Induced Hypothermia for Acute Stroke

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Abstract—Induced hypothermia is one of the most promising neuroprotective therapies. Technological limitations and homeostatic mechanisms that maintain core body temperature have impeded the clinical use of hypothermia. Recent advances in intravascular cooling catheters and successful trials of hypothermia for cardiac arrest and neonatal asphyxia renewed interest in hypothermia for stroke, resulting in early phase clinical trials and plans for further development. This review elaborates on the clinical implications of hypothermia research in stroke and technical and logistical issues associated with the application of hypothermia. (Stroke. 2007;38[part 2]:794-799.)

Key Words: acute care ■ hypothermia ■ neuroprotection

The Stroke Therapy Academic Industry Roundtable (STAIR) criteria have been proposed to assess different neuroprotective strategies for viability and promise in clinical application.1 Hypothermia is one of the best studied and most highly effective modes of neuroprotection.2

Hypothermia has neuroprotective effects in animal models of brain3 and myocardial4 ischemia. In recent reviews of preclinical literature, hypothermia was one of the most promising neuroprotective approaches studied.2 In adult patients, hypothermia improves neurological outcome in survivors of cardiac arrest,5,6 and its use after cardiac arrest is recommended by the International Liaison Committee on Resuscitation (ILCOR).7 The use of hypothermia in patients with ischemic heart injury is currently under evaluation.8 In infants with hypoxic-ischemic encephalopathy, hypothermia of 33.5°C for 72 hours was safe, reduced fatality, and improved neurodevelopmental outcome.9

The Cooling for Acute Ischemic Brain Damage (COOL-AID) study group completed 2 clinical trials of hypothermia in acute ischemic stroke. The first study used surface cooling,10 and the second used endovascular cooling.11 Both trials demonstrated feasibility but were not powered to answer questions regarding safety and efficacy.

The Intravascular Cooling in the Treatment of Stroke–Longer tPA Window (ICTuS-L)12 study group completed 2 trials of hypothermia in acute ischemic stroke. The first study used surface cooling,10 and the second used endovascular cooling.11 Both trials demonstrated feasibility but were not powered to answer questions regarding safety and efficacy.

The precise mode of neuroprotective action in hypothermia is not known. Krieger and Yenari25 (2004) reviewed the variety of animal models of hypothermia in stroke. Most likely, hypothermia exhibits multiple and synergistic effects on brain metabolism. Hypothermia decreases the cerebral metabolic rates of glucose and oxygen and slows ATP...
breakdown.\textsuperscript{26} In the range of 22°C to 37°C, brain oxygen consumption is reduced by \( \approx 5\% \) for every degree fall in body temperature.\textsuperscript{27} Hypothermia reduces glutamate release,\textsuperscript{28} inflammation, and free radical generation. It lowers metabolic rate, limits edema formation, and interrupts necrosis/apoptosis.\textsuperscript{29,30} In addition, hypothermia reduces intracellular calcium rises after ischemia; the mechanism of this effect is not clear. Hypothermia may impair glutamate-mediated calcium influx or directly inhibit calcium-mediated effects on calcium/calmodulin kinase.\textsuperscript{31,32}

Hypothermia has significant effects on the production of hydroxyl radicals and suppresses nitric oxide and peroxynitrite formation. Additionally, granulocyte and intercellular adhesion molecule-1 upregulation in response to ischemia is attenuated.\textsuperscript{33} Wang et al\textsuperscript{34} showed that inflammatory responses are suppressed as late as 1 week after 2 hours of hypothermia.

In summary, hypothermia may reduce damage from excitotoxins, inflammation, free radicals, and necrosis. This could lead to longer neuronal survival and improved outcome after restoration of blood flow through revascularization methods such as thrombolysis. It may also reduce edema after ischemia and lower the risk of posts ischemic hemorrhage.\textsuperscript{35}

**Target Temperature**

Animal models of transient and permanent cerebral ischemia have used temperatures from 24°C to 33°C.\textsuperscript{25} Although infarct size was reduced in most models, animals with moderate hypothermia experienced greater recovery than those with severe hypothermia.\textsuperscript{36} This may be caused by a reduction of regional cerebral blood flow at very low temperatures.\textsuperscript{37}

Terms used to describe hypothermia are not clearly defined. Most consider severe hypothermia as temperature below 28°C, moderate as 28°C to 34°C, and mild as 34°C to 36°C.\textsuperscript{38} Severe hypothermia was never tested in stroke patients because medical complications of temperatures below 28°C such as severe hypokalemia, arrhythmia, infections, hypothyroidism, and heart failure in an elderly stroke population make severe hypothermia impractical. Moderate hypothermia was used after cardiac arrest in both the study of Bernard et al\textsuperscript{5} and the Hypothermia After Cardiac Arrest study,\textsuperscript{6} in neonatal asphyxia in the National Institute of Child Health and Human Development (NICHD) study,\textsuperscript{9} and for stroke patients in the COOL-AID pilot studies.\textsuperscript{10,11} The ICTUS and ICTUS-L studies use moderate hypothermia to 33°C but avoid endotracheal intubation by using a novel antishivering protocol.\textsuperscript{38} Mild hypothermia of 35.5°C was induced via cooling blankets in a small Danish study of stroke patients\textsuperscript{39} and via a cooling helmet in a series of stroke and traumatic brain injury patients in Illinois.\textsuperscript{40}

Although hypothermia below 35°C is still being investigated in stroke, avoiding fever\textsuperscript{41,42} and controlling temperature below 36.5°C have proven to correlate with good clinical outcome after stroke.\textsuperscript{43,44} The 2003 Guidelines for the Early Management of Patient With Ischemic Stroke by the American Stroke Association include the recommendation to treat sources of fever and to use antipyretics for temperature control in the setting of acute stroke.\textsuperscript{45}

**Surface Versus Endovascular Cooling**

Surface cooling methods include convective air blankets, water mattresses, alcohol bathing, cooling jackets, and ice packing. These methods have been used for many years in the treatment of fever and earlier studies of neuroprotection. Both cardiac arrest and the neonatal asphyxia study used such techniques. Patients in these conditions, however, are usually comatose and endotracheally intubated and ventilated. Patients who are on a respirator can be heavily sedated and paralyzed, effectively negating shivering and discomfort, which might otherwise interfere with therapy. In the first COOL-AID study, which used surface cooling,\textsuperscript{10} all patients were intubated, as were patients treated by Schwab et al\textsuperscript{46} for herniation after large middle cerebral artery stroke. Only a minority of stroke patients, however, require endotracheal intubation. Any successful application of hypothermia in the majority of moderate or severely affected stroke patients would be practical only if intubation was not needed in the treatment course.\textsuperscript{38}

Advantages of surface cooling are that it does not require advanced equipment or expertise in catheter placement and averts the risk associated with central venous catheter placement. Cooling through external methods, however, requires many hours to reach and maintain a temperature below 35°C and, in most cases, necessitates the use of sedatives and paralytics to prevent discomfort and shivering. Using paralysis and sedation requires endotracheal intubation and ventilation, which in turn are associated with significant risks of ventilator-associated pneumonia and other complications. Patients under paralytics render neurological assessments and detection of neurological worsening during the cooling period virtually impossible. In addition, cooling of the skin leads to vasoconstriction and reduces the heat exchange in cooled patients, which makes temperature control very difficult. This may lead to target temperature overshoot (COOL-AID I) and lack of control during passive rewarming, which may be associated with reactive brain edema.\textsuperscript{10}

In patients who are awake, surface cooling is only achieved as an approach for mild hypothermia and fever control. New surface cooling devices, such as energy-transferring skin pads,\textsuperscript{47} may demonstrate a reduction in the time to target temperature and allow better temperature control.\textsuperscript{48}

Endovascular cooling has become feasible via newly developed catheters with antithrombotic coverings that can be inserted into the central venous system and allow cooling via indwelling heat transfer devices. Prior attempts at endovascular cooling were limited by the need to infuse large volumes of chilled saline\textsuperscript{49} or caused thrombotic complications surrounding the heat exchange device. The new devices exchange heat via transduction through internal circulation within the catheter; no fluid enters the patient.\textsuperscript{50} Thrombotic complications are reduced with the use of the antithrombotic-eluting catheter.

Endovascular cooling allows rapid heat exchange and faster cooling toward target temperature. Shivering is in part driven through skin receptors. Endovascular cooling allows skin warming during cooling and, in turn, reduces shivering to make heat exchange more efficient and temperature control tighter. This avoids target temperature overshoot and inciden-
nal rewarming, which can lead to increases in brain edema and intracranial pressure (Figure).

**Treatment Window and Duration**
In animal studies, hypothermia during ischemia abolished the ischemic damage completely, and hypothermia within 3 hours significantly reduced infarct size.\(^51\),\(^52\) Some reports found that delaying hypothermia for \(>3\) hours after ischemia showed no significant neuroprotection,\(^23\) whereas Colbourne and Corbett\(^53\) have shown that cooling over 24 hours has neuroprotective effects, even when the treatment was delayed by 6 hours. A recent study in fetal sheep confirmed the neuroprotective effect of delayed hypothermia. In this model of 72 hours of brain cooling, hypothermia was initiated with a 2- or 6-hour delay and compared with sham-operated animals. Both the 6- and 2-hour treatment delay groups showed significant neuroprotective effects.\(^54\) This long therapeutic window is very promising because patients often present to the emergency department with a delay of a few hours after stroke onset.

The duration of cooling with best neuroprotective effects is not known. Yanamoto et al\(^55\) compared cooling for 22 and 3 hours after transient middle cerebral artery occlusion. Animals in the 22-hour group had better neuroprotection. In the gerbil 2-vessel occlusion model, intraischemic hypothermia completely prevented hippocampal cell damage when continued for 4 to 6 hours, cooling for 2 hours showed less of a protective effect, and 0.5 to 1 hour showed no protective effect.\(^23\) In addition, shorter periods of cooling may lead to only transient neuroprotection. In many experimental models, the animals are euthanized within a few days and potentially miss late neuronal cell death after hypothermia. The studies with the best long-term outcome involved treatment for 24 hours with hypothermia.\(^56\)

Treatment duration and time window may be interdependent because 24 hours of cooling prevented neuronal damage in 2 models when delayed by up to 6 or 3 hours.\(^57\) Two hours of cooling was only effective when initiated within 2 hours, implying a shorter time window for brief hypothermia.\(^58\)

**Temperature Control and Shivering**
The thermoregulatory system tightly controls core body temperature near 37°C. Defenses against cooling include shivering and cutaneous vasoconstriction. Cutaneous vasoconstriction reduces heat conduction through the skin; shivering produces energy and heat through repetitive muscle contractions.\(^59\) Shivering is the only heat-producing mechanism in humans and is the main factor in combating hypothermia.

To effectively cool patients and to avoid discomfort, shivering must be avoided. Shivering can be reduced with centrally active substances that alter hypothalamic thermoregulatory centers via skin warming, which reduces the trigger of shivering through skin temperature sensors and through muscle relaxation. Most anesthetics and narcotics change thermoregulatory control, and in general the effect on thermoregulatory mechanisms is proportionate to their anesthetic properties. Most drugs that effectively control shivering therefore lead to either sedation or respiratory depression.\(^60\)

Meperidine is the most important and clinically relevant drug that inhibits thermoregulatory responses.\(^61\),\(^62\) The anti-shivering action of meperidine decreases the shivering threshold twice as fast as the vasoconstriction threshold and can be achieved at blood levels that do not lead to severe respiratory depression or sedation. A low dose of meperidine (25 mg IV), which does not affect alertness or respiratory function, decreases the shivering threshold by 2°C.\(^63\)

Mokhtarani et al\(^64\) showed a synergistic effect of buspirone and meperidine. Buspirone reduces the shivering threshold to 35.0±0.8°C, high-dose meperidine reduces the threshold to 33.4±0.3°C, and the combination of buspirone and low-dose meperidine reduces the shivering threshold to 33.4±0.7°C.\(^64\) The combination did not cause sedation or respiratory de-
pression. The mechanism of this synergistic effect is unknown. In patients who are awake, the use of buspirone and meperidine in conjunction with skin warming allows cooling to 33°C.

**Thrombolysis and Hypothermia**

Hypothermia was most effective in preclinical models of transient ischemia. Combining hypothermia with therapies to restore blood flow, such as thrombolysis, may be the most promising strategy to use hypothermia in humans.

However, many serine proteases are affected by temperature, and the activity of tPA may be reduced in hypothermia. In vitro analysis shows that cooling to 30°C to 33°C decreases tPA activity by 2% to 4%. Wolberg et al reported that tPA activity declined to 50% when the clot temperature decreased from 40°C to 30°C. Whereas thrombolysis is reduced by low temperature, other aspects of coagulation and platelet function are also affected by hypothermia. Platelet function decreases when temperature is lowered from 37°C to 33°C, and in trauma patients platelet function and coagulation activity are decreased at temperature below 34°C.

The experience regarding safety and efficacy of thrombolytic use and hypothermia is limited in stroke patients. In the first COOL-AID study that used surface cooling, 4 of 10 patients received intra-arterial thrombolysis, and 2 received intravenous therapy. In the second study, 3 of 18 were treated with intra-arterial therapy, and 10 received intravenous thrombolysis. One patient who was treated with hypothermia and intra-arterial thrombolysis experienced retroperitoneal hemorrhage.

The data available thus far are insufficient to address the effect of hypothermia on tPA activity and the resulting safety. The ICTuS-L study will provide further feasibility and early safety data regarding the use of thrombolysis in stroke patients treated with hypothermia, with the use of state of the art endovascular heat exchangers and intravenous tPA.

Whether hypothermia affects hemorrhagic complications after stroke is unknown. One could hypothesize opposite effects. On the one hand, cooling may reduce hemorrhage after stroke by reducing the activities of matrix metalloproteinases after ischemia. On the other hand, cooling might reduce the activity of the recombinant tPA inhibitors, such as plasminogen activator-I, sufficiently that the lytic effect of recombinant tPA is enhanced, resulting in more hemorrhages. Again, trials such as ICTuS-L will begin to generate data on this point.

**Combination Therapy With Other Neuroprotective Agents**

The possibility of combining neuroprotective strategies was reviewed recently. Over the last decades, many neuroprotective trials were undertaken and failed to prove clinical benefit in patients after stroke. It is possible that compounds failing to protect when used alone might interact synergistically with other treatments to produce a more effective neuroprotective strategy. Hypothermia is an ideal addition to neuroprotective compounds. In animal models, the combination of hypothermia with tirilazad and magnesium was neuroprotective. Magnesium may also have a minor role in reducing the shivering threshold in men. The combination of hypothermia, caffeine, and alcohol is currently being tested in Houston.

**Conclusions**

Hypothermia is one of the most promising neuroprotective therapies yet identified in preclinical studies. Until recently, its use in unanesthetized patients after stroke was not feasible. The development of safer endovascular heat exchangers and novel antishivering protocols, which avoid sedation, makes the routine clinical use of hypothermia after stroke practical. Future studies will need to investigate the effect of hypothermia on clinical outcome, the safety in combination with thrombolysis, and its potential use in conjunction with other neuroprotective strategies.

**Disclosures**

None.

**References**


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