Therapeutic Hypothermia for Brain Ischemia  
Where Have We Come and Where Do We Go?  

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Abstract—Mild hypothermia is an established neuroprotectant in the laboratory, showing remarkable and consistent effects across multiple laboratories and models of brain injury. At the clinical level, mild hypothermia has shown benefits in patients who have experienced cardiac arrest and in some pediatric populations experiencing hypoxic brain insults. Its role, however, in stroke therapy has yet to be established. Translating preclinical data to the clinical arena presents unique challenges with regard to cooling in patients who are generally awake and may require additional therapies, such as reperfusion. We review the state of therapeutic hypothermia in ischemic and hemorrhagic stroke and provide an outlook for its role in stroke therapy. (Stroke. 2010;41[suppl 1]:S72-S74.)

Key Words: stroke ■ hypothermia ■ neuroprotection

Hypothermia is a robust neuroprotectant and has consistently shown benefit against a variety of brain injuries at the experimental level. It has recently been shown to improve neurological outcome in comatose survivors of cardiac arrest and neonatal hypoxia ischemia and is being increasingly used by many centers for these conditions. However, the role of therapeutic hypothermia for stroke is not yet clear. Stroke itself presents unique challenges. For instance, unlike patients cooled following cardiac arrest, most stroke patients are awake and not endotracheally intubated. Thus, measures are needed to prevent shivering and other discomfort experienced by deliberate cooling. Return of circulation following cardiac arrest is generally associated with return of cerebral perfusion. In the case of stroke, the affected vessel often remains occluded for days or indefinitely in the absence of reperfusion therapies.

Optimal Conditions for Hypothermic Protection

Reviews of the experimental literature indicate that factors that affect the efficacy of hypothermia include the duration of cooling, the time when cooling begins, and reperfusion of the occluded vessel.1,2 Thus, longer periods of hypothermia instituted soon after the onset of ischemia in patients treated with recanalization therapies would be expected to have the best chance for good outcomes.

The depth of cooling seems to be a less critical factor, provided brain temperature is lowered below 35°C. Laboratory research has suggested that small decreases in temperature are as protective as larger decreases. In animal models of stroke, the extent of neuroprotection is similar whether temperature is reduced to 34°C or 25°C. One potential explanation for this might be the increased occurrence of adverse side effects such as nonfatal cardiac arrhythmias with lower temperature.3

The optimal duration of hypothermia after cerebral ischemic injury is unclear, but longer durations, especially in studies of global cerebral ischemia, seem to be associated with more consistent and long-lasting protection.4 Brief durations of at least 2 hours of hypothermia have led to sustained protection in animals with reperfusion after transient ischemia. However, longer durations may be necessary, especially when the initiation of cooling is delayed. Intra- but not postischemic cooling led to lasting protection in a global cerebral ischemia model. In experimental stroke, neuroprotection has been documented when hypothermia was delayed by a few hours, provided cooling was maintained for more than 24 hours.

The time to cooling is another critical factor, because it is well known that earlier treatment increases the chances of good outcome. From laboratory studies, it is clear that cooling is more consistently neuroprotective when applied soon after or even before the onset of ischemia. Therefore, hypothermia should be initiated as soon as possible to achieve its optimal beneficial effect. Because many patients do not present to the emergency room immediately after symptom onset, a critical question is how long after stroke can cooling be applied and still be effective. Rodent global cerebral ischemia models have been extensively studied in terms of delaying the initiation of cooling.4,5 Hypothermia commencing 30 minutes into the start of reperfusion was reported to be ineffective for protection of the hippocampal neurons, but in

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a gerbil forebrain ischemia model, hypothermia begun even 1 hour after the start of reperfusion was reported to be effective if cooling was maintained for 6 hours. Yet, postischemic hypothermia for a few hours merely delayed the onset of irreversible neuronal injury, unless combined with a second neuroprotectant. More recent rodent experiments have shown that a prolonged cooling (12 to 48 hours) can provide sustained behavioral and histological neuroprotection as far as 6 months postischemia onset. Thus, neuroprotection is influenced by the length of the delay and the duration of hypothermia. For focal cerebral ischemia, delays of 2 to 3 hours have been shown to protect, provided cooling is maintained for at least 2 to 3 hours. The need for prolonged cooling in focal cerebral ischemia is less clear compared with the global ischemia models in which the temporal therapeutic window can be expanded from a few minutes to as long as 6 hours. One study, in which rodents were subjected to focal cerebral ischemia for 90 minutes and cooling began 2.5 hours after the onset of ischemia for 48 hours, demonstrated long-term protection. Thus, it is not entirely clear whether longer cooling times will necessarily allow for longer cooling delays.

Recanalization and return of cerebral perfusion is another factor that may increase the likelihood of a beneficial effect. Laboratory studies have shown consistent protection by hypothermia against temporary ischemia, but data from permanent ischemia models are less consistent. This observation has obvious implications at the clinical level, where early recanalization may require pharmacological or mechanical approaches.

**Hypothermia and Thrombolysis**

Because recanalization often increases the chances of good outcome after stroke, hypothermia might be combined with thrombolysis or mechanical thrombectomy. Currently, the only proven therapy after ischemic stroke is recombinant tissue plasminogen activator (rt-PA). The safety of combining hypothermia with rt-PA should be considered because fatal hemorrhage is the most feared complication of fibrinolytic use. The fibrinolytic systems, being a cascade of temperature-dependent enzymes, are most certainly affected by hypothermia. In fact, in vitro clot lysis is temperature-dependent, with spontaneous clot lysis increasing by 0.5% for each 1°C decrease in temperature. In the presence of rt-PA, a 1°C drop in temperature actually decreased clot lysis by a similar amount. In another study of rabbits cooled to 32°C, endogenous anticoagulant activity was found to decrease, whereas fibrinolytic protein activity (plasminogen and α(2)-antiplasmin) increased.

Preliminary work from our laboratory suggests that the combination should at least be safe. When mice subjected to 2 hours of middle cerebral artery occlusion were given rt-PA 3 hours after ischemia onset, increased cerebral hemorrhage was observed among normothermic animals, but hemorrhage scores among hypothermic rt-PA–treated mice were similar to untreated normothermic ischemic mice (X.N. Tang, et al, unpublished data, 2009).

In models of embolic stroke, it is not clear whether hypothermia and rt-PA are synergistic. Two different studies failed to support synergy between the 2 treatment modalities. In either study, rt-PA was effective in improving recanalization, and cooling reduced infarct size, but the combination of the 2 did not clearly show synergy. However, other applications of combination therapy, such as using hypothermia to expand the temporal therapeutic window of rt-PA, should certainly be explored.

**Hypothermia in Hemorrhagic Stroke**

Although several studies have revealed the beneficial effects of hypothermia in animal models of ischemic stroke, its effect in hemorrhagic stroke has been less studied, and results have been less consistent. In a model of intracerebral hemorrhage (ICH) where either autologous blood or collagenase was injected into the brain, hypothermia (durations spanning 12 hour to 6 days) reduced blood brain barrier disruption and edema but failed to significantly affect histological and behavioral outcomes. In contrast to ischemic brain insults, outcomes were actually better if cooling began 12 hours after the onset of injury than earlier. In fact, early cooling seemed to exacerbate hemorrhage. However, other studies suggest that mild hypothermia for 2 hours improves outcome in animal models of subarachnoid hemorrhage. The reasons for these discrepancies are unclear, but it is possible that any beneficial effect of hypothermia in subarachnoid hemorrhage might actually be directed toward the associated ischemia, rather than the hemorrhage itself.

**Hypothermia in Stroke Patients**

Observational studies have indicated that temperature at presentation in acute stroke patients is related to outcome, with higher temperatures associated with worsened outcome. However, a recent study reported rt-PA response in relation to body temperature at stroke presentation. Investigators studied 111 acute stroke patients given rt-PA and found that patients presenting with a higher body temperature were more likely to have a favorable outcome compared with patients presenting with lower body temperatures. The authors suggested that this surprising finding might be explained by the benefit of improved clot lysis by rt-PA at higher temperatures compared with the potential neuroprotective benefit of lower body temperature.

A few pilot studies in ischemic stroke patients have been published indicating feasibility, although efficacy remains to be established (reviewed). The ICTuS-L study, a randomized multicenter trial of hypothermia and rt-PA in acute stroke patients, is the most recent study of catheter-based cooling. Here, 58 patients were randomized, 28 to hypothermia at 33°C for 24 hours and 30 to normothermia. In the hypothermia group, 24 were also given rt-PA. Cooling was well tolerated in this study and did not affect the occurrence or severity of brain hemorrhage in patients given rt-PA. There were no differences in 90-day outcomes, although the study was not powered to determine efficacy. Pneumonia was the main adverse event that seemed to occur more frequently in cooled patients.

Combination strategy with hypothermia, caffeine, and ethanol or caffeinol has shown salutary effects of the combination of caffeine and ethanol in rodent stroke models when...
either therapy alone was ineffective. A pilot clinical study of combination therapy with hypothermia, rt-PA, and caffeine showed that in the 20 patients studied, this approach was feasible. Like the ICTuS-L study, there seemed to be an increased incidence of pneumonia. Thus, therapeutic hypothermia is feasible in stroke patients, but it is not totally without risk.

Future Directions
Although there is a clear need for clinical trials of therapeutic hypothermia to establish efficacy in stroke, pilot studies have shown the need for improved cooling approaches. Such approaches might be less invasive, such as exploring pharmacological means of cooling. A few preclinical studies have shown that neurotensin and its analogs, 3-iodothyronamine, and hydrogen sulfide can all decrease body temperature to the depth and for durations previously shown to be neuroprotective in animal models (reviewed). Brain-selective cooling might also be further explored as a means of reducing adverse effects such as shivering and infection. Combinatorial approaches could also be studied as means for further protecting the brain or as adjuncts to cooling when early or prolonged cooling may not be feasible.

Conclusions
Hypothermia is a robust protectant against brain ischemia, but its effect in hemorrhagic stroke is less clear. Early clinical studies have shown feasibility, but the potential for neurological improvement needs to be weighed against the higher occurrence of pneumonia and the potential for reduced thrombolytic efficacy. Combination of hypothermia with other neuroprotectants and modern reperfusion therapies should be explored. Future studies may include newer, less invasive cooling methods that include pharmacological cooling strategies.

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Disclosures
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References
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