REVIEW

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# Acute ischemic stroke: Is there a role for hypothermia?

## ABSTRACT

Preliminary clinical trials suggest that therapeutic hypothermia might improve the outcomes of patients with acute stroke. Definitive trials are under way.

## KEY POINTS

Therapeutic hypothermia works by decreasing cell death, reperfusion injury, and cerebral edema.

Suitable patients may be identified using new imaging techniques designed to distinguish the core of the infarct from penumbra tissue.

Endovascular cooling to mildly hypothermic temperatures (33°C; 91.4°F), maintained for 24 hours, followed by slow rewarming (≤ 0.5°C/hour), under monitored conditions in an intensive care unit, is both feasible and safe.

Future topics of research: local application of hypothermia to the ischemic area; protocols combining hypothermia plus tissue plasminogen activator (tPA).

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DO PATIENTS benefit from having their core body temperature cooled to hypothermic levels for the first 24 hours after the onset of stroke? Preliminary results of trials that used an endovascular cooling device have been encouraging, and larger trials are under way.

In this paper, a conceptual introduction to the use of hypothermia for stroke, we briefly review the scientific basis for the therapeutic use of hypothermia, examine the early clinical experience with this technique, and discuss its possible future applications.

## TWO STRATEGIES FOR STROKE TREATMENT

The treatment of acute ischemic stroke has been the topic of much research, especially in the last few decades.

Most of this work has been directed at how to restore arterial blood flow to the ischemic brain tissue, using intravenous and intra-arterial infusions of thrombolytic drugs and mechanical intra-arterial interventions.

Thrombolytic therapy has been shown to be beneficial, but has two drawbacks: it must be given within a short time after the onset of stroke, and it causes intracranial hemorrhage in 5% to 10% of patients.[1,2]

Another strategy is to try to halt the cascade of destructive events that occur in ischemic brain tissue, regardless of whether the arterial supply has been restored. The use of neuroprotective agents is an example of this approach. Although neuroprotective agents have shown encouraging results in animal models, they have not yet proven to be clinically beneficial.

Hypothermia is another example of this defensive strategy, with numerous simultane-

**TABLE 1**

## Physiologic effects of various levels of hypothermia

| LEVEL | CORE TEMPERATURE | POTENTIAL APPLICATIONS | ADVERSE SYSTEMIC EFFECTS |
|---|---|---|---|
| **Mild** | > 32°C (> 89.6°F) | Therapeutic hypothermia for focal or global ischemia | Confusion<br>Shivering<br>Catecholamine release<br>Peripheral vasoconstriction<br>Cold-induced diuresis |
| **Moderate** | 28–32°C (82.4–89.6°F) | Same | Stupor<br>Ventricular arrhythmias<br>Hypotension<br>Coagulopathies |
| **Severe** | 20–28°C (68–82.4°F) | Cardiac procedures requiring circulatory arrest<br>Local application for spine (currently) or for ischemic brain (future) | Coma<br>Metabolic acidosis<br>Ventricular fibrillation<br>Severe hypotension<br>Hyperkalemia |
| **Profound** | < 20°C (< 68°F) | Same | Mimic brain death<br>Asystole<br>Flat electroencephalogram |

ously acting neuroprotective mechanisms. Hypothermia may increase the time window for thrombolysis and reduce detrimental effects, such as reperfusion injury and intracerebral hemorrhage. We will examine the evidence for combining both approaches.

## WHY HYPOTHERMIA?

A stroke is any sudden, focal, neurologic deficit caused by a pathologic process of the cerebral vasculature. An ischemic stroke is caused by loss of blood supply to a region of the brain.

The fate of this region of ischemic tissue depends on whether the blood supply is restored, how soon it is restored, and how much collateral blood supply feeds the tissue. The outcome is also modulated by certain well-recognized systemic variables, such as blood pressure, serum glucose levels, and body temperature. We may influence the outcome by intervening early to restore blood flow (with thrombolysis, for example), by increasing arterial blood pressure (induced hypertension), by normalizing serum glucose levels, and by reducing increased body temperature.

The brain is exquisitely sensitive to temperature; even minimal increases in temperature have deleterious effects on injured brain tissue.[3] Conversely, small decreases in brain temperature have been shown to reduce ischemic brain injury.[4,5]

**The brain is exquisitely sensitive to temperature**

### History of hypothermia research

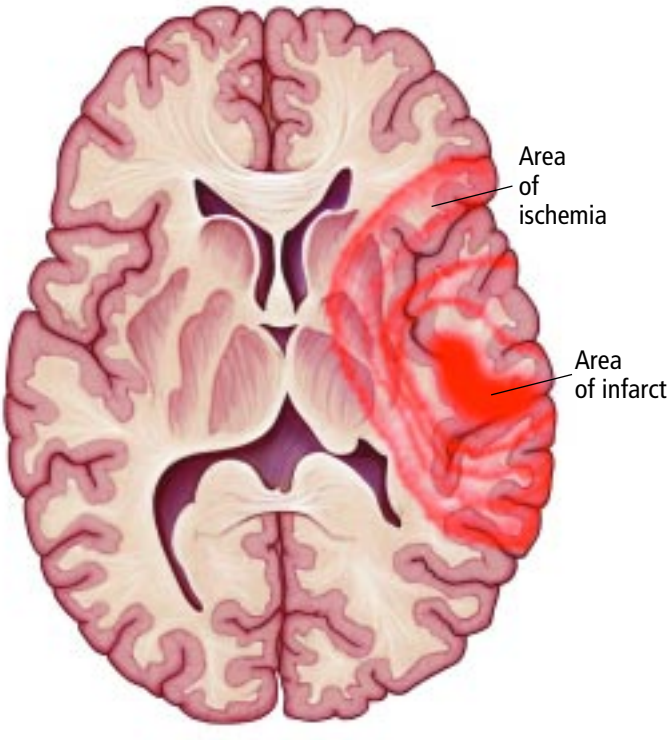
The neuroprotective effects of hypothermia have been studied since the 1950s, when studies of hibernation physiology showed that profound hypothermia (TABLE 1) allows animals to tolerate very low cerebral blood flow.[6]

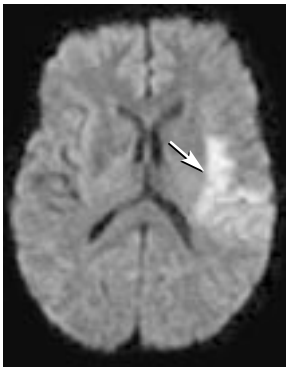
**During cardiac surgery.** Hypothermia was subsequently used to prevent ischemia throughout the body during cardiac surgery, first in animals,[7] then in humans.[8] Then, controlled experiments in animals demonstrated that hypothermia protects the brain during periods of global ischemia.[9,10] Today, profound hypothermia is used extensively to provide neuroprotection during neurosurgical or cardiac surgical procedures that necessitate circulatory arrest.[11–14]

**After traumatic brain injury.** Following several small trials of moderate hypothermia,[15,16] Clifton et al[17] performed a random-

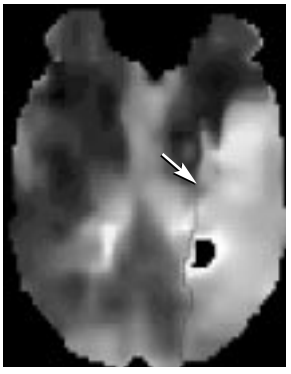
## Acute stroke: The infarct and the penumbra

Brain damage in an acute stroke is thought to proceed from an infarcted core to a surrounding penumbra of ischemic tissue



**Diffusion-weighted magnetic resonance imaging** (MRI) can display an area of infarction (arrow)



**Perfusion-weighted MRI** can show the wider area of ischemia (arrow); the difference between the lesion as shown on perfusion-weighted MRI and diffusion-weighted MRI represents tissue that is potentially salvageable



**FIGURE 1**

ized trial in 392 comatose patients with traumatic brain injury, half of whom were cooled to mild hypothermic levels. There was no difference between the hypothermic and normothermic groups in mortality or neurologic outcomes. This study has been criticized, however, because of certain inherent problems (reviewed elsewhere[18]).

**After cardiac arrest.** The prophylactic effects of hypothermia were then applied to the setting of cardiac arrest. Immediate, moderate, postischemic hypothermia was shown to improve outcome in animals, as measured histologically[19,20] and behaviorally.[21] After several successful preliminary studies in humans,[22–24] two randomized, controlled trials published in 2002 convincingly demonstrated that delayed mild to moderate hypothermia reduces the mortality rate and improves neurologic outcomes in patients resuscitated from cardiac arrest.[25,26]

**In acute stroke.** Most recently, hypothermia has been used to protect the brain against focal ischemia. In animal models of transient occlusion of the middle cerebral artery, moderate hypothermia decreases infarct size[27,28]; mild hypothermia also confers modest protection.[29–32]

Although the findings of these experiments in animals may not be directly translat-

ed into benefit in humans, human studies have nonetheless yielded promising results so far. After two successful feasibility studies,[33,34] the Cooling for Acute Ischemic Brain Damage (COOL AID) project was begun at The Cleveland Clinic with an open pilot study, published in 2001.[35]

The COOL AID pilot study showed that a group of 10 patients with massive cerebral infarctions who underwent mild hypothermia had better neurologic outcomes than a similar group who did not undergo hypothermia, although the differences did not reach statistical significance. Preliminary results from the follow-up study have been submitted for publication and appear promising.

## HOW DOES HYPOTHERMIA LIMIT ISCHEMIC BRAIN INJURY?

The mechanisms by which hypothermia protects brain tissue are not completely understood, but it seems to affect several pathways simultaneously.

The notion that hypothermia simply reduces cerebral metabolism and puts the brain in "suspended animation" dates to the 1950s and is based on studies using profound and prolonged hypothermia, which now is used only during cardiopulmonary bypass (TABLE 1). This preservative effect may only marginally apply to the mild degree of hypothermia proposed for patients with acute neurologic injuries.

**The COOL AID study has shown promising preliminary results**

Instead, mild hypothermia is thought to shield the brain from the adverse consequences of stroke mainly by preventing reperfusion injury and breakdown of the blood-brain barrier. To further explore these mechanisms, we must first briefly review the molecular effects of brain ischemia.

### How brain tissue dies

Acute ischemic stroke is usually caused by an arterial occlusion, which may be either transient or permanent. Several effects follow. The region of brain tissue supplied by that artery becomes ischemic. Over minutes to hours, if the blood flow is not restored, the ischemic tissue becomes infarcted. The infarction is thought to progress from the area with least collateral flow (the core of the infarct) to the area with best collateral flow (the penumbra; FIGURE 1). Whatever penumbra exists at any given time is potentially salvageable.[36,37]

The mechanisms of tissue damage during ischemia have been well reviewed elsewhere.[38] In brief, the ischemic neuron loses potassium into the extracellular space, while allowing calcium to pour in. This triggers a cascade of events that compromise the cell's ability to control ion fluxes and that lead to mitochondrial failure.

In addition, decreased oxygen availability leads to formation of oxygen free radicals that peroxidize plasma membranes. Further, ischemic cells produce lactic acid through anaerobic glycolysis, leading to acidosis. Finally, injured cells release excitatory amino acids that flood the extracellular space and reach toxic levels.

The multiple molecular events that take place within ischemic tissue become a self-perpetuating cycle of cell death. Even if blood flow is restored, a secondary wave of excitotoxicity and free radical formation may occur, a process termed *reperfusion injury*, which may exacerbate the initial effects of blood deprivation. Concurrently, the blood-brain barrier breaks down, leading to cerebral edema and perhaps also to hemorrhage.

### Beneficial effects of hypothermia

Hypothermia limits ischemic damage at many different levels, eg:

- It decreases cellular metabolism by retarding high-energy phosphate depletion and facilitating postischemic glucose utilization[39]
- It reduces the cytotoxic cascade by suppressing elevations of intracellular calcium, inhibiting release of excitotoxic amino acids, and reducing intracellular acidosis[40–42]
- It suppresses the breakdown of the blood-brain barrier[43,44]
- It reduces free radical formation.[42,45]

Experimental evidence in acute stroke models suggests that mild to moderate hypothermia prevents the toxic effects of tPA on the injured neurovascular tissues, while the lytic effects of tPA are unaffected.[46]

Taken together, the combined effects of hypothermia attenuate cell death, reperfusion injury, and cerebral edema.

# Hypothermia for acute stroke: Intravascular cooling

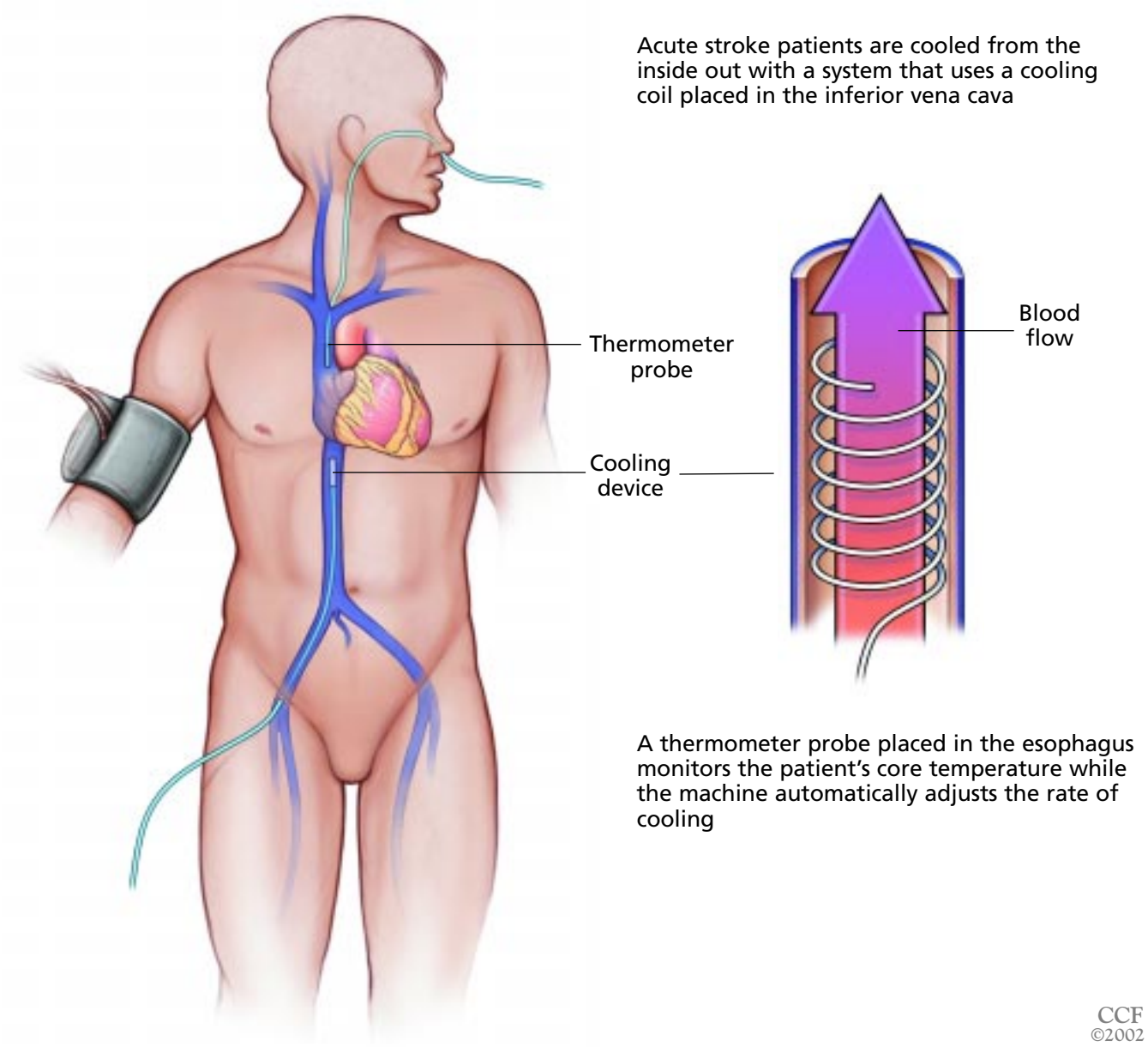



**FIGURE 2**

## CAN WE PREDICT WHO MAY BENEFIT?

New brain imaging techniques are bringing us tantalizingly closer to being able to image the theoretical ischemic core and penumbra.

**Diffusion-weighted MRI** (DWI) highlights areas of brain tissue in which diffusion of water is restricted.[47] This restriction is attributed to regional cytotoxic edema caused by reduced blood flow, and may correspond roughly to the central infarcted core.

**Perfusion-weighted MRI** (PWI) can demonstrate regional differences in tissue per-

fusion. An area that shows decreased tissue perfusion may roughly correspond to the ischemic penumbra.[48] One can often see a large diffusion-perfusion mismatch, in which the area of low perfusion is much larger than the area of infarct (FIGURE 1). The penumbra is therefore believed to be approximated by the area showing decreased perfusion that exceeds the area of the DWI lesion.[48] Once the stroke is successfully treated, the patient may be left with only a small DWI-positive infarct.[49]

**Computed tomography.** Recent developments in computed tomography (perfusion CT) have led to an analogous "decision map" based on measured changes in cerebral blood flow and volume within a region of ischemic tissue.[50]

The value of MRI and CT to image the infarcted core and the ischemic penumbra is that they may help identify acute stroke patients who have salvageable tissue[50–52] and who may therefore benefit from aggressive therapies such as thrombolysis and hypothermia.

## HOW ARE PATIENTS COOLED?

**MRI and CT may help identify patients with salvageable tissue**

Hypothermia continues to evolve as a therapy for acute neurologic emergencies. It is still not known how soon to initiate hypothermia, how far down to bring the temperature, and how long to maintain it. However, these questions are becoming clearer with time. Furthermore, the size of the "therapeutic window"—how soon after the stroke that hypothermia must be begun to be beneficial—is not known. The COOL AID study used an 8-hour postischemic window.[35]

We now know that a target temperature of 33°C (91.4°F), maintained for 24 hours, is feasible and safe.[17,22,33–35] This temperature and duration may maximize the benefits of hypothermia while minimizing deleterious effects (see below).

### Surface cooling

The patient's temperature can be lowered by surface cooling—rubbing the patient with ethanol and ice water.[17,22,33–35] This method has disadvantages: it takes many hours to reach and maintain the target temperature and necessitates the use of sedatives and paralytics to prevent discomfort and shivering. Paralysis and sedation, in turn, prohibit neurologic assessment during the long periods for which patients are cooled.

Other methods that have been used, although not for stroke patients, include cooling jackets, iced gastric lavage, and room temperature inspired gases.[15,53]

### Intravascular cooling

Today, we induce hypothermia using a central venous catheter inserted into the femoral vein connected to a heat-exchange cassette and a controller (FIGURE 2). The device is intended to maintain a desired patient temperature within the range of 32 to 37°C by circulating warm or cool saline through the catheter. The controller is set to the desired temperature and rate of temperature change. Warm or cool sterile saline is continuously circulated through the catheter, thereby adding heat to or removing heat from the blood by means of counterflow heat exchange. The heat exchange is achieved without direct contact of saline with blood. As this exchange takes place, the saline is returned from the catheter to the cassette, which contains a second heat exchange surface and a pump head that drives the circulation of the saline between the cassette and catheter.

This method achieves the target temperature in approximately 1 hour, maintains that temperature automatically, eliminates patient discomfort, and obviates the use of paralytics (although minimal sedation may still be required to minimize shivering), thereby allowing physicians to continue to monitor their patients' clinical status.[54]

If therapeutic hypothermia proves to be beneficial, then even more refined techniques may be developed. The aim might be to provide local hypothermia to the injured brain, thereby avoiding systemic hypothermia altogether. This would allow the establishment of profound hypothermia in isolated, injured tissue, without risking systemic side effects.

When surface cooling is used, the patient's core temperature is measured via a thermometer attached to a bladder catheter; when intravascular cooling is used, temperature is measured in the esophagus or intravascularly. This "core" temperature may not be equiva-

lent to cerebral temperatures, however. It is possible that with the development of a method of delivering local hypothermia directly to the injured brain, we may also be able to measure and alter that injured tissue in isolation.

All patients treated with hypothermia must be monitored in an intensive care unit, where hemodynamic parameters can be controlled and clinical status can be carefully monitored. The goals of monitoring are to keep patients normotensive and euvolemic, to keep their serum electrolytes (especially magnesium and phosphate) at normal levels, and to ensure that arrhythmias are rapidly detected and treated (see below).

## COMPLICATIONS OF HYPOTHERMIA

Systemic hypothermia can cause a variety of cardiac, pulmonary, renal, electrolytic, infectious, and other complications. These complications tend to occur with more profound levels of hypothermia; the mild-to-moderate level of hypothermia used in acute ischemic stroke is generally safe and well tolerated.

**Hypovolemia.** Hypothermia causes an increase in peripheral vascular resistance.[55] This, together with a renal tubular natriuresis, precipitates a "cold-induced diuresis"[56] that in turn decreases intravascular volume. This same process also contributes to increased plasma viscosity. Therefore, volume status must be carefully monitored, and patients must be kept well hydrated.

**Arrhythmias.** Ventricular ectopy may occur, but ventricular fibrillation is not common with mild or moderate hypothermia. Hypothermia should be avoided in patients with a history of atrial fibrillation and congestive heart failure. Bradycardia is commonly seen in mild-to-moderate hypothermia. Arrhythmias are rare above 32°C (89.6°F), uncommon between 30 and 32°C (86.0–89.6°F), and frequent only at temperatures below 28°C (82°F).[6,15,29] This is the basis for choosing 33°C as the target for stroke treatment.

**Hypertension, hypotension.** Surface induction of hypothermia causes a catecholamine surge, which may in turn cause hypertension. Blood pressure must be carefully monitored to avoid extreme hypertension, which could be especially dangerous in a patient with acute stroke. We have not seen these blood pressure surges with intravascular hypothermia. Hypothermia may also cause a *decrease* in blood pressure, which tends to stabilize during the maintenance phase.[35]

**Pulmonary complications,** especially aspiration pneumonia, are prevalent in intubated patients undergoing hypothermia.[15,53] Preliminary experience suggests that this type of complication is significantly reduced in patients who are cooled intravascularly and do not require intubation.[54]

**Electrolyte abnormalities.** Hypothermia causes mild hypokalemia, hyperglycemia, and metabolic acidosis due to intracellular shifts caused directly by lowering the temperature.[53] These electrolyte changes do not cause symptoms and normalize upon rewarming. Replacement can cause "rebound" hyperkalemia upon rewarming, and is avoided.

**Increased intracranial pressure.** Rewarming, if done too quickly, can precipitate severe increases in intracranial pressure with resulting transtentorial herniation.[34] Controlled rewarming (≤ 0.5°C/hour) significantly reduces this effect and should be done routinely until more experience is gained with hypothermia in acute stroke patients.[57]

**A target of 33°C, maintained for 24 hours, is feasible and safe**

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