1 hour or more in the immediate peri-infarct period produced a 1.5- to 1.6-fold increase in the volume of infarction compared with normothermic (37°C) animals.\textsuperscript{17}

Other studies in focal ischemia have shown that mild hyperthermia may nullify the effect of an otherwise neuroprotective drug. Rats receiving 2 hours of MCA occlusion were treated before and after ischemia with MK-801,\textsuperscript{18} an extensively studied N-methyl-D-aspartate antagonist known to be protective in focal ischemia.\textsuperscript{19} In one group of rats, temperature was allowed to rise spontaneously (to 39°C to 39.5°C) during ischemia, while in another group it was controlled at near-normal levels. MK 801 reduced infarct volume markedly in the temperature-controlled group but failed to have a therapeutic effect in rats with mild spontaneous hyperthermia.\textsuperscript{18}

Hyperthermia has also been shown to have a detrimental effect in focal ischemia when combined with thrombolytic therapy. In a rat model of blood clot embolization to the carotid artery territory, hyperthermia alone (39°C for 2 hours) increased the mean infarct volume by 1.4-fold and enhanced mortality.\textsuperscript{20} In animals treated with tissue plasminogen activator 2 hours after embolization, hyperthermic rats, despite showing the most complete recanalization by angiography, now had 2.8-fold larger infarct volumes than treated normothermic animals (P < .02). The results of this study take on added meaning in the context of the recent clinical approval of thrombolytic therapy in the management of hyperacute ischemic stroke.\textsuperscript{21,22}

### Hyperthermia May Act Through Several Mechanisms to Worsen Cerebral Ischemia

#### Neurotransmitter Release

Release of neurotransmitters in both global and focal ischemia is accentuated by hyperthermia and diminished by hypothermia. In a microdialysis study of 20-minute forebrain ischemia (produced by bilateral carotid artery occlusions plus hypotension), normothermic rats showed a 21-fold increase in basal ganglionic glutamate levels during ischemia, which returned to normal by 20 to 30 minutes of recirculation. By contrast, glutamate levels in hyperthermic (39°C) brains increased by 37-fold during ischemia (P = .02) and tended to persist longer during the recirculation period.\textsuperscript{21} Intraischemic hyperthermia also accentuated the release of \(\gamma\)-aminobutyric acid and doubled the release of glycine. Importantly, the excitotoxic index, a composite measure of neurotransmitter release,\textsuperscript{21} rose by only 2-fold in normothermic rats but showed a 20-fold elevation after hyperthermic ischemia—implying that the potential for greatly enhanced excitotoxicity may exist under hyperthermic conditions.\textsuperscript{23}

In focal ischemia, we studied this problem in a model of 2-hour temporary MCA clip-occlusion in rats monitored for cortical blood flow (by laser-Doppler flowmetry) and for glutamate release (by intracortical microdialysis).\textsuperscript{21} In hyperthermic (39°C) rats, peak glutamate release in the penumbral cortex during MCA occlusion averaged 31-fold above baseline compared with 6.5-fold elevations in normothermic (37°C) rats. Furthermore, this glutamate release occurred at a substantially higher blood flow threshold in hyperthermic rats (61% of control flow) than in normothermic animals (33% of control flow).

#### Oxygen Radical Production

We used in vivo microdialysis to sample the brain’s extracellular fluid for evidence of hydroxyl radical production (as reflected in the formation of the stable adducts 2,3- and 2,5-dihydroxybenzoic acid after salicylate administration).\textsuperscript{26} We showed that cortical oxygen radical production during the early recirculation period after a global ischemic insult is markedly influenced by intraschismic brain temperature: while no elevation of these radical adducts occurred after moderately hypothermic (30°C) ischemia, 2- to 3-fold elevations were observed after a normothermic (36°C) period of global ischemia, and 4- to 5-fold elevations were observed after mildly
hyperthermic (39°C) ischemia. These results have been strongly confirmed in a recent study by another group.

**Blood-Brain Barrier Changes**

Ischemia-induced blood-brain barrier opening is remarkably sensitive to brain temperature. The mild extravasation of protein tracers across the barrier observed after periods of normothermic global ischemia is attenuated by mild to moderate (30°C to 33°C) intraischemic hyperthermia but is markedly exaggerated by mild intraischemic hyperthermia (39°C).

**Ischemic Depolarizations**

Focal vascular occlusion is known to trigger repetitive episodes of ischemic depolarization (so-called peri-infarct depolarizations) within the cortical penumbra. These events are associated with severe transmembrane ionic dyshomeostasis (elevations of extracellular potassium ion and of intracellular calcium ion), and they obligate an inordinate energy expenditure to restore ion gradients in ischemically threatened cortex, resulting in the eventual irreversible deterioration of the penumbra and expansion of the zone of infarction. Intraischemic hyperthermia (40°C) both increases the numbers of these depolarizing shifts and, pari passu, enlarges the size of the resulting infarct. Conversely, hypothermia diminishes both.

**Brain Metabolism and Second Messengers**

In cats subjected to 16 minutes of global cerebral ischemia, metabolic recovery was assessed with 1H MR spectroscopy. Hyperthermia (mean, 40.6°C) induced 1 hour or more before ischemia and maintained for 1.5 to 2 hours after recirculation enhanced the degree of intracellular acidosis and impaired the recovery of cerebral ATP and phosphocreatine levels compared with normothermic cats. We obtained similar findings in a study in which we directly assayed regional brain energy metabolites in rats recovering from 20 minutes of high-grade global ischemia performed at different cranial temperatures. Again, there was less complete recovery of ATP levels and adenylate energy charge in both cortex and subcortical regions of rats with intraischemic hyperthermia (39°C).

Hyperthermia also appears to affect the manner in which various protein kinases are influenced by ischemia. Calcium/calmodulin-dependent protein kinase II is a mediator of many of the second-messenger actions of calcium, including neurotransmitter release, synaptic transmission, and cytoskeletal function. Hyperthermia (39°C) during ischemia was found to exacerbate the degree of inhibition of calcium/calmodulin-dependent protein kinase II induced by a brief period of global ischemia. Similarly, hyperthermia significantly influenced patterns of protein kinase C alteration induced by global ischemia.

**Cytoskeletal Degradation**

Calpain is a calcium-sensitive cysteine protease that, when activated, degrades neuronal cytoskeletal proteins such as spectrin and microtubule-associated protein 2 (MAP2). Calpain activation and spectrin proteolysis have been implicated in neuronal injury produced by hypoxia and ischemia. In a study of 1-hour transient proximal MCA occlusion, hyperthermia (39°C) during the period of focal ischemia led to spectrin proteolysis in cortical pyramidal neurons soon after the onset of reperfusion, which became marked by 4 and 24 hours, in association with morphological evidence of irreversible neuronal injury. By contrast, after normothermic MCA occlusion, only occasional neurons showed spectrin proteolysis, and this subsided by 24 hours.

In a related study, three groups of gerbils received 5 minutes of global forebrain ischemia (by bilateral carotid artery occlusions) while scalp temperatures were maintained at either 33.3°C, 36.7°C, or 39.7°C; brains were subsequently studied by immunohistochemistry for calmodulin and MAP2. The marked decrease in calmodulin and MAP2 immunoreactivity induced in the vulnerable hippocampal CA1 sector at 48 hours in normothermic animals and the subsequent delayed death of these neurons were both aggravated by mild intraischemic hyperthermia.

**Hyperthermia, Even If Delayed, Worsens Ischemic and Traumatic Injury**

In recent studies from our laboratory, the core-body temperature of rats receiving mild to moderate focal or global ischemic insults was increased by external warming 1 day after the initial ischemic insult. In each case, a dramatic accentuation of neural injury resulted. In the first of these studies, the MCA of normothermic rats was occluded for 60 minutes with an intraluminal suture. A focal ischemic insult of this duration normally gives rise only to restricted basal ganglionic infarction with a very small cortical component. However, when brain temperature was elevated to 40°C for a 3-hour period 24 hours after the MCA occlusion, the resulting cortical infarct volume enlarged dramatically (on average, by 6.4-fold), as did the total infarct volume (by 3-fold), and neurobehavioral scores worsened. Since postischemic hyperthermia of 39°C failed to produce significant worsening, the threshold for this effect thus appears to be 40°C. This study established that the postischemic brain is abnormally sensitive to the effects of delayed temperature elevation, which is capable of greatly enlarging an otherwise modest histopathological lesion resulting from a short period of focal vascular occlusion.

We conducted a similar study in a model of global forebrain ischemia produced by bilateral carotid artery occlusions and hypotension for either 5 or 7 minutes in the rat. Twenty-four hours later, rats were placed into a warming chamber in which rectal temperature was elevated to 39°C to 40°C for 3 hours. Hippocampal histopathology was quantitated after an 8-day survival. In rats with the 7-minute ischemic insult, delayed hyperthermia resulted in a 2.5- to 3-fold increase in numbers of ischemic neurons throughout the vulnerable CA1 sector of hippocampus; a similar (but nonsignificant) trend was noted in rats with a 5-minute ischemic insult. These results support the highly deleterious effect of delayed temperature elevations in the context of a brief global ischemic insult, such as might occur in patients with cardiac arrest followed by resuscitation.

Delayed hyperthermia also worsens outcome after experimental traumatic injury. Twenty-four hours after undergoing moderate fluid-percussion brain injury, rats received a 3-hour period of either brain hyperthermia (39°C) or normothermia (36.5°C). Compared with normothermic rats, delayed hyperthermia resulted in a 2.6-fold increase in mortality rate, a
13-fold enlargement of cortical contusion volume, a 6-fold increase in the area of early hemorrhage and blood-brain barrier breakdown (to horseradish peroxidase), and increased numbers of abnormally swollen axons.

Brain Temperature Monitoring Is Feasible in Patients With Traumatic and Ischemic Injury; Cerebral Hyperthermia Is Common in the Injured Brain

Several groups have independently reported direct measurements of brain temperature in patients with head injury or other neurological conditions. In 15 neurosurgical patients (with brain tumors, head trauma, subarachnoid or intracerebral hemorrhage, or hydrocephalus), intracerebroventricular temperatures were monitored by means of a thermocouple introduced through an intracranial pressure-monitoring catheter. Intraventricular temperature exceeded rectal temperature in approximately 90% of measurements, with the maximal gradient being 2.3°C. In another, smaller series, the intracranial temperature of acutely head-injured patients exceeded body temperature by 0.5°C to 2.5°C, and a gradient of temperature was present within the brain, with ventricular temperatures 1°C to 1.5°C higher than the superficial cortex. Other groups have also documented that moderate to severe elevations of brain temperature and intracerebral temperature gradients may be present in head-injured patients. Hyperthermia has also been described after cardiopulmonary resuscitation. Cardiopulmonary bypass procedures (CPB) are associated with a substantial incidence of neuropsychological sequelae. In this context, it may be relevant that a recent report has called attention to the regular occurrence of cerebral hyperthermia in patients during the rewarming phase after hypothermic CPB: In 10 adults undergoing hypothermic (27°C) CPB for cardiac surgery, jugular venous and nasopharyngeal temperatures were monitored. Cerebral temperature (as reflected in jugular venous temperature) was found to rise very quickly during rewarming, and all 10 patients had peak cerebral venous temperatures of at least 39°C, for an average duration of 15 minutes. These authors rightly hypothesize that hyperthermia may accentuate an ischemia-related injury cascade, and they urge that rewarming procedures be modified to avoid cerebral hyperthermia.

The feasibility of brain temperature monitoring and modulation has recently been demonstrated in patients with severe ischemic infarction. In 15 patients with large MCA territory ischemic strokes, measurements were made of intracerebroventricular, epidural, or parenchymal brain temperature (measured by means of an implanted thermistor or thermocouple over a 3- to 7-day period, in conjunction with the monitoring of core-body (bladder) and jugular venous temperatures. In all patients of that series, brain temperature exceeded core-body temperature by 1.0°C to 2.1°C, and ventricular temperature exceeded epidural temperature by 0.6°C to 2.0°C. Systemic cooling by means of cooling blankets and alcohol washing was effective in achieving sustained brain hypothermia (33°C to 34°C). This important study established both the disparity between brain and body temperature in patients with acute neural injury, as well as a temperature gradient within regions of the brain (ventricles warmer than the cortical surface). These conclusions are consistent with the observations described above in patients with traumatic brain injury. Importantly, the success of external cooling in lowering brain temperature was convincingly established.

Elevated Temperature Is Associated With Poor Outcome in Patients With Acute Stroke

In a retrospective analysis of 110 patients admitted within 24 hours of stroke, fever and “subfebrility” (temperatures between 37.5°C and 38.0°C) were associated with more severe symptoms. A similar conclusion was reached in a second small prospective study and in two more recent, larger studies of this problem. In the first of the latter reports, 183 patients with acute ischemic or hemorrhagic stroke (excluding subarachnoid hemorrhage) were followed prospectively; fever occurred in 43% of this cohort during the first week of hospitalization (mean value of maximum temperature, 38.3°C). High fever (≥37.9°C) proved to be an independent factor predicting a worse prognosis (odds ratio, 3.4). Patients with high fever were far more likely to die within the first 10 days than those with lower temperatures.

In a second recent prospective study of this problem in 390 consecutive cases of acute stroke, Reith et al classified patients into three admission-temperature groups: hypothermic (≤36.5°C), normothermic (>36.5°C to 37.5°C), and hyperthermic (>37.5°C). By multiple regression analysis, admission body temperature proved to be highly correlated with initial stroke severity (P = .009), infarct size (P < .0001), mortality (P = .01), and poor outcome (P = .001). For a 1°C difference in body temperature, the relative risk of poor outcome (death or Scandinavian Stroke Scale score ≤30 on discharge) increased by 2.2-fold (95% confidence interval, 1.4 to 3.5). The relationship between body temperature and poor outcome was independent of stroke severity on admission.

A recent report studying the antecedents of brain infarction has called attention to an increased prevalence of “infection/inflammation” in patients with acute stroke during the 1 week preceding stroke onset compared with community control subjects or hospitalized neurological patient controls.

Moderate Brain Cooling Appears to be Neuroprotective in Clinical Head Injury

While no randomized clinical trials of therapeutic hypothermia in acute ischemic stroke have yet been announced, encouraging results have been recently reported in the setting of acute traumatic brain injury, and a National Institutes of Health–funded phase III clinical trial is presently in progress, based on improved neurological outcome with minimal toxicity observed in a phase II study. In the former report, 82 patients with severe closed head injury (Glasgow Coma Scale score 3 to 7) were randomized to normothermia or hypothermia (cooling to 33°C within 10 hours of injury, maintenance at 32°C to 33°C for 24 hours, then gradual rewarming). In the patient subgroup with somewhat less severe initial injuries (Glasgow Coma Scale score 5 to 7), hypothermia significantly improved outcome at 3 and 6 (but not at 12) months. Physiological observations of severely head-injured patients treated with hypothermia (32°C to 33°C) have described a normalization of
Conclusions and Recommendations

The considerable evidence reviewed above leaves little doubt that the acutely ischemic or traumatized brain is inordinately susceptible to the damaging influence of even relatively modest degrees of brain temperature elevation, such as commonly occurs in the setting of fever in patients with acute stroke and head injury. Even temperature elevations occurring many hours after an acute stroke are capable, in experimental studies, of engendering secondary injury. Fever occurs very commonly in patients with acute stroke and head injury. Direct measurements of brain temperature in such patients have substantiated that systemic fever is associated with even higher degrees of brain temperature elevation—indeed, to levels known from experimental studies to be capable of inflicting substantial secondary injury.

The message, therefore, is clear: Fever may aggravate the outcome of brain ischemia and should be combated assiduously in stroke patients. It is obvious that the therapeutic application of frank hypothermia in acute stroke patients must await the completion of controlled clinical investigations establishing the efficacy and safety of this therapy; one hopes that such trials will be expeditiously undertaken. In the meantime, however, we believe that the available evidence is sufficiently compelling to justify the recommendation, at this time, that clinicians institute measures, as part of their routine acute stroke care, to counteract incipient fever, even if ostensibly “minor” in degree, and even when it arises many hours after stroke onset, in order to avert secondary hyperthermic brain injury. We suggest that body temperature be maintained in a safe normothermic range (eg, 36.7°C to 37.0°C, [98.0°F to 98.6°F]) for at least the first several days after acute stroke or head injury. Similarly, steps should be taken in CPB patients to avoid hyperthermia during the rewarming phase.51

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References

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