Combination Drug Therapy and Mild Hypothermia
A Promising Treatment Strategy for Reversible, Focal Cerebral Ischemia

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Background and Purpose—Hypothermia has been suggested to be the most potent therapeutic approach to reduce experimental ischemic brain injury identified to date, and mild hypothermia is increasingly used for neuroprotection during neurovascular surgery. We have recently demonstrated that combined administration of tirilazad mesylate and magnesium provides for an overall enhanced neuroprotective effect. The present study was designed to determine whether the efficacy of mild hypothermia (33°C) can be increased by combination pharmacotherapy with tirilazad and magnesium (MgCl₂).

Methods—Forty Sprague-Dawley rats were subjected to transient, middle cerebral artery occlusion and were randomly assigned to 1 of 4 treatment arms (n=10 each): (1) normothermia + vehicle, (2) normothermia + tirilazad + MgCl₂, (3) hypothermia + vehicle, or (4) hypothermia + tirilazad + MgCl₂. Cortical blood flow was monitored by a bilateral laser-Doppler flowmeter, and the electroencephalogram was continuously recorded. Functional deficits were quantified by daily neurological examinations. Infarct volume was assessed after 7 days.

Results—Tirilazad + MgCl₂, hypothermia, and hypothermia + tirilazad + MgCl₂ reduced total infarct volume by 56%, 63%, and 77%, respectively, relative to controls. In animals treated with both hypothermia and combination pharmacotherapy, cortical infarction was almost completely abolished (≈99%), and infarct volume in the basal ganglia was significantly reduced by 55%. In addition, this treatment provided for the best electrophysiological recovery and functional outcome.

Conclusions—The neuroprotective efficacy of hypothermia can be increased by pharmacological antagonism of excitatory amino acids and free radicals by using clinically available drugs. This treatment strategy could be of great benefit when applied during temporary artery occlusion in cerebrovascular surgery. (Stroke. 1999;30:1891-1899.)

Key Words: cerebral ischemia • focal • drug therapy • hypothermia • laser-Doppler flowmeter

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Cell death after cerebral ischemia is mediated by a massive release of excitatory amino acids, generation of free radicals, and—a crucial step—calcium influx into cells.¹ This knowledge has led to research into the pharmacological agents to antagonize excitatory amino acids, inhibit the production of free radicals, and prevent calcium influx into cells. The pathophysiological mechanisms leading to neuronal death are so complex that, apart from thrombolytic therapy, 1 agent alone has never been shown to be sufficient to significantly reduce cerebral infarction in humans. This has led to a number of recent articles and editorials regarding the need for clinical trials involving combinations of pharmacological agents.²–⁴ Combinations of agents may act synergistically, but it is also possible for undesirable interactions to occur. Therefore, clinical trials of combinations of drugs should be preceded by animal experiments that are capable of identifying interactions.⁵⁶ We have recently shown that combined administration of tirilazad mesylate and magnesium provides for an overall enhanced neuroprotective effect

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in rats subjected to transient, focal cerebral ischemia.⁷ Tirilazad is a free-radical scavenger and lipid peroxidation inhibitor.⁸ Magnesium is a naturally occurring calcium antagonist and a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors.⁹ Both drugs have proven their beneficial effects in numerous animal studies of focal and global cerebral ischemia, subarachnoid hemorrhage (SAH), traumatic brain injury, and spinal cord ischemia.¹₀,¹¹ Furthermore, these drugs offer the advantage that they are clinically available without severe side effects at the neuroprotective dosage.¹¹–¹³ Tirilazad (Freedox) is licensed for clinical use in Australia and in many European and other countries. Magnesium is an over-the-counter drug with an established safety profile. It is conceivable that this drug combination could be improved or supplemented by other more potent agents, especially compounds that affect glutamate receptors. However, most glutamate antagonists have severe psychomimetic
and cardiorespiratory-depressant side effects and are not suitable for awake stroke patients or for those undergoing elective cerebrovascular surgery.14

Barone et al15 stated that cerebral hypothermia is the most potent therapeutic approach to reduce experimental ischemic brain injury identified to date. Multiple mechanisms for hypothermia-induced neuroprotection have been identified: (1) reduced metabolic rate and energy depletion, (2) decreased excitatory transmitter release or enhanced postsynaptic reuptake of glutamate, (3) decreased generation of free radicals, (4) improved ion homeostasis, and (5) reduced vascular permeability, blood-brain barrier disruption, and edema.16–18 In view of these multiple protective mechanism, it seems questionable whether the efficacy of hypothermia can be enhanced by pharmacological agents.

Because mild hypothermia is increasingly used for neuroprotection during neurovascular surgery,19 we conducted the present study to investigate whether the neuroprotective efficacy of hypothermia (33°C) could be improved by combined administration of tirilazad and magnesium.

Materials and Methods
A total of 42 male, Sprague-Dawley rats (270 to 300 g body weight) were used for this study. Animals were purchased from Charles River Laboratory (Sulzfeld, Germany) and were cared for before and at all stages of the experiment in compliance with applicable institutional guidelines and regulations of the government of Bavaria.

Animal Preparation and Monitoring
Rats were fasted overnight before surgery with free access to water. For the operative procedures, the animals received atropine (0.5 mg/kg SC), and anesthesia was induced with 4% halothane. The animals were orally intubated and mechanically ventilated with 0.8% oxygen, 0.9% saline and 5 received the same volume of 0.02 mol/L citric acid. Each dose of tirilazad mesylate (Freedox, Upjohn) was 3 mg/kg and each dose of MgCl2 (Sigma-Aldrich Chemie) was 1 mmol/kg. Isovolumetric doses of vehicle or drugs were administered intravenously over 15 minutes. Each animal received 2 doses of vehicle or drugs, with the first dose being administered before ischemia and the second dose at reperfusion. In the hypothermic groups, whole-body hypothermia was induced with the use of ice packs until a temperature of 33°C in the rectal and temporalis muscle areas was reached and maintained. Before induction of ischemia, an interval of 20 minutes was allowed for physiological stabilization. Rewarming (1°C/10 min) was started 30 minutes after reperfusion. A study flow diagram is presented in Figure 1.

Figure 1. Study flow diagram of the acute phase depicting the course of experimental ischemia and the timing of hypothermia, drug administration, and monitoring. EEG indicates electroencephalography.

Drug Administration and Treatment Arms
Rats were randomly assigned to 1 of 4 treatment arms (n = 10 each): (1) vehicle-treated, normothermic controls at 37°C (rectal and temporalis muscle temperatures); (2) tirilazad and MgCl2 at 37°C; (3) vehicle-treated, hypothermic controls at 33°C; or (4) tirilazad and MgCl2 at 33°C. In the vehicle-treated groups, 5 animals received 0.9% saline and 5 received the same volume of 0.02 mol/L citric acid. Each dose of tirilazad mesylate (Freedox, Upjohn) was 3 mg/kg and each dose of MgCl2 (Sigma-Aldrich Chemie) was 1 mmol/kg. Isovolumetric doses of vehicle or drugs were administered intravenously over 15 minutes. Each animal received 2 doses of vehicle or drugs, with the first dose being administered before ischemia and the second dose at reperfusion. In the hypothermic groups, whole-body hypothermia was induced with the use of ice packs until a temperature of 33°C in the rectal and temporalis muscle areas was reached and maintained. Before induction of ischemia, an interval of 20 minutes was allowed for physiological stabilization. Rewarming (1°C/10 min) was started 30 minutes after reperfusion. A study flow diagram is presented in Figure 1.

Quantification of Ischemic Damage
Neurological deficits and infarct volume were assessed by a colleague who was “blinded” to the animals’ treatments. Postoperatively, each animal’s neurological function was evaluated daily on a 6-point grading scale: 5, no apparent deficit; 4, contralateral forelimb flexion; 3, lowered resistance to lateral push without circling; 2, circling if pulled by tail; 1, spontaneous circling; and 0, no
spontaneous activity. In addition, each animal’s body weight was determined daily.

Seven days after transient cerebral ischemia, each rat was again anesthetized and perfused transcardially with isotonic heparinized saline, followed by 2% paraformaldehyde for fixation of tissues. The brain was removed, embedded in paraffin, and cut into 4-μm-thick coronal sections at 400-μm intervals. The brain slices were stained with hematoxylin and eosin. Twenty-four slices from each brain containing the entire infarct were used, and the infarct area on each slice was planimetrically determined (OPTIMAS 5.1, BioScan Inc).

The total infarct volume (I_t) expressed in mm³ was calculated to be the sum of the area of infarct on each slice (I_s), multiplied by the distance (400 μm) between successive slices (I_s=0.4[I_1+I_2+…+I_24] mm³). The volumes of infarcts in the cortex and basal ganglia were determined by measuring the area of infarct in sections obtained 2.0, 3.6, 5.2, 6.8, and 8.4 mm from the frontal pole.

Statistical Analysis
Statistical analyses were performed with the use of SigmaStat 2.0 Statistical Software (Jandel Scientific). Physiological data for each time point and infarct volumes were analyzed with 1-way ANOVA, laser-Doppler and EEG data were analyzed with 2-way ANOVA for repeated measures, and neurological function scores were analyzed with Kruskal-Wallis ANOVA on ranks for each of the 7 postoperative days. When multiple comparisons were indicated, Dunnett’s test or the Student-Newman-Keuls test for neurological function scores was applied. Differences were considered significant at the P<0.05 level. Results are presented as mean±SD.

Results

Physiological Variables
There were no statistically significant differences in mean physiological values, cortical CBF, neurological deficits, or infarct volume between normothermic animals that received normal saline or citric acid and no significant differences between hypothermic animals that received drug vehicles. Therefore, data from all normothermic and all hypothermic rats receiving vehicle were included in a normothermic or hypothermic control group, respectively.

Blood pressure dropped by 10 to 15 mm Hg during drug infusion of MgCl₂, but this effect did not significantly influence the mean values during and after ischemia. Furthermore, blood glucose levels increased after drug administration in rats that received MgCl₂ and in hypothermic animals, while blood glucose levels decreased in vehicle-treated normothermic animals. This difference was significant in drug-treated hypothermic animals compared with vehicle-treated normothermic controls. There were no statistically significant differences among groups in any of the other mean values, but hypothermic animals had a trend toward a lower PaCO₂, a higher PaO₂, and higher pH values.

LDF Measurements
In normothermic animals, MCA occlusion resulted in an immediate reduction of LCBF to ~20% of baseline in the territory supplied by the ipsilateral artery, while contralateral blood flow remained unchanged throughout the experiment. After reperfusion, a short period of postischemic hyperemia was followed by a decrease in ipsilateral LCBF to ~70% of baseline. Delayed hypoperfusion persisted until the end of the 2-hour postreperfusion observation period. There was no significant difference in cortical CBF between normothermic vehicle-treated animals and normothermic animals that received tirilazad and magnesium (Figure 2).

In the hypothermic groups, ipsilateral and contralateral LCBF decreased to ~80% of baseline during cooling. MCA occlusion resulted in an immediate reduction of ipsilateral LCBF to ~20% of baseline. Reperfusion was followed by a prolonged period of postischemic hyperemia, compared with normothermic animals, before ipsilateral CBF gradually decreased to ~70% of baseline. Delayed hypoperfusion persisted until the end of the 2-hour postreperfusion observation period. Contralateral LCBF recovered to baseline values (Figure 2) during rewarming.

Electroencephalography
In normothermic animals, the ipsilateral EEG amplitude decreased immediately after MCA occlusion to ~40% of baseline. EEG changes appeared, with a delay of ~4 seconds, after the onset of LCBF reduction as indicated by the LDF. After reperfusion, the amplitude slowly recovered to 60% to 70% of baseline. There were no significant differences between normothermic vehicle-treated animals and normothermic animals that received tirilazad and magnesium (Figure 3).

In the hypothermic groups, the ipsilateral and contralateral EEG amplitude significantly decreased to ~80% of baseline during cooling. Immediately after MCA occlusion, the ipsilateral EEG amplitude decreased to ~40% of baseline. After reperfusion and rewarming, the contralateral EEG amplitude recovered to baseline values. In animals subjected to hypothermia alone, the ipsilateral EEG amplitude slowly recovered to ~80% of baseline, which was not quite statistically significant. In hypothermic animals that received tirilazad and magnesium, the ipsilateral EEG amplitude recovered faster to 80% of baseline and more. This increase was significant when compared with normothermic animals (Figure 3).

Functional Outcome and Weight Gain
Except for the 2 animals that experienced SAH under anesthesia, there was no additional mortality. Normothermic animals that received tirilazad and MgCl₂ had significantly (P<0.05) less neurological deficits from postoperative days 4 to 7 compared with normothermic vehicle-treated controls. Hypothermic animals that received the drug vehicle had significantly fewer neurological deficits from postoperative days 4 to 7. Hypothermic animals that received tirilazad and MgCl₂ had significantly fewer neurological deficits from postoperative days 1 to 7 compared with normothermic controls and fewer deficits from postoperative days 1 to 3 compared with all other groups. None of the animals in this group showed any residual functional deficit at the end of the observation period (Figure 4).

Hypothermic animals that received tirilazad and MgCl₂ also exhibited the best weight gain from postoperative days 1 to 7, although this difference was not significant owing to interanimal variations.

Infarct Volume
There was no difference in brain size between the groups and between the ipsilateral and contralateral hemispheric volumes.
of each individual animal on postoperative day 7. Therefore, indirect measurements of infarct volumes to correct for brain size or edema were not necessary.

The total infarct volume was $70.2 \pm 6.17.4 \text{ mm}^3$ (mean $\pm$ SD) in normothermic vehicle-treated controls, $30.8 \pm 6.9.6 \text{ mm}^3$ in normothermic animals that received tirilazad and MgCl$_2$, $25.9 \pm 6.12.3 \text{ mm}^3$ in hypothermic animals that received the drug vehicle, and $15.8 \pm 6.8.2 \text{ mm}^3$ in hypothermic animals that received tirilazad and MgCl$_2$. Compared with those in normothermic vehicle-treated controls, total infarct volumes were significantly ($P<0.05$) smaller in normothermic animals treated with tirilazad and MgCl$_2$ ($256\%$), hypothermic vehicle-treated animals ($263\%$), and hypothermic animals that received tirilazad and MgCl$_2$ ($277\%$) (Figure 5).

When infarct volume was determined separately for cortical brain tissue and the basal ganglia, all treatment strategies were significantly ($P<0.05$) effective in limiting cortical infarct volume. The average cortical infarct volume was $36.2 \pm 612.2 \text{ mm}^3$ in normothermic vehicle-treated controls (mean $\pm$ SD), $10.8 \pm 65.8 \text{ mm}^3$ in normothermic animals treated with tirilazad and MgCl$_2$ ($70\%$), $1.7 \pm 62.2 \text{ mm}^3$ in hypothermic animals that received drug vehicle ($95\%$), and $0.4 \pm 61.3 \text{ mm}^3$ in hypothermic animals that received tirilazad and MgCl$_2$ ($99\%$) (Figure 6).

Similarly, tirilazad and MgCl$_2$ and the combination therapy of tirilazad and MgCl$_2$ plus hypothermia significantly ($P<0.05$) reduced infarct volume in the basal ganglia. Compared with normothermic vehicle-treated controls ($32.9 \pm 65.3 \text{ mm}^3$, mean $\pm$ SD), the infarct volume in the basal ganglia in normothermic rats treated with tirilazad and MgCl$_2$ was $19.4 \pm 65.4 \text{ mm}^3$ ($41\%$) and in hypothermic rats treated with tirilazad and MgCl$_2$, it was $14.9 \pm 67.6 \text{ mm}^3$ ($55\%$). The reduction in basal ganglia infarct volume in hypothermic rats that received drug vehicle ($24.2 \pm 610.4 \text{ mm}^3$; $26\%$) was not significant (Figure 6).

**Discussion**

The present study demonstrates that combination drug therapy with tirilazad and MgCl$_2$ accompanied by mild hypothermia provides significant cerebroprotection to rats subjected to
transient MCA occlusion. Even the most potent therapeutic approach, mild hypothermia, can be improved by additional pharmacotherapy. Animals treated with the drug combination and hypothermia had the best electrophysiological recovery, the fewest postoperative neurological deficits, the best weight gain, and the smallest infarct volume.

Cerebral Blood Flow

In accordance with the results of other studies, neither tirilazad nor MgCl₂ seems to exert its beneficial effects by improving CBF.6,7,22,23 In contrast, Chi et al.24 found that magnesium sulfate increased CBF after permanent MCA occlusion in rats. Magnesium is involved in the regulation of smooth muscle tone and may induce cerebral vasodilation.9 One or more of several factors might explain our failure to note a significant effect on LCBF with administration of MgCl₂. First, we measured CBF in the somatosensory cortex near the core of the infarct, and it is possible that improvements in CBF might have occurred in more peripheral areas. Second, it is conceivable that a different magnesium salt or a higher dosage of MgCl₂ than the one we used is required to influence CBF,25 but high dosages of magnesium cause arterial hypotension and hyperglycemia.

In the present study, mild hypothermia (33°C) decreased CBF and the EEG amplitude to \( \approx 80\% \) of baseline. The average decrease in LCBF per degree of temperature was 5% of control flow. This effect was first described by Rosomoff and Holaday26 and later confirmed in experiments with dogs, monkeys, cats, rabbits, and rats.27-29 There was no difference in LCBF during ischemia and delayed hypoperfusion between normothermic and hypothermic animals, but hypothermia resulted in a prolonged hyperemic phase. This effect was even more pronounced in animals that additionally received tirilazad and magnesium, possibly as a result of alterations in ion homeostasis including calcium, potassium, and magnesium fluxes.30 Increased serum magnesium levels were found in animals subjected to hypothermia.31 It is conceivable that a greater and more prolonged elevation in magnesium levels may act to ameliorate ischemic damage by virtue of magne-

Figure 3. Changes in the electroencephalographic (EEG) amplitude in the ipsilateral (○) and contralateral (●) hemisphere from before induction of hypothermia and ischemia until 2 hours after reperfusion. Values shown are averages of measurements made during 1-minute periods every 10 minutes and expressed as percent of baseline (mean±SD) for \( n=10 \) in each group. The course of temporalis muscle temperature (Temp.) is indicated. Middle cerebral artery occlusion significantly reduced ipsilateral EEG amplitude to 40% of baseline in all groups (\( P<0.05 \) vs baseline; not indicated). *\( P<0.05 \) vs ipsilateral amplitude in normothermic vehicle-treated controls for each time point; §\( P<0.05 \) vs contralateral amplitude in normothermic vehicle-treated controls for each time point, by 2-way ANOVA for repeated measures followed by Dunnett’s test.
sium’s ability to block the NMDA channel noncompetitively and to cause vasodilatation.9,32

In accordance with our results, Baldwin et al33 and Oku et al34 found that transient hypothermia is associated with a more pronounced postischemic hyperemia but does not alter delayed hypoperfusion after global ischemia in dogs. Other authors failed to demonstrate any influence of brain temperature on CBF in rats subjected to global35 or focal36 ischemia. Interestingly, Kuluz et al37 observed in rats that during selective brain cooling, LCBF increased to 215% of baseline at a cortical brain temperature of 30.9°C and a rectal temperature of 37.5°C. They concluded that this probably occurs secondary to a decrease in cerebral vascular resistance, independent of the increased resistance of other vascular beds. It seems that the cerebrovascular response varies, depending on the depth of hypothermia, the method of cooling, the model of ischemia, and animal species. These differences may be the key factors in determining the local hemodynamic consequences of hypothermia.18

Morphological and Functional Outcome
Combination drug therapy with tirilazad and MgCl₂ reduced total infarct volume by 56% compared with drug vehicle. This finding is consistent with the results of an earlier study wherein we compared the neuroprotective efficacy of tirilazad and MgCl₂ alone and in combination.7 The fact that tirilazad was more potent than MgCl₂ underlines the detrimental role that reactive oxygen species play in brain damage after transient ischemia. However, the combination of both drugs still resulted in an overall enhanced neuroprotective effect with respect to infarct volume and functional outcome. In the present study, hypothermia was the most potent, single therapeutic approach, but the morphological protection occurred mainly in the cortex and was not significant in the basal ganglia. Also, the effect of the combined pharmacotherapy was more prominent in the cortex than in the basal ganglia, which is consistent with observations that antioxidants and antie excitotoxic drugs have maximal effects on the
ischemic penumbra, which is believed to be potentially salvageable. Combined treatment with tirilazad, magnesium, and hypothermia almost abolished cortical infarction and reduced the infarct volume in the basal ganglia significantly by 55%. No animal in this group had any residual neurological deficits on postoperative day 7. In addition, this was the only group with a statistically significant improved electrophysiological recovery. The hyperglycemic and hypotensive effect of MgCl₂ present in this study had already been observed by several investigators. Magnesium-induced hyperglycemia was increased by hypothermia, probably by further suppression of insulin release from pancreatic islet cells and increased glycogenolysis. No evidence of hyperglycemia has been found in human studies with magnesium, but hyperglycemia and arterial hypotension might have reduced the efficacy of this treatment strategy in our study.

**Combination of Hypothermia and Pharmacotherapy**

Most studies that evaluated the effects of hypothermia combined with pharmacological neuroprotection were performed with NMDA antagonists in models of global ischemia. MK-801 combined with moderate hypothermia (30°C) resulted in an overall enhanced neuroprotection in rats after forebrain ischemia. The combination of postsischemic hypertension (30°C) and dextromethorphan, a noncompetitive NMDA antagonist and calcium channel blocker, was synergistically protective in a rat model of bilateral carotid artery occlusion plus hypotension. The neuroprotective activity of memantine, another noncompetitive NMDA antagonist, was increased by hypothermia in a rat model of forebrain ischemia. The efficacy of CGS-19755, a competitive NMDA antagonist, was significantly enhanced when combined with pharmacological neuroprotection were performed in transient focal ischemia, mannitol provided no further significant protection to hypothermia in rats, and triple therapy with hypertension, mannitol, and hypothermia in rabbits resulted in a smaller infarct volume than each single therapy alone, but the difference was not significant.

In summary, it is not possible from our study to point to a single mechanism that underlies the marked neuroprotection provided by combination pharmacotherapy and hypothermia. Because tirilazad and magnesium increased the neuroprotective efficacy of hypothermia despite its multiple protective mechanisms, it is possible that the main mechanisms respon-

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### References


It is now being tested in a clinical trial for acute stroke. The safety of MgCl₂ is well established, since it is presumed related to its effects in reducing glutamate-related neurotoxicity. The time required to induce hypothermia in patients is much smaller than in rats, and therefore, surface cooling is much slower. To substantially increase the rate of hypothermia induction in humans, it may well increase the “window of opportunity” for some other form of therapy.

Tirilazad is a drug that was tested extensively in animal stroke models and in clinical trials. It has free radical-scavenging properties that were thought to be its mechanism of action. Although the preclinical studies were encouraging, the trials for acute stroke therapy were disappointing, and the drug was shown not to be a useful form of therapy for ischemic stroke. It is possible that for patients, the drug has beneficial effects that are too small to be detected in the types of clinical trials that were conducted.

Magnesium has also been shown to be effective in reducing neurological damage in several animal models. This is presumably related to its effects in reducing glutamate-related neurotoxicity. The safety of MgCl₂ is well established, since it has been used for many years as a treatment for eclampsia. It is now being tested in a clinical trial for acute stroke.

The article by Schmid-Elsaesser and colleagues demonstrates that in a standard rat model of middle cerebral artery occlusion, the combination of drugs and hypothermia reduced damage better than did the individual agents. The authors suggest that this strategy may be useful as a method of preventing cerebral injury during cerebrovascular surgery. They also propose that this treatment regimen may be useful for acute stroke management.

A problem for use of this technique for acute stroke therapy is that the time required to induce hypothermia in patients is likely to be considerably longer than for rats. Humans have a much smaller surface-to-volume ratio than do rats, and therefore, surface cooling is much slower. To substantially increase the rate of hypothermia induction in humans, it will almost certainly be necessary to use some sort of invasive procedure, such as a heat exchanger to cool the circulation. Furthermore, people find even small decrements of core body temperature to be quite uncomfortable, and thus, they will have to be sedated in some fashion.

It has become a common expectation that combination therapy is likely to be better than monotherapy for treatment of strokes, but it is far from certain that many combinations will be effective. For example, hypothermia may reduce the efficacy of some neuroprotective drugs if the beneficial effects of therapy are substantially diminished by a decreased metabolic rate. Therefore, careful testing of combinations will be essential.

**Editorial Comment**

It is well established that hypothermia can reduce stroke-induced neurological damage in animal models. Whether hypothermia produces a permanent reduction in the ultimate injury is not yet clear. However, even if hypothermia only delays the onset of permanent damage, it may well increase the “window of opportunity” for some other form of therapy.

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