

# **Canadian Association of Emergency Physicians**

## **Position Statement and Guidelines For the use of Hypothermia after cardiac arrest**

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## Statement of Position

Patients who present with non-perfusing ventricular tachycardia or ventricular fibrillation, are resuscitated to hemodynamic stability, and remain unresponsive should undergo therapeutic hypothermia. These patients should be cooled to a core temperature of 32-34°C for the purpose of neuroprotection. Cooling should begin as soon as the clinical situation allows.

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## Summary of Recommendations

### **Primary recommendations – the use of therapeutic hypothermia (32-34°C) after cardiac arrest.**

- 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)

### **Secondary Recommendations – the practical application of therapeutic hypothermia**

- Therapeutic hypothermia should be initiated as soon as possible (Grade A).
- Patients who are successfully cooled within eight or more hours of return of spontaneous circulation may still derive benefit from this therapy. (Grade B)
- Patients undergoing therapeutic hypothermia should be given paralytic agents and sedation (Grade B).

- **In a patient who is sedated and paralyzed, therapeutic hypothermia can be attained using ice packs to the groin, axillae, and neck. (Grade A) Potentially helpful adjuncts include cooling helmets, cooling blankets, fan and mist, and cooled saline boluses. (Grade C)**
- **Patients undergoing therapeutic hypothermia should have their core temperature continuously or frequently monitored. Bladder, esophageal, rectal and 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)**
- **For patients presenting to community hospitals, cooling should be considered prior to transfer to a tertiary care center. Temperature monitoring should continue during transport. (Grade D)**
- **When readily available, PCI (Percutaneous Coronary Intervention) is the treatment of choice for STEMI (ST segment Elevation Myocardial Infarction) in the hypothermic patient. (Grade D)**
- **Thrombolysis may be used in the hypothermic patient with STEMI. 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)**

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## **Introduction:**

In April of 2004 the Canadian Association of Emergency Physicians (CAEP) Critical Care Committee undertook as one of its goals a review of the literature with the purpose of examining the evidence for therapeutic hypothermia after cardiac arrest and making recommendations on its use in the emergency department.

The primary review committee (PRC) was made-up of five members of the CAEP Critical Care Committee. All five members signed statements that confirmed that they had no potential or perceived conflict-of-interest. The PRC began by developing a set of questions to be addressed by the position statement, with the goal of addressing both the indications and the practical application of therapeutic hypothermia. The definitions used by the PRC are found in Table I.

A literature search for the terms “hypothermia” and “cardiac arrest” was made in Medline and EMBASE from 1996 to September 2004, the results were reviewed, and 79 relevant articles were identified. These results, along with copies of the major articles were circulated to the PRC. The PRC developed a series of statements in response to the questions, based on the circulated material and more specific literature reviews. 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 II. The statements were collated along with summary background materials in to a draft position statement.

The draft was circulated to 20 physicians representing emergency physicians, cardiologists, neurologists, intensivists, anesthesiologists, community and tertiary care physicians from across Canada for critical review. Eighteen 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 of it in July 2005. On August 29, 2005 the CAEP executive adopted the statement.

This document will review the mechanism for therapeutic hypothermia, briefly summarize the literature and outline the rationale for the position statement and guidelines.

### **Mechanism Of Action Of Therapeutic Hypothermia:**

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

Cardiac arrest immediately decreases cerebral blood flow despite ongoing consumption of oxygen, ATP 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 and cerebral edema worsens; 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 from two studies[2, 3] published in 2002.

The Hypothermia after Cardiac Arrest (HACA)[2] study was a multi-centre, randomized, controlled trial conducted in nine centers in five 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 unable to respond 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. This was maintained for 24 hours. The investigators assessed neurologic outcome at 6 months with a standard neurological assessment tool (Pittsburgh Cerebral Performance Score). They measured mortality in hospital and within 6 months, and complications within 7 days of cooling. In total 275 patients were enrolled with 136 randomized to therapeutic hypothermia. Patients randomized to mild hypothermia had an absolute risk reduction (ARR) for poor neurological outcome of 16%, a risk ratio of 1.40 (95% confidence interval 1.08-1.81). Mortality also was significantly reduced with an ARR of 14%, a risk ratio of 0.74 (95% confidence interval 0.58-0.95). There was no statistically significant difference in the incidence of complications in the groups, but there was a trend towards increased bleeding and infection in the hypothermic group.

The Bernard study[3] was an Australian multi-centre, quazi-randomized, controlled trial published concurrently with the HACA study. The 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, cooling was initiated in the field. Paramedics applied cold packs with the goal of reducing the core temperature to 33° C within two hours and to maintain it for 12 hours. The control group was treated with standard resuscitation measures. Outcomes assessed included neurological outcome at discharge, survival to discharge, and in-hospital complications. Patients randomized to hypothermia had an ARR of 23% for poor neurological outcome. Mortality was reduced by 17%, but the study lacked sufficient power to demonstrate statistical significance, with a p-value of 0.145. The primary outcome, survival to hospital discharge with sufficient neurologic function to be discharged home or to a rehabilitation facility, had an adjusted odds ratio of 5.25 (95% confidence interval 1.47-18.76) for good outcome in the hypothermic group.

Hachimi-Idrissi[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. Hypothermia was induced using a cooling helmet, with a goal of 34 °C within 4 hours. Once the 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 four hours, in hospital mortality, and associated complications. Overall, only four patients survived, three of the sixteen randomized to mild hypothermia, and one of the fourteen treated with standard normothermic care. In the three surviving patients randomized to the hypothermia group, two had an overall performance category (OPC) of 1 (good recovery) and one had an OPC of 3 (severe disability). The one surviving normothermia patient had an OPC of 3.

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

***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)**

**Background:**

The studies that best address these questions are the two large randomized trials published in the New England Journal of Medicine in 2002[2, 3]. Both included patients who had a cardiac arrest due to ventricular fibrillation or ventricular tachycardia (VF/VT), and both cooled patients to the 32-34°C range. The results of both studies indicated that this cohort of cardiac arrest survivors benefits from induced hypothermia. Other patient categories are more problematic, as there are no randomized trials to guide decision-making.

Adults who present in cardiac arrest with rhythms other than VF/VT have been included in pilot studies assessing the validity of induced hypothermia[34, 36, 37] These studies were small, and while they did not show any harm and perhaps some benefit, the low number of enrolled subjects made subgroup analysis impossible. The purpose of therapeutic hypothermia is to ameliorate the anoxic brain injury, not to treat the primary problem. It seems reasonable that patients presenting with other rhythms could benefit from this treatment.

Some patients present in asystole or pulseless electrical activity for non-cardiac reasons such as subarachnoid hemorrhage or trauma, primary insults for which the coagulopathy of hypothermia could be harmful. It is also possible that these rhythms represent patients

who have progressed farther in their anoxic injury. The effect of hypothermia on this subgroup hasn't been evaluated and could show an increase in patients surviving with poor neurological outcomes. An early CT scan of the head should be considered to rule out intracranial bleeding if therapeutic hypothermia is to be used in these patients.

Data in the pediatric population is lacking. There have been early studies using hypothermia post arrest showing negative outcome[38], but these used longer duration of cooling and cooler temperatures. As the underlying pathophysiology of the anoxic injury is similar to that of adults, children would likely benefit if they otherwise met the inclusion criteria. This is an extrapolation based on the pathophysiology of anoxic brain injury.

Pregnant women form another group where there is no literature to define clinical safety with respect to the fetus. This group was excluded from the large trials, and has not been looked at in smaller studies. From a maternal perspective, the anoxic injury is the same and would be expected to respond to therapeutic hypothermia. However, the effect of hypothermia on the fetus is unknown. There are mixed results from the cardiac surgery literature, suggesting potential harm to the fetus during hypothermia with cardiopulmonary bypass[39, 40]. The duration and depth of hypothermia are much different, making it difficult to know how much of this data can be extrapolated. Until further data is available treatment of these patients should be individualized.

**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 eight or more hours of return of spontaneous circulation may still derive benefit from this therapy. (Grade B)

**Background:**

A number of trials have demonstrated that hypothermia prior to or during ischemic events provides neuroprotection[7, 19, 41-44]. In clinical situations, physicians rarely have the opportunity to cool patients until after the ischemic insult. The available evidence supports cooling patients as soon as possible post-ischemia [19, 32, 44-49], perhaps starting in the pre-hospital setting.[50] Delayed cooling can also be efficacious [11, 19, 46-48, 51-58] ;the HACA trial [2, 59] had a median time to target temperature of 8 hours and still demonstrated mortality and neurological outcome benefits.

To date, there are no randomized controlled trials that compare different timing strategies.

***Question: What medications should be given to patients receiving therapeutic hypothermia to assist in the cooling process?***

- **Patients undergoing therapeutic hypothermia should be given paralytic agents and sedation (Grade B).**

**Background:**

Shivering during cooling increases tissue oxygen demand and makes cooling more difficult. Anecdotally some clinicians have suggested that adequate sedation alone prevents shivering, however both of the large trials[2, 3] employed neuromuscular blockade with pancuronium or vecuronium.

Adequate sedation is essential for patients undergoing therapeutic hypothermia. The European trial[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. The disadvantage is that there is no reversal agent, potentially making it difficult to quantify residual drug effect on neurological assessment.

Sedation or paralysis should not be given until after the baseline neurological examination.

**Question: How should therapeutic hypothermia be induced?**

- **In a patient who is 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)**

**Background**

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 groins[2, 3]. 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. Cooling with ice packs reduced core temperature by 0.3-0.9°C/hr.

Hachimi-Idrissi *et al.*[34] investigated the feasibility of a cooling helmet that contained 4°C aqueous glycerol. In this study patients were cooled at a rate of 0.6°C/hr.

Bernard *et al.*[60] reported the use of cold intravenous fluid (IV) administration as an option for inducing hypothermia in cardiac arrest survivors. The authors administered 30 ml/kg of 4°C lactated ringers to 22 comatose patients after out-of-hospital cardiac arrest and found a decrease of core temperature by 1.6°C over 30 minutes (3.2°C/hr). There was no evidence of increased adverse events (pulmonary edema), but the sample size limits the power of this finding.

Other invasive methods of cooling have been described, but not prospectively or in cardiac arrest patients. Ice-cold lavage (pleural, gastric, peritoneal and bladder), intravascular cooling devices, fan and mist, cool partial liquid ventilation and extracorporeal heat exchange have all been reported.

***Question: How should temperature be monitored for patients undergoing therapeutic hypothermia?***

- **Patients undergoing therapeutic hypothermia should have their core temperature continuously or frequently monitored. Bladder, esophageal, rectal and 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)**

**Background**

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. Tympanic temperature is considered core, but is inaccurate and therefore discouraged[61-63]. It should be noted that not all thermometers are designed to be accurate at hypothermic temperatures.

***Question: For patients who otherwise qualify for therapeutic hypothermia and present to a community hospital, should transfer be initiated first, or can they be cooled in these centers?***

- **For patients presenting to community hospitals, cooling should be considered prior to transfer to a tertiary care center. Temperature monitoring should continue during transport. (Grade D)**

### **Background**

Inducing hypothermia in patients who survive cardiac arrest is not complicated, and is well within the skill set of any emergency department treatment team regardless of location. An algorithm published by Green and Howes for the CAEP critical care committee[64] can be modified for use in any center . Transfer protocols are best arranged with the referral center well in advance.

For patients requiring transfer for percutaneous coronary intervention, priorities should be discussed with the accepting cardiologist. If transport time will be of significant duration, core temperature should be monitored throughout.

There are no scientific papers looking at who can effectively cool a patient and in what clinical setting, but it is currently being performed in centers of all sizes across Canada.

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

- **When readily available, PCI (Percutaneous Coronary Intervention) is the treatment of choice for STEMI (ST segment Elevation Myocardial Infarction) in the hypothermic patient. (Grade D)**
- **Thrombolysis may be used in the hypothermic patient with STEMI. 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)**

#### **Background:**

A joint task force of the American College of Cardiology and American Heart Association has published guidelines on the management of patients with STEMI[65]. In the absence of contraindications, patients who present within three 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 fewer than 60 minutes, they should receive PCI. For patients presenting later than three hours after the onset of symptoms, a time difference of 90 minutes is recommended.

Neither PCI nor thrombolytic therapy has been specifically trialed in patients treated with therapeutic hypothermia. There are theoretical reasons why thrombolytic therapy might be contraindicated. Medications relying on plasminogen activity may have decreased activity at lower temperatures, and the coagulopathy that accompanies hypothermia can increase the risk of bleeding.

The use of therapeutic hypothermia was not a contraindication to thrombolysis in either of the multicenter trials. The European trial used thrombolytic therapy in just under 20% of its patients, but the proportion of patients undergoing either PCI or thrombolytic therapy was much smaller in the Australian trial. Data was not presented specifically for these subgroups, as the numbers of patients would have been too small to make any meaningful statistical comparisons.

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

## References

1. Phillips, B., et al., *Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)*. 2001.
2. Holzer, M., et al., *Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest*. New England Journal of Medicine. Vol. 346(8)(pp 549-556), 2002. Date of Publication: 21 FEB 2002.
3. Bernard, S.A., et al., *Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.[see comment]*. New England Journal of Medicine, 2002. **346**(8): p. 557-63.
4. Bart, R.D., et al., *Interactions between hypothermia and the latency to ischemic depolarization: implications for neuroprotection*. Anesthesiology, 1998. **88**(5): p. 1266-73.
5. Jenkins, L.W., et al., *Intraischemic mild hypothermia increases hippocampal CA1 blood flow during forebrain ischemia*. Brain Research, 2001. **890**(1): p. 1-10.
6. Safar, P., et al., *Systematic development of cerebral resuscitation after cardiac arrest. Three promising treatments: cardiopulmonary bypass, hypertensive hemodilution, and mild hypothermia*. Acta Neurochirurgica - Supplementum, 1993. **57**: p. 110-21.
7. Olsen, T.S., U.J. Weber, and L.P. Kammersgaard, *Therapeutic hypothermia for acute stroke*. Lancet Neurology, 2003. **2**: p. 410-16.
8. Auer, R.N., *Non-pharmacologic (physiologic) neuroprotection in the treatment of brain ischemia*. Annals of the New York Academy of Sciences, 2001. **939**: p. 271-282.
9. Gunn, A.J., *Cerebral hypothermia for prevention of brain injury following perinatal asphyxia*. Current Opinion in Pediatrics, 2000. **12**(2): p. 111-5.
10. Hammer, M.D. and D.W. Krieger, *Hypothermia for acute ischemic stroke: not just another neuroprotectant*. Neurologist, 2003. **9**(6): p. 280-9.
11. Sterz, F., et al., *Mild resuscitative hypothermia and outcome after cardiopulmonary resuscitation*. Journal of Neurosurgical Anesthesiology, 1996. **8**(1): p. 88-96.
12. Sakoh, M. and A. Gjedde, *Neuroprotection in hypothermia linked to redistribution of oxygen in brain*. American Journal of Physiology - Heart & Circulatory Physiology, 2003. **285**(1): p. H17-25.

13. Laptook, A.R., et al., *Neonatal ischemic neuroprotection by modest hypothermia is associated with attenuated brain acidosis*. Stroke, 1995. **26**(7): p. 1240-6.
14. Laptook, A.R., et al., *Quantitative relationship between brain temperature and energy utilization rate measured in vivo using 31P and 1H magnetic resonance spectroscopy*. Pediatric Research, 1995. **38**(6): p. 919-25.
15. Quinones-Hinojosa, A., et al., *Metabolic effects of hypothermia and its neuroprotective effects on the recovery of metabolic and electrophysiological function in the ischemic retina in vitro*. Neurosurgery, 2003. **52**(5): p. 1178-86.
16. Williams, G.D., et al., *Modest hypothermia preserves cerebral energy metabolism during hypoxia-ischemia and correlates with brain damage: a 31P nuclear magnetic resonance study in unanesthetized neonatal rats*. Pediatric Research, 1997. **42**(5): p. 700-8.
17. Gupta, A.K., et al., *Effect of hypothermia on brain tissue oxygenation in patients with severe head injury*. British Journal of Anaesthesia, 2002. **88**(2): p. 188-92.
18. Gunn, A.J. and T.R. Gunn, *The 'pharmacology' of neuronal rescue with cerebral hypothermia*. Early Human Development, 1998. **53**(1): p. 19-35.
19. Colbourne, F., G. Sutherland, and D. Corbett, *Postischemic hypothermia. A critical appraisal with implications for clinical treatment*. Molecular Neurobiology, 1997. **14**(3): p. 171-201.
20. Bacher, A., J.Y. Kwon, and M.H. Zornow, *Effects of temperature on cerebral tissue oxygen tension, carbon dioxide tension, and pH during transient global ischemia in rabbits*. Anesthesiology, 1998. **88**(2): p. 403-409.
21. Nakashima, K., M.M. Todd, and D.S. Warner, *The relation between cerebral metabolic rate and ischemic depolarization: a comparison of the effects of hypothermia, pentobarbital, and isoflurane*. Anesthesiology, 1995. **82**(5): p. 1199-208.
22. Zeevalk, G.D. and W.J. Nicklas, *Hypothermia and metabolic stress: narrowing the cellular site of early neuroprotection*. Journal of Pharmacology & Experimental Therapeutics, 1996. **279**(1): p. 332-9.
23. Thoresen, M., et al., *Post-hypoxic hypothermia reduces cerebrocortical release of NO and excitotoxins*. Neuroreport, 1997. **8**(15): p. 3359-62.
24. Fujisawa, H., et al., *Effects of mild hypothermia on the cortical release of excitatory amino acids and nitric oxide synthesis following hypoxia*. Journal of Neurotrauma, 1999. **16**(11): p. 1083-93.
25. Nakane, M., et al., *Rewarming eliminates the protective effect of cooling against delayed neuronal death*. Neuroreport, 2001. **12**(11): p. 2439-42.

26. Tymianski, M., et al., *Characterization of neuroprotection from excitotoxicity by moderate and profound hypothermia in cultured cortical neurons unmasks a temperature-insensitive component of glutamate neurotoxicity*. Journal of Cerebral Blood Flow & Metabolism, 1998. **18**(8): p. 848-67.
27. Kvrivishvili, G., *Glycine and neuroprotective effect of hypothermia in hypoxic-ischemic brain damage*. Neuroreport, 2002. **13**(16): p. 1995-2000.
28. Zornow, M.H., *Inhibition of glutamate release: a possible mechanism of hypothermic neuroprotection*. Journal of Neurosurgical Anesthesiology, 1995. **7**(2): p. 148-51.
29. Marion, D.W., et al., *Resuscitative hypothermia*. Critical Care Medicine, 1996. **24**(2S): p. 81S-89S.
30. Caputa, M., J. Rogalska, and A. Nowakowska, *Effect of temperature on postanoxic, potentially neurotoxic changes of plasma pH and free iron level in newborn rats*. Brain Research Bulletin, 2001. **55**(2): p. 281-6.
31. Safar, P., et al., *Cerebral resuscitation potentials for cardiac arrest*. Critical Care Medicine, 2002. **30**(4 Suppl): p. S140-4.
32. Tisherman, S.A., A. Rodriguez, and P. Safar, *Therapeutic hypothermia in traumatology*. Surgical Clinics of North America, 1999. **79**(6): p. 1269-89.
33. Ginsberg, M.D., *Adventures in the pathophysiology of brain ischemia: penumbra, gene expression, neuroprotection: the 2002 Thomas Willis Lecture*. Stroke, 2003. **34**(1): p. 214-23.
34. Hachimi-Idrissi, S., et al., *Mild hypothermia induced by a helmet device: a clinical feasibility study*. Resuscitation, 2001. **51**(3): p. 275-81.
35. Mori, K., et al., *A multivariate analysis of prognostic factors in survivors of out-of-hospital cardiac arrest with brain hypothermia therapy. (abst.)*. Critical Care Medicine, 2000. **28**(12(suppl.)): p. A168.
36. Bernard, S.A., B.M. Jones, and M.K. Horne, *Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest*. Annals of Emergency Medicine, 1997. **30**(2): p. 146-53.
37. Yanagawa, Y., S. Ishihara, and e. al., *Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest*. Resuscitation, 1998. **39**: p. 61-66.
38. Bohn DJ, et al., *Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity after near-drowning*. Critical Care Medicine, 1986. **14**: p. 529-534.

39. Pomini F, Mercogliano D, and e. al., *Cardiopulmonary bypass in pregnancy*. Annals of Thoracic Surgery, 1996. **61**(1): p. 259-268.
40. Buffolo E, Palma JH, and e. al., *Successful use of deep hypothermic circulatory cardiopulmonary arrest in pregnancy*. Annals of Thoracic Surgery, 1994. **58**(5): p. 1532-1534.
41. Laptook, A., et al., *Modest hypothermia provides partial neuroprotection for ischemic neonatal brain*. Pediatric Research, 1994. **35**(4 Pt 1): p. 436-42.
42. Xiao, F., P. Safar, and A. Radovsky, *Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats*. American Journal of Emergency Medicine, 1998. **16**(1): p. 17-25.
43. Jenkins, L., et al., *Intraischemic mild hypothermia increases hippocampal CA1 blood flow during forebrain ischemia*. Brain Research, 2001. **890**(1): p. 1-10.
44. Hammer, M. and D. Krieger, *Hypothermia for acute ischemic stroke: not just another neuroprotectant*. Neurologist, 2003. **9**(6): p. 280-9.
45. Kuboyama, K., et al., *Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study*. Critical Care Medicine, 1993. **21**(9): p. 1348-58.
46. Auer, R., *Non-pharmacologic (physiologic) neuroprotection in the treatment of brain ischemia*. Annals of the New York Academy of Sciences, 2001. **939**: p. 271-282.
47. Gunn, A., *Cerebral hypothermia for prevention of brain injury following perinatal asphyxia*. Current Opinion in Pediatrics, 2000. **12**(2): p. 111-5.
48. Gunn, A. and T. Gunn, *The 'pharmacology' of neuronal rescue with cerebral hypothermia*. Early Human Development, 1998. **53**(1): p. 19-35.
49. Al-Senani, F.M. and J.C. Grotta, *Neuroprotection after cardiac arrest*. Lancet Neurology. Vol. 1(3)(pp 146), 2002. Date of Publication: 01 MAR 2002.
50. Virkkunen, I., A. Yli-Hankala, and T. Silfvast, *Induction of therapeutic hypothermia after cardiac arrest in*. Resuscitation, 2004. **62**(3): p. 299-302.
51. Colbourne, F., et al., *Hypothermia rescues hippocampal CA1 neurons and attenuates down-regulation of the AMPA receptor GluR2 subunit after forebrain ischemia*. Proceedings of the National Academy of Sciences of the United States of America, 2003. **100**(5): p. 2906-10.
52. Corbett, D., S. Nurse, and F. Colbourne, *Hypothermic neuroprotection. A global ischemia study using 18- to 20-month-old gerbils*. Stroke, 1997. **28**(11): p. 2238-42.

53. Garnier, Y., et al., *Effects of mild hypothermia on metabolic disturbances in fetal hippocampal slices after oxygen/glucose deprivation depend on depth and time delay of cooling.* Journal of the Society of Gynecologic Investigation, 2001. **8**(4): p. 198-205.
54. Wagner, B.P., J. Nedelcu, and E. Martin, *Delayed postischemic hypothermia improves long-term behavioral outcome after cerebral hypoxia-ischemia in neonatal rats.* Pediatric Research, 2002. **51**(3): p. 354-60.
55. Taylor, D.L., et al., *Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat.* Pediatric Research, 2002. **51**(1): p. 13-9.
56. Colbourne, F., H. Li, and A. Buchan, *Indefatigable CAI sector neuroprotection with mild hypothermia induced 6 hours after severe forebrain ischemia in rats.* Journal of Cerebral Blood Flow & Metabolism, 1999. **19**(7): p. 742-9.
57. Gunn, A., et al., *Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep.* Pediatrics, 1998. **102**(5): p. 1098-106.
58. Nolan, J.P., et al., *Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison committee on Resuscitation.* Resuscitation, 2003. **57**(3): p. 231-5.
59. Bernard, S., et al., *Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.* New England Journal of Medicine, 2002. **346**(8): p. 557-63.
60. Bernard, S., et al., *Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report.* Resuscitation, 2003. **56**(1): p. 9-13.
61. Giuliano K, Guiliano A, and e. al., *Temperature measurement in critically ill adults: a comparison of tympanic and oral methods.* American Journal of Critical Care, 2000. **9**(4): p. 254-261.
62. Amoateng-Adjepong Y and e. al, *Accuracy of an infrared tympanic thermometer.* Chest, 1999. **115**(4): p. 1002-1005.
63. Fisk J and A. S., *Tympanic membrane vs pulmonary artery thermometry.* Nursing Management, 2001. **32**(6): p. 45-48.
64. Green, R.H., D, *Hypothermic modulation of brain injury in adult survivors of cardiac arrest: a review of the literature and an algorithm for emergency physicians.* Canadian Journal of Emergency Medicine, 2005. **7**(1): p. 41-7.
65. Antman, E., et al., *ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction.* 2004.

Table I -

**Definitions - For the purpose of this position statement the committee adopted the following definitions:**

**Unresponsive:** Patients with a GCS<10 or who are not following 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 II – **Levels of Evidence** – Based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)[1]. An abbreviated summary is shown here. CI – confidence interval, RCT – Randomized controlled trial, SR – Systematic review.

Level	Research
<b>1a</b>	SR with homogeneity of RCT's
<b>1b</b>	Individual RCT with narrow CI
<b>1c</b>	All or none
<b>2a</b>	SR with homogeneity of cohort studies
<b>2b</b>	Individual cohort study or low quality RCT
<b>2c</b>	Outcomes research, ecological studies
<b>3a</b>	SR with homogeneity of case-control studies
<b>3b</b>	Individual case-control Study
<b>4</b>	Case series, poor quality cohort and case-control
<b>5</b>	Expert opinion based on physiology or bench research

Grades of Recommendation	
<b>A</b>	Consistent level 1 studies
<b>B</b>	Consistent level 2 or 3 studies, extrapolations from level 1 studies
<b>C</b>	Level 4 studies or extrapolations from level 2 or 3 studies
<b>D</b>	Level 5 evidence or troublingly inconsistent studies of any level.