

Induced Hypothermia in Neurocatastrophes: Feeling the Chill

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Reducing core temperature to protect the injured brain has become a new therapeutic measure. The scientific underpinnings based on animal experiments seem sound. Evidence of the therapy's effect in human trials is insufficient or even possibly absent, but the techniques to produce moderate hypothermia are available, without apparent significant complications, and are relatively easy to use for neurointensivists. This review summarizes the mechanisms of neuroprotection due to hypothermia and its application in clinical practice.

[Rev Neurol Dis. 2004;1(1):10-15]

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Key words: Hypothermia • Intensive care unit • Neuroprotection

We do not expect much good from the cold, but the effects of hypothermia can be twofold. Severe environmental hypothermia will cause asystole, and patients might not be revived; milder degrees of hypothermia might protect the brain and other vital organs from injury. The use of hypothermia in intensive care units is not new, has been sporadically used in the past, went out of vogue, and has recently seen resurgence. Hypothermia has also undergone redefinition, being classified as mild (33°–36°C), moderate (28°–32°C), and deep (less than 28°C).

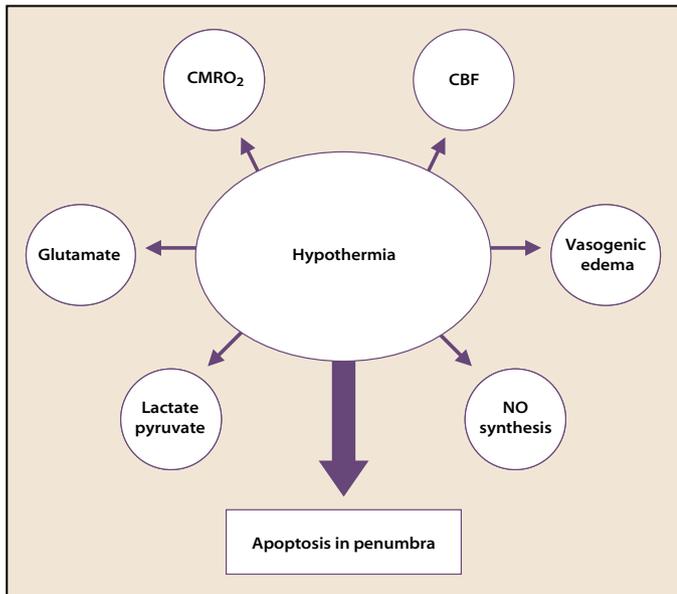


Figure 1. Possible mechanisms of hypothermia. CMRO₂, cerebral metabolic rate of oxygen; CBF, cerebral blood flow; NO, nitric oxide.

in controlled laboratory experiments (using global and focal ischemia models) is that lowering the core temperature to 33°C reduces infarct size, even if delayed until hours after the insult. The most pronounced effect of hypothermia is the delay of reperfusion injury and swelling and the suppression of apoptosis (Figure 1). However, hypothermia reduces glutamate (one of the excitatory amino acids), reactive oxygen, and nitrogen intermediates (known to impair and eventually damage mitochondria).⁵

A major focus of research in the ischemic cascade is apoptosis, and hypothermia might exert its neuroprotective effects through this mechanism rather than through preventing or attenuating necrosis of neurons. Apoptosis, unlike necrosis, is a regulated and orderly process of cell death that is genetically programmed. Apoptosis is essential for maintenance of tissue homeostasis, growth, and development resulting in cell regeneration, but it is also implicated in many pathologic processes. Hypothermia reduces the cytosolic translocation of cytochrome C and increases BCL-2 expression (a gene known

There has long been a search for a simple method of neuroprotection, and clinical data have emerged to suggest that induced hypothermia could be effective. A major surge in interest in this therapy is demonstrated by the recent completion of two randomized, controlled trials involving patients admitted after cardiac resuscitation; both studies claimed benefit.^{1,2} Neurologists have also been interested in using the technique in the treatment of large hemispheric stroke, predominantly when swelling occurs. Despite its promise, however, the benefits of therapeutic hypothermia remain unclear.

Mild hypothermia for brain injury has recently become a major field of experimental research and has even been recommended to treat anoxic-ischemic brain injury after cardiac resuscitation.³ The momentum in the literature is quite strong, with editorial endorsements⁴ and advising statements.³ To quote a recent study, "Each year, cardiac arrest occurs in approximately 375,000 people in Europe, about 30,000 of whom would meet our inclusion criteria. We can be 95% confident that treatment

with hypothermia would prevent an unfavorable neurologic outcome in 1200 to 7500 of these patients."¹ More worrisome, there is a major business interest in the development and aggressive marketing of cooling catheters and other technologies to apply direct cooling to the cortex.

Thus, it is appropriate to review the current state of the art in induced

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hypothermia and to describe the complex techniques. It might be appropriate to obtain hard, incontrovertible data before considering this therapy established and standard.

Protective Mechanisms of Hypothermia

Hypothermia has been studied with current concepts of ischemia in mind, and its neuroprotective effects have been demonstrated along these routes. What seems to be established

to prevent apoptosis), although not likely through caspase activity (a major downstream component in the ischemic cascade leading to apoptosis).⁶⁻¹⁰ Hypothermia's effect is predominantly in the penumbra and not in the core of the infarct. Hypothermia might reduce brain swelling, because rapid development of swelling has been noted during rewarming.⁷

With any claim of a neuroprotective effect, the essential questions are

1) what is the therapeutic window? 2) how long should it be administered? and 3) at what level? Accumulating data now indicate that hypothermia can be effective within 1 hour after ischemic injury but that the effect can be nullified when the core temperature is less than 30°C¹¹ and when intracranial pressure (ICP) (particularly in traumatic head injury) is not controlled.

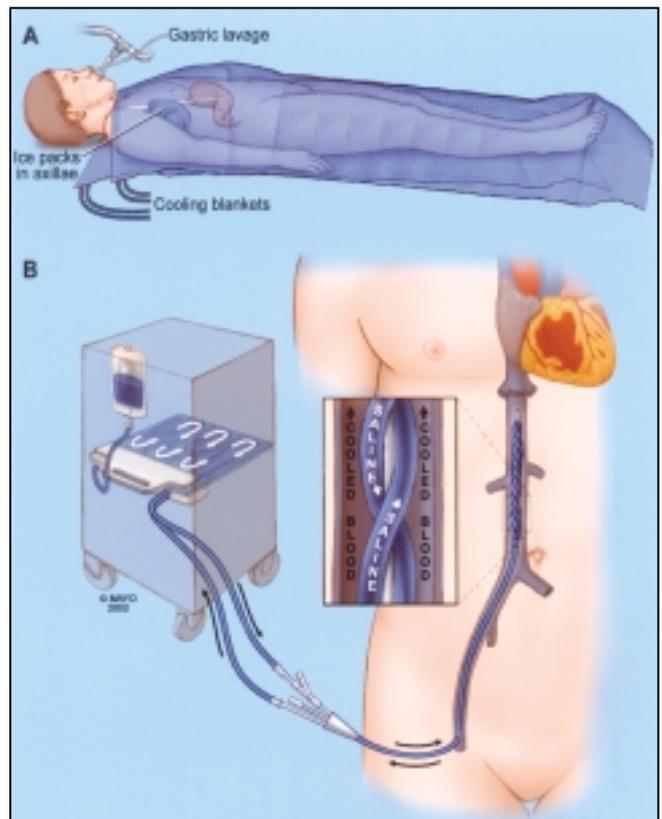
In addition, there are some early data to suggest that rapid rewarming (in animal experiments using heating pads and heating lamps aiming to reach normothermic levels within 30 minutes!) impaired the endothelial response to acetylcholine—an effect not seen with slow rewarming (defined in these experiments as a 90-minute period).¹² One study in rats found that a delay of 6 hours but 48 hours of hypothermia still had a marked protective effect.¹³

Techniques in Clinical Practice

The appropriate time to induce hypothermia is not well defined. Obviously, hypothermia is a very unpleasant experience (owing to extensive shivering) and thus requires sedation with neuromuscular blockade. Currently, it is started when patients are comatose or have become stuporous in need of endotracheal intubation and mechanical ventilation. Sedation of alert and cooperative patients followed by intubation for the sole purpose of applying early hypothermia is currently not standard practice.

Hypothermia requires a cooling device. A noninvasive technique is to “sandwich” the patient between flat, water-cooled blankets. This technique of applying direct cooling to the skin is more effective than delivering cold air with a mattress that fans the entire body. Both techniques use ice packs in the axillae or repeated ice water gastric lavage to

Figure 2. Superficial and invasive cooling devices. Reproduced with permission from Wijdicks EFM. *The Clinical Practice of Critical Care Neurology*. 2nd ed. Oxford, UK: Oxford University Press; 2003.



maintain hypothermia. With these systems (conduction vs convection), it is possible to maintain hypothermia until an intercurrent infection emerges. It is difficult to maintain hypothermia in patients with central fever due to aneurysmal subarachnoid hemorrhage, dysautonomia in head injury, and drug fever.

Most clinical studies of hypothermia have reported a delay of 2 to 3 hours to reach the desired target, and this could be relevant if efficacy of this intervention is time dependent. Two recent studies have shown that rapid cooling can be achieved by infusion of ice-cold saline (4°C) with a central venous catheter.^{10,14,15}

Table 1
Hypothermia in the Intensive Care Unit

- Use cooling blankets (conduction preferred)
- Ice packs in axilla
- Start infusing 30 mL/kg ice cold (4°C) crystalloids
- Aim at 33°C core temperature
- Use gastric lavage with ice water hourly
- Sedation with propofol (infusion up to 200 mcg/kg/min)
- Consider vecuronium if shivering continues
- Rewarming (passive) after 48 hours

Core temperatures decreased plus or minus 2°C within plus or minus 30 minutes without the adverse effects of pulmonary edema due to congestive heart failure.¹⁶ Several companies have marketed a cooling catheter inserted into the vena cava (superior or inferior) (Figure 2). The catheter is highly effective in cooling; it both initiates hypothermia and maintains a set point. Ice-cold fluid is circulated within this catheter through a console maintaining a previously set temperature. A protocol for hypothermia is shown in Table 1.

Despite major concerns about complications, the experience with induced hypothermia has been rather favorable. Infectious complications, clotting abnormalities, and cardiac arrhythmias have not been frequently observed^{17,18} (Table 2). In two large trials in which patients were treated with hypothermia after cardiac arrest, there were more infectious complications (pneumonia, sepsis) in the hypothermia group but creatinine kinase and hemodynamic parameters (cardiac index and systemic vascular resistance) in the hypothermia group were not significantly different from those in controls after 6 hours of therapy. Undoubtedly, the complications are expectedly higher in moderate hypothermia.

Clinical Trials

Randomized, controlled trials of induced hypothermia for the treatment of traumatic brain injury¹⁹ and anoxic-ischemic encephalopathy²⁰ have been published, as have feasibility studies in settings of stroke²¹ and subarachnoid hemorrhage. The results are briefly critiqued here.

Anoxic-Ischemic Encephalopathy

Results have recently been published for the Hypothermia After Cardiac Arrest trial, which included

Table 2
Complications of Hypothermia

Complication	Mechanism
Pneumonia	Ventilator associated
Bronchus (mucus) obstruction	Neuromuscular junction blockers
Hypokalemia	Decreased absorption (loop of Henle)
Hyperglycemia	Decreased insulin release Decreased motility
Sepsis	Decreased white blood cells
Thrombocytopenia	Only with prolonged hypothermia

275 resuscitated patients after cardiac arrest who were not able to respond to verbal commands. Patients were included who were resuscitated 15 minutes after arrest and regained circulation within 1 hour. External cooling with target temperature reached at 8 hours was compared with standard therapy and outcome determined (blindly) at 6 months. The hypothermia group had better outcomes (mortality and disability), and 55% ranked as favorable, as opposed to 39% in the normother-

Much enthusiasm has been generated by these two trials. Although the study authors are promising information regarding important neurologic prognosticators, Glasgow coma score, myoclonus status epilepticus neuroimaging, and electroencephalogram patterns have not been provided (even when asked for in letters to the editor).²³ Outcomes in both studies were measured as comparing minimal disability and discharge to a rehabilitation facility with severe disability (discharge to a

With these crude measures of outcome, it is impossible to definitively claim the success of hypothermia.

mic group. Sepsis, pneumonia, and hemorrhagic complications were not statistically different but were more prevalent in the patients receiving hypothermic treatment.¹

A much smaller trial (of 77 patients) found similar benefit, but target temperature was reached at 2 hours because of cooling initiated in the field. Twelve hours of hypothermia was associated with 49% good outcome, compared with 26% in the normothermic group. In this study, mortality was 51% and 68%, respectively, and not statistically different.²²

nursing home). Mortality was higher in the normothermia group but not statistically significant. With these crude measures of outcome, it is impossible to definitively claim the success of hypothermia. More studies with detailed neurologic assessment on admission and follow-up are needed. These studies should preferably use invasive devices or other techniques to rapidly cool patients.

Traumatic Brain Injury

Induced hypothermia did not improve long-term outcome in a

large, multicenter, randomized clinical trial. In 392 patients with Glasgow coma sum scores of 3 to 8, surface cooling led to higher complications, longer hospital stay, and no improved outcome. The long delay of therapy (± 8 hours) and differences in ICP control between certain centers have been critiqued, prompting new prospective trials.^{18,24,25} One recent study documented that increased ICP could not be prevented in 80% of 22 patients, and despite hypothermia, outcome was very poor.^{19,26,27} A recent meta-analysis with pooling of seven trials found no reductions in mortality and morbidity. (The authors greatly acknowledged the flaws of such analyses.) This careful review also noted that some trials restricted involvement of patients with increased ICP, and others *only* enrolled patients with increased ICP, further complicating comparison.²⁸

Ischemic Stroke and Subarachnoid Hemorrhage

Multiple cohorts in massive ischemic stroke have been published.²⁹⁻³¹ However, comparison has been between a treated series and historical controls. Unsubstantiated claims have included reduction in mortality and reduction of swelling. Concerns have been raised regarding increased ICP with rewarming and high incidence of thrombocytopenia and bradycardia. Most studies in ischemic stroke tar-

geted cooling temperatures of 32°C to 33°C. In the largest study, by Schwab and colleagues (50 patients), the target temperature was 33°C within 28 plus or minus 17 hours after stroke onset.³¹ Varying periods of hypothermia have been used, with 6 hours in one study and 2 to 3 days in most others. Studies with lesser degrees of cooling (35°C) and no need for anesthesia support are under way.

A preliminary study in poor-grade subarachnoid hemorrhage using 16 days of hypothermia after clipping resulted in severe infectious thrombocytopenia requiring platelet infusions, but outcome was surprisingly good in almost 50% of the patients.³² Hypothermia has been used in patients receiving cardiopulmonary bypass to repair complex, often giant, aneurysms. Prolonged use in the neurological-neurosurgical intensive care unit (pre- or postoperatively) has not been studied.

Conclusion

Induced hypothermia can be successfully managed in the intensive care unit. More academic institutions and intensive care units will be interested in this technique, despite the lack of hard evidence of its effect. The complications of brief induced hypothermia in patients already intubated and ventilated or on vasopressor drugs are fairly minimal. The next step is to gather reliable data in controlled clinical trials. ■

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Main Points

- Mild induced hypothermia (33°C–36°C) is an emerging neuroprotective therapy.
- The best reported data to date are two randomized, controlled trials in comatose patients after cardiac resuscitation. Mortality did not decrease, but significantly better outcomes were documented according to crude outcome scales.
- Promising new applications of induced hypothermia are in the treatment of hemispheric stroke and poor-grade subarachnoid hemorrhage.
- Invasive cooling techniques have been introduced on the market and could enable better maintenance of temperature set points.

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