STATE OF THE ART

Evidence for the use of hypothermia after cardiac arrest

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FOR THE CAEP POSITION STATEMENT SEE PAGE 106.
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Development of the CAEP therapeutic hypothermia position statement

In April 2004, the Canadian Association of Emergency Physicians (CAEP) Critical Care Committee committed to examine the evidence for therapeutic hypothermia after cardiac arrest and make recommendations on its use in the emergency department. The primary review committee (PRC) was made up of 5 members of the CAEP Critical Care Committee. All 5 members signed statements confirming that they had no potential or perceived conflicts-of-interest. The PRC developed a set of questions to be addressed by the position statement. These questions focused on both the indications and the practical application of therapeutic hypothermia. (See Table 1 for key definitions used by the PRC.)

A search of Medline and EMBASE, from 1996 to September 2004, using the terms "hypothermia" and "cardiac arrest," yielded 79 relevant articles. These articles were circulated to the PRC and used to develop a series of statements in response to the questions. The committee evaluated and graded the support for each of the statements, using the Oxford Centre for Evidence-based Medicine Levels of Evidence,[1] summarized in Table 2. The statements were collated along with summary background materials in to a draft position statement.

The draft was circulated to 20 physician experts, including emergency physicians, cardiologists, neurologists, intensivists, anesthetists, community and tertiary care physicians from across Canada for critical review. Eighteen of these physicians submitted written reports. Their comments and suggestions were brought back to the PRC for incorporation and synthesis. The final draft was approved by the PRC on May 30, 2005, and forwarded to the CAEP Standards committee, who approved it in July 2005. On Aug. 29, 2005, the CAEP executive adopted the statement.

This document reviews the postulated mechanism for therapeutic hypothermia, summarizes the existing literature, and outlines the rationale for the position statement and guidelines.

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Mechanism of action for therapeutic hypothermia

There are 3 phases of cerebral injury after hypoxic insult: early, intermediate and late. Therapeutic hypothermia is considered to be neuroprotective by acting at each of the 3 stages of injury, perhaps synergistically.[2–8]

Cardiac arrest immediately decreases cerebral blood flow despite ongoing consumption of oxygen, adenosine triphosphate and glucose.[9–11] In this early stage, hypothermia decreases energy utilization,[12–19] consumption of oxygen,[11,20] and glucose.[21]

The intermediate or latent phase occurs in the hours post-arrest. Excitatory amino acids and glutamate are released in the brain, activating cytotoxic cascades including free radicals and nitric oxide.[10] Hypothermia decreases the release of excitatory amino acids[8,22–28] and other neurotoxic mediators.[11,17–19,29–33] Cooling lessens nitric oxide production[7,23] and delays the peak of nitric oxide.[24]

The late phase of cerebral injury can occur up to 24 hours after cardiac arrest. At this stage, the blood–brain barrier breaks down, cerebral edema worsens, and seizures and neuronal death may occur.[9,10] Hypothermia slows the deterioration of the blood–brain barrier and decreases cerebral edema.[7,10,32]

Summary of clinical trials

Four trials have prospectively evaluated the use of induced hypothermia in cardiac arrest survivors. A total of 436 patients were studied, 231 of whom were cooled to a core temperature of 32°–34°C. The majority of patients were enrolled in 2 studies[2,3] published in 2002.

The Hypothermia after Cardiac Arrest (HACA)[2] study was a multicentre, randomized, controlled trial conducted in 9 centres in 5 European countries. Cardiac arrest patients with primary ventricular fibrillation or pulseless ventricular tachycardia who had a return of spontaneous circulation (ROSC) were randomized to either normothermic standard therapy or mild induced hypothermia after admission to the emergency department. All patients had a decreased level of consciousness and were unresponsive to verbal commands. In the hypothermia group, a cooling mattress and ice packs as necessary were used to reach a target core temperature of 32°–34°C, which was maintained for 24 hours. The investigators assessed neurologic outcome at 6 months with a standard neurologic assessment tool, the Pittsburgh Cerebral Performance Score. In addition, they measured in-hospital and 6-month mortality, and complications within 7 days of cooling. In total, 275 patients were enrolled and 136 randomized to therapeutic hypothermia. Those in the hypothermia group had an absolute risk reduction (ARR) for poor neurologic outcome of 16%, a risk ratio of 1.40 (95% confidence interval (CI), 1.08–1.81). Mortality was also significantly reduced with an ARR of 14% and a risk

Table 1. Definitions for the CAEP Position Statement on the use of hypothermia after cardiac arrest

Definitions — For the purpose of this position statement the committee adopted the following definitions.

Unresponsive: Patients with a Glasgow Coma Scale score <10 or who are not responding to verbal commands.

Hemodynamic stability: The return of spontaneous circulation and a mean arterial pressure capable of perfusing vital organs. Inotropes and vasopressors may be used to establish hemodynamic stability.

Therapeutic hypothermia: The induction of mild hypothermia (core temperature 32°–34°C) with the purpose of minimizing neurological injury after cerebral hypoperfusion.

Table 2. Levels of Evidence and Grades of Recommendation – Based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001).[1] An abbreviated summary is shown here.

Variable	Research
Level of Evidence	
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow CI)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT)
2c	"Outcomes" research; Ecological studies
3a	SR (with homogeneity) of case–control studies
3b	Individual case–control study
4	Case series (and poor quality cohort and case–control studies)
5	Expert opinion based on physiology or bench research
Grades of Recommendation	
A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies **or** extrapolations from Level 1 studies
C	Level 4 studies **or** extrapolations from Level 2 or 3 studies
D	Level 5 evidence **or** troublingly inconsistent or inconclusive studies of any level.

SR = systematic review; RCT = randomized controlled trial; CI = confidence interval

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ratio of 0.74 (95% CI, 0.58–0.95). There was no statistically significant difference in the incidence of complications in the groups, but there was a trend toward increased bleeding and infection in the hypothermic group.

Bernard and colleagues' study[3] was an Australian multicentre, quazi-randomized, controlled trial published concurrently with the HACA study. These authors enrolled 77 patients (43 in the induced hypothermia group) with out-of-hospital ventricular fibrillation who remained comatose after regaining a pulse. In the hypothermia group, paramedics initiated cooling by applying cold packs in the field, with the goal of reducing the core temperature to 33°C within 2 hours and maintaining this level for 12 hours. The control group was treated with standard resuscitation measures. Outcomes assessed included survival to discharge, neurologic outcome at discharge, and in-hospital complications. Patients randomized to hypothermia had lower mortality rates (ARR = 17%) and were less likely to have poor neurologic outcome (ARR = 23%), but the study lacked sufficient power to demonstrate statistical significance ($p = 0.145$). Based on the primary outcome, survival with sufficient neurologic function to be discharged home or to a rehabilitation facility, patients in the hypothermic group were more likely to have favourable outcomes (adjusted odds ratio = 5.25; 95% CI, 1.5–18.8).

In a 2001 study, Hachimi-Idrissi and colleagues[34] randomized 30 patients after asystole or pulseless electrical activity to either cooling with a helmet device or normothermia. Patients were enrolled in the pre-hospital setting, and hypothermia was induced using a cooling helmet, with a goal of 34°C within 4 hours. Once target temperature was achieved, the helmet was removed and the patient was allowed to passively rewarm over 8 hours. Measured outcomes included feasibility of the use of a localized cooling helmet to reach the target temperature within 4 hours, in-hospital mortality and associated complications. Overall, only 4 patients survived, 3 of the 16 hypothermia patients (18.8%) and 1 of 14 controls (7.1%). Two of the 3 hypothermia survivors had favourable recoveries (overall performance category [OPC] = 1) and one had severe disability (OPC = 3). The only surviving normothermia patient had severe disability (OPC = 3).

The final study by Mori and coworkers,[35] available in abstract only, randomized 54 out-of-hospital cardiac arrest patients to mild induced hypothermia or normothermic care for 3 days. The primary outcome measure was neurologic outcome at 1 month as measured by the Glasgow Coma Scale. The authors report that patients randomized to the hypothermic group had a statistically significant absolute risk reduction of 39% for poor neurologic outcome.

Key questions addressed by the review committees

Question

Should therapeutic hypothermia be used in the treatment of patients after cardiac arrest? If so, which patients should be considered for treatment?

- Cardiac arrest patients who present with ventricular fibrillation or nonperfusing ventricular tachycardia, are resuscitated to hemodynamic stability, but remain unresponsive should receive therapeutic hypothermia. (Grade A)
- Cardiac arrest patients who present with asystole or pulseless electrical activity felt to be of cardiac origin, are resuscitated to hemodynamic stability, but remain unconscious should be considered for therapeutic hypothermia. (Grade D)
- Patients under 18 years of age and pregnant women may benefit from this therapy, but its role is unproven. Consideration in these populations should be on a case-by-case basis. (Grade D)

Supporting evidence

The 2 randomized trials[2,3] published in the *New England Journal of Medicine* in 2002 demonstrated that patients with ventricular fibrillation or ventricular tachycardia (VF/VT) cardiac arrest who were cooled to 32°–34°C benefited from induced hypothermia. The evidence is not clear for other patient categories, as there are no randomized trials to guide decision-making.

Pilot studies of induced hypothermia show no harm and some potential benefit for adult cardiac arrest victims with rhythms other than VF/VT; however, these studies are too small to allow meaningful subgroup analysis.[34,36,37] Despite the lack of convincing evidence, it seems logical that patients in these other subgroups could benefit from this therapy, since hypothermia is intended to ameliorate the anoxic brain injury that occurs during cardiac arrest, not to treat the cause of the arrest.

Hypothermia has not been evaluated in patients with cardiac arrest related to non-cardiac events such as subarachnoid hemorrhage or trauma. These patients may have more severe anoxic brain injury and hypothermia-related coagulopathy could be harmful, perhaps increasing the number of patients who survive with adverse neurologic outcomes. If therapeutic hypothermia is considered in such circumstances, an early CT scan should be considered to rule out intracranial bleeding.

Pediatric data are lacking. Early pediatric studies using hypothermia post arrest showed negative outcomes,[38] but

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these regimens exposed children to lower temperatures and more prolonged cooling. The review committee's opinion is that, because the pathophysiology of anoxic brain injury is similar in adults and children, hypothermia will likely benefit pediatric cardiac arrest victims if they otherwise meet recommended inclusion criteria. It is important to reiterate that this conclusion is based on extrapolation of adult data — not on the availability of valid pediatric data.

Pregnant women would be expected to respond favourably to therapeutic hypothermia, but these patients have been excluded from hypothermia trials; consequently there are no data clarifying fetal safety. Selected data from the cardiac surgery literature suggest potential harm to the fetus during cardiopulmonary bypass induced hypothermia;[39,40] however, the duration and depth of hypothermia are much different, making it difficult to extrapolate to the cardiac arrest setting. Until further data are available, it is difficult to make recommendations for or against hypothermia for pregnant cardiac arrest victims, and treatment of these patients should be determined on an individualized basis.

Question

How soon should therapeutic hypothermia be initiated?

- Therapeutic hypothermia should be initiated as soon as possible. (Grade A)
- Patients who are successfully cooled within 8 or more hours of return of spontaneous circulation may still derive benefit from this therapy. (Grade B)

Supporting evidence

Several trials have demonstrated that hypothermia is neuroprotective when administered before or during ischemic events.[5,7,10,19,41,42] Evidence from cardiac arrest trials supports cooling patients as soon as possible post-ischemia,[8–10,19,32,43] even in the pre-hospital setting if this is feasible, particularly if transport times are prolonged.[8,9,11,18,19,45–53] The HACA trial showed neurologic outcome and mortality benefit, even with a median time to target temperature of 8 hours, suggesting that delayed cooling can also be efficacious.[2,3]

Question

What adjunctive medications should be given to patients receiving therapeutic hypothermia?

- Patients undergoing therapeutic hypothermia should receive paralytic agents and sedation (Grade B).

Supporting evidence

Shivering increases tissue oxygen demand and inhibits cooling. Adequate sedation is, therefore, essential. The European trial (HACA)[2] used a combination of fentanyl and midazolam, and the Australian study[3] used midazolam alone for sedation. Propofol has also been used as a sedating agent, with the potential advantages of peripheral vasodilation (assisting cooling) and a short duration of action. But there is no reversal agent for propofol, potentially making it difficult to quantify residual drug effect on neurologic assessment. Some clinicians have suggested that sedation alone can prevent shivering; however both of the large trials[2,3] employed neuromuscular blockade with pancuronium or vecuronium. Sedation or paralysis should not be given until after the baseline neurologic examination.

Question

How should therapeutic hypothermia be induced?

- In patients who are sedated and paralyzed, therapeutic hypothermia can be attained using ice packs to the groin, axillae and neck. (Grade A) Helpful adjuncts include cold saline boluses, cooling blankets, and fan and mist. (Grade C)

Supporting evidence

The optimal method of inducing hypothermia is unclear. Various methods of cooling have been described, from external to invasive and local (cerebral) to systemic. Two influential studies used an external cooling method in which ice packs were applied to the patient's head, neck, axillae and groin.[2,3] Ice packs reduced core temperature by 0.3°–0.9°C/h. In one study, cooling was initially attempted with a specialized cooling bed,[2] but ice packs were required for adequate cooling in 70% of those patients.

Bernard and colleagues[54] administered 30 mL/kg of cold (4°C) intravenous lactated Ringers solution to 22 comatose out-of-hospital cardiac arrest survivors and reported that core temperature fell by 1.6°C over 30 minutes (3.2°C/h). There was no evidence of adverse events (e.g., pulmonary edema), but the sample size was too small to make any conclusions about safety. In a unique study, Hachimi-Idrissi and coauthors[34] reported that a cooling helmet containing 4°C aqueous glycerol reduced body temperature by 0.6°C/h.

Other methods of cooling have been studied, but not prospectively; nor in cardiac arrest patients. These alternative methods include ice-cold pleural, gastric, peritoneal or bladder lavage, intravascular cooling devises, fan and mist, cool partial liquid ventilation, and extracorporeal heat exchange.

Question

How should temperature be monitored in patients undergoing therapeutic hypothermia?

- Patients undergoing therapeutic hypothermia should

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have their core temperature continuously or frequently monitored. Bladder, esophageal, rectal or pulmonary artery temperatures are acceptable, but tympanic membrane temperatures should be avoided. The device must be designed to measure temperatures in the hypothermic range. (Grade D)

Supporting evidence

During cooling it is important to have at least one site available to monitor core temperature. Current options include esophageal, bladder, rectal or pulmonary artery temperature. Although tympanic temperatures are considered core, they are inaccurate and therefore discouraged.[55–57] Not all thermometers are designed to provide accurate temperatures in the hypothermic range.

Question

Should patients who qualify for therapeutic hypothermia be cooled in community hospitals, or should they first be transferred to referral centres?

- Community hospitals should consider cooling eligible patients before tertiary care transfer. Temperature monitoring should continue during transport. (Grade D)

Supporting evidence

There is no published research looking at what types of centres should induce therapeutic hypothermia but the process is relatively simple, it is feasible in any ED setting, and it is currently being performed in centres of all sizes across Canada. The CAEP Critical Care Committee has published a useful algorithm[58] that can be modified for use in any centre. For patients who do require transfer, transfer protocols are best arranged with the referral centre well in advance, and for patients requiring transfer for percutaneous coronary intervention, priorities should be discussed with the accepting cardiologist. If transport time is significant, core temperature should be monitored throughout.

Question

For patients with ST elevation myocardial infarction (STEMI), what is the reperfusion strategy of choice?

- When readily available, percutaneous coronary intervention (PCI) is the treatment of choice for ST segment elevation myocardial infarction in hypothermic patients. (Grade D)
- Thrombolysis may be used in hypothermic patients with STEMI, but there are theoretical reasons why the effectiveness of some thrombolytics may be reduced in hypothermic patients. (Grade D)
- Mild therapeutic hypothermia should not be delayed for either PCI or thrombolytic therapy and should be initiated concurrently when indicated. (Grade D)

Supporting evidence

A joint task force of the American College of Cardiology and American Heart Association has published guidelines on the management of patients with STEMI.[59] In the absence of contraindications, patients who present within 3 hours of symptom onset should receive fibrinolytic therapy if the difference between expected door-to-balloon time and door-to-needle time is longer than 60 minutes. If the difference is less than 60 minutes, they should receive PCI. For patients presenting later than 3 hours after symptom onset, a time difference of 90 minutes is recommended.

Neither PCI nor thrombolysis has been specifically studied in patients undergoing therapeutic hypothermia, but there are theoretical reasons why thrombolytic therapy might be contraindicated. Plasminogen activators may have decreased activity at lower temperatures, and hypothermia-induced coagulopathy may increase bleeding risk. Thrombolysis was not contraindicated in either of the multicentre hypothermia trials. Almost 20% of patients enrolled in the HACA trial[2] received thrombolytic therapy, but the proportion of patients undergoing PCI or thrombolysis was much smaller in the Australian trial,[3] and the overall number of patients receiving thrombolysis and hypothermia is too small to permit subgroup analysis or meaningful statistical comparison.

Our opinion is that, in most cases, there is no reason that therapeutic hypothermia cannot be performed simultaneously with whichever reperfusion strategy is appropriate. When simultaneous therapy is not possible, it may be necessary to prioritize based on the expected neurologic and mortality benefits of hypothermia and the cardiovascular and mortality benefits of reperfusion therapy. This should be a multidisciplinary decision involving the consulting cardiologist and critical care physician.

Competing interests: None declared.

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