Hypothermic modulation of anoxic brain injury in adult survivors of cardiac arrest: a review of the literature and an algorithm for emergency physicians

Robert S. Green, BSc, MD, DABEM,* Daniel Howes, MD;† on behalf of the CAEP Critical Care Committee

ABSTRACT
Anoxic brain injury is a common outcome after cardiac arrest. Despite substantial research into the pathophysiology and management of this injury, a beneficial treatment modality has not been previously identified. Recent studies show that induced hypothermia reduces mortality and improves neurological outcomes in patients resuscitated from ventricular fibrillation. This article reviews the literature on induced hypothermia for anoxic brain injury and summarizes a treatment algorithm proposed by the Canadian Association of Emergency Physicians Critical Care Committee for hypothermia induction in cardiac arrest survivors.

Key words: cardiac arrest; hypothermia, induced; anoxic brain injury; hypothermia algorithm, induced

RÉSUMÉ
La lésion cérébrale anoxique est fréquente après un arrêt cardiaque. Malgré des recherches importantes quant à la physiopathologie et à la prise en charge de cette lésion, aucune modalité de traitement bénéfique n’a encore été identifiée. Des études récentes démontrent que l’hypothermie provoquée réduit le taux de mortalité et améliore le statut neurologique des patients ayant survécu à une fibrillation ventriculaire. Le présent article fait une revue de la littérature concernant l’hypothermie provoquée pour les lésions cérébrales anoxiques et résume un algorithme de traitement proposé par le Comité des soins critiques de l’Association canadienne des médecins d’urgence pour la provocation de l’hypothermie chez les personnes ayant survécu à un arrêt cardiaque.

Introduction
Canadian data show that overall survival after pre-hospital cardiac arrest is less than 5%,1 ranging from <1% with asystole or pulseless electrical activity, to as high as 33% with ventricular fibrillation (VF) or tachycardia (VT).2 Early aggressive resuscitation increases the chance of survival, but even brief periods of hypoxia can compromise neurons in the central nervous system.2 Consequently, anoxic brain injury (ABI) is common: 40% of cardiac arrest survivors never regain consciousness, and one-third of those who do suffer irreversible cognitive deficits.3

Despite extensive research into ABI pathogenesis and treatment, no specific therapies have been shown to reduce morbidity and mortality;4 however, recent studies have demonstrated that mild hypothermia can significantly improve neurological outcomes,4,5 and hypothermic modulation of ABI (HMABI) is now recommended as standard care for a subset of patients who are successfully resuscitated from cardiac arrest.6,7


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Submitted: June 21, 2004; final submission: Dec. 5, 2004; accepted: Dec. 8, 2004
This article has been peer reviewed.

https://doi.org/10.1017/S1481803500012926
https://www.cambridge.org/core
This paper reviews the pathophysiology of ABI and the relevant literature describing induced mild hypothermia after cardiac arrest. In addition, we propose an algorithm based on recent clinical trials and the expert opinion of the Canadian Association of Emergency Physicians (CAEP) Critical Care Committee for the use of HMABI in cardiac arrest survivors.

Pathophysiology of anoxic brain injury and rationale for hypothermic modulation

Cardiac arrest causes an immediate cessation of blood flow, leading to a rapid depletion of cerebral oxygen and adenosine triphosphate stores, and depressed cerebral function. Damage to neurons in the central nervous system occurs during cardiac arrest (Phase I, “No Flow”) and following the return of spontaneous circulation (Phase II, “Low Flow”). The viability of neurons differs, depending on the type, location and duration of global anoxia. In general, neurons in the cerebral cortex, hippocampus and basal ganglia are the most vulnerable.

Following return of spontaneous circulation, cerebral blood flow initially achieves supranormal levels but falls to below normal over several hours. Endothelin release causes cerebral vasospasm and reduces cerebral perfusion pressure. Leukocyte clumping and microvascular coagulation further compromise cerebral blood flow. In the face of increasing cerebral oxygen requirements, this low-flow phase often leads to a secondary period of ischemia.

Inflammatory responses that begin during resuscitation are sustained following return of spontaneous circulation. The release of excitatory neurotransmitter amino acids (e.g., glutamate) and matrix metalloproteinases, N-methyl-D-aspartate (NMDA) receptor activation, and increased microvascular permeability results in calcium influx that leads to cerebral edema, raised intracranial pressure and brainstem herniation. Additional contributing factors in ABI include free radical formation, autodigestion by activated proteases, and apoptosis. Unfortunately, therapies directed at reducing intracellular edema, including NMDA receptor antagonists, mannitol, albumin and hypertonic saline, have not proven beneficial.

Evidence for hypothermic modulation of anoxic brain injury

In animal models, mild hypothermia mitigates post-ischemic hypoperfusion, stabilizes plasma membranes, suppresses free radical formation and reduces intracranial pressure. Hypothermia may also act by reducing cerebral metabolic rate and cerebral oxygen demand.

The human study of hypothermic modulation for ABI began in the 1950s, but the most compelling evidence comes from 2 recent prospective randomized controlled trials comparing standard advanced cardiac life support (ACLS) resuscitation to standard resuscitation plus mild hypothermia. These studies enrolled comatose patients resuscitated from VF or pulseless VT. Table 1 and Table 2 describe study eligibility criteria, and Table 3 shows that the study designs were similar. All patients received standard ACLS resuscitation and post-resuscitation care, all were sedated, paralyzed and ventilated, and those in the experimental group underwent induced hypothermia to 32°C–34°C within 6 hours of arrest. There were, however, key differences in the hypothermia protocols. In the Australian study, cooling began in the prehospital setting and continued for 12 hours, followed by active rewarming; in the European trial, cooling began in the emergency department (ED) and continued for 24 hours, with passive rewarming.

Table 3 shows that, in both studies, mild hypothermia significantly improved the primary endpoint: favourable neurological outcome, based on a functional outcome score at 6 months or the ability to be discharged home or to a rehabilitation facility (number needed to treat [NNT] = 4–6). Mortality was significantly decreased in the European study (absolute risk reduction = 14%; NNT = 7) but not in the smaller Australian trial. Neither study found significant adverse events associated with HMABI.

Both trials were well designed but not without limitations. The European trial was limited by a low enrollment rate: 3551 patients were screened, but only 275 were actually studied. Reasons for the high exclusion rate are not described, and similar enrollment data were not provided in the study design.

### Table 1. Inclusion criteria for 2 recent prospective RCTs comparing standard ACLS resuscitation to standard resuscitation plus mild hypothermia

<table>
<thead>
<tr>
<th>Variable</th>
<th>RCT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest rhythm</td>
<td>Variable</td>
</tr>
<tr>
<td>Age, yr</td>
<td>Cardiac arrest rhythm: VF or VT; Age: 18–75 yrs</td>
</tr>
<tr>
<td>Collapse to resuscitation, min</td>
<td>Age &gt;50 yr for women because of the possibility of pregnancy</td>
</tr>
<tr>
<td>Persistent coma</td>
<td>Persistent coma: Yes†</td>
</tr>
<tr>
<td>Persistent coma</td>
<td>Persistent coma: Yes†</td>
</tr>
</tbody>
</table>

**Variable**
- **Cardiac arrest rhythm**
- **Age**
- **Collapse to resuscitation, min**
- **Persistent coma**

**RCT** = randomized controlled trial; **ACLS** = advanced cardiac life support; **HACA** = Hypothermia after Cardiac Arrest Group; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia; **ROSC** = return of spontaneous circulation

† Persistent coma were not formal inclusion criteria but are implied by study design.
the Australian trial. Both trials were unblinded, and treating physicians knew which patients received hypothermia, raising the potential for treatment bias; however, importantly, neurologic outcome assessments were conducted in a blinded fashion.

These 2 important trials demonstrated significant improvements in neurologic outcome and possibly mortality; consequently the International Liaison Committee on Resuscitation (ILCOR) has recommended HMABI as the standard of care (Level 1 evidence) for resuscitated sur-

<table>
<thead>
<tr>
<th>Variable</th>
<th>HACA⁴</th>
<th>Bernard et al⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>&lt;30°C on emergency department admission</td>
<td>Not described</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Drug-related coma prior to arrest, Response to verbal command after ROSC</td>
<td>Not described</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Pregnancy</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Hymodynamic</td>
<td>Blood pressure &lt;60 mm Hg for &gt;30 min after ROSC</td>
<td>SBP &lt;90 mm Hg despite epinephrine infusion</td>
</tr>
<tr>
<td>Gas exchange</td>
<td>SaO₂ &lt;85% for &gt;15 min after ROSC</td>
<td>Not described</td>
</tr>
<tr>
<td>Other</td>
<td>Terminal illness, Cardiac arrest after arrival of EHS, Known pre-existing coagulopathy, Uncertain compliance with follow-up, Enrolment in other study</td>
<td>No intensive care unit bed available</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial; ACLS = advanced cardiac life support; HACA = Hypothermia after Cardiac Arrest Group; ROSC = return of spontaneous circulation; SBP = systolic blood pressure; SaO₂ = oxygen saturation (arterial); EHS = Emergency Health Services

<table>
<thead>
<tr>
<th>Variable</th>
<th>HACA⁴</th>
<th>Bernard et al⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>True</td>
<td>Alternate day</td>
</tr>
<tr>
<td>Study sample, no. of patients</td>
<td>Hypothermia 136</td>
<td>43</td>
</tr>
<tr>
<td>Hypothermia duration</td>
<td>24 h</td>
<td>12 h</td>
</tr>
<tr>
<td>Cooling method</td>
<td>Cooling blanket* ± ice packs</td>
<td>Ice packs (initiated prehospital)</td>
</tr>
<tr>
<td>Temperature goal</td>
<td>32°C–34°C</td>
<td>33°C</td>
</tr>
<tr>
<td>Rewarming method</td>
<td>Passive</td>
<td>Active</td>
</tr>
<tr>
<td>Morbidity assessment</td>
<td>PCP† score, category 1 or 2: ARR = 16%; NNT = 6</td>
<td>Discharge to home or rehab: ARR = 17%; NNT = 4</td>
</tr>
<tr>
<td>Six-month mortality</td>
<td>ARR = 14%; NNT = 7</td>
<td>ARR = 17% (p = 0.145)</td>
</tr>
<tr>
<td>Adverse events, % of patients (p value)</td>
<td>Sepsis: 13 v. 7 (NS)</td>
<td>Decreased cardiac index (&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia: 36 v. 32 (NS)</td>
<td>Increased SVR (&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td>Bleeding: 26 v. 19 (NS)</td>
<td>Hyperglycemia rate (&lt;0.05)</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial; ACLS = advanced cardiac life support; HACA = Hypothermia after Cardiac Arrest Group; ARR = absolute risk reduction; NNT = number needed to treat; NS = not significant; SVR = systemic vascular resistance

*Cooling blanket initially used, but 93 of 132 patients (70%) required the addition of ice packs.

†Pittsburgh Cerebral Performance score: 1 = Good recovery; 2 = Moderate disability; 3 = Severe disability; 4 = Vegetative state; 5 = death.

Adapted, with permission of the publisher, from Green RS. Saving the brain after cardiac arrest [Table 1]. Perspect Cardiol 2004;June/July:29-33.
vivors of out-of-hospital VF/VT cardiac arrest. The use of HMABI in non-VF/VT cardiac arrest is considered possibly beneficial.

A recent systematic review of HMABI after successful resuscitation identified 4 prospective randomized trials of induced hypothermia after cardiac arrest (1 was in abstract form only). These included 436 patients, with 231 cooled to a core temperature of 32°–34°C. Three of the studies provided mortality data, and poor neurologic outcome was defined by either discharge location or by objective cerebral performance testing. Pooled data showed that mild hypothermia improved in-hospital mortality (fixed effect relative risk [RR] = 0.75) and reduced the incidence of poor neurologic outcome (fixed effect RR = 0.74). Overall, NNT for 1 improved neurologic outcome was 5, and NNT to save 1 life was 7. Despite well-designed trials and expert consensus opinion, questions about this therapy remain unanswered, and further research is required.

**Practical considerations for instituting hypothermic modulation of anoxic brain injury**

Hypothermic modulation of anoxic brain injury is currently used in several Canadian centres. CAEP has no official position on this modality; however, the CAEP Critical Care Committee (C4) supports the ILCOR recommendations and has developed a treatment algorithm (Fig. 1) based on expert opinion, recent randomized controlled studies and current Canadian critical care practice to guide the appropriate use of HMABI.

**Pre-hospital care**

Pre-hospital personnel should initiate resuscitation utilizing standard ACLS guidelines. The benefit of HMABI may be increased if initiated immediately after cardiac arrest, therefore the C4 recommends that, as much as possible, pre-hospital personnel expose cardiac arrest patients to ambient air during resuscitation, recognizing the importance of maintaining patient privacy and dignity.

**Emergency department care**

The primary goal in all cardiac arrest victims is to maintain adequate gas exchange (O₂ saturation >98%) and stable hemodynamics (mean arterial pressure >75 mm Hg). Vasopressors should be utilized as needed to achieve these physiologic goals.

Following return of spontaneous circulation and stabilization, patients should be assessed for HMABI. Comatose survivors of VT or VF arrest with short arrest times are most likely to benefit. Figure 1 summarizes appropriate eligibility criteria. The use of HMABI may be beneficial in patients with a Glasgow Coma Scale score <10, however, it should not be used in patients with improving neurologic status, arrest secondary to non-cardiac factors (e.g., head injury, intracerebral space occupying lesion, toxic ingestion), persistent shock (>30 min) not responsive to vasopressor therapy, or in patients with a pre-existing terminal illness.

The use of HMABI has not been evaluated thoroughly in non-VF/VT survivors, although it is of theoretical benefit. The decision to initiate HMABI in these patients should be made in conjunction with the consulting service that will assume responsibility for ongoing patient care.

**Baseline neurological assessment**

Prognosis in patients who sustain ABI is determined by serial neurological exams. Emergency department physicians should document key neurological findings prior to the initiation of HMABI because assessment after cooling and paralysis is inaccurate (see Baseline Neurological Exam, Fig. 1).

**Sedation and paralysis**

Hypothermia is uncomfortable for patients and difficult to achieve in the presence of shivering; hence adequate sedation and paralysis is recommended prior to the implementation of HMABI. Repeated assessment of the adequacy of sedation and paralysis while in the ED is advised.

**Induction of mild hypothermia**

Hypothermia should be instituted as rapidly as possible in the post-arrest survivor; the objective is to reach a core temperature of 32°–34°C within 2–6 hours of cardiac arrest. The optimal method of inducing hypothermia is not clear, but in the ED, patient exposure and the application of ice packs to the head, axilla and groin may be the most practical method. The addition of small amounts of water to bagged ice may be of added benefit because it will increase the total contact area. A sheet should be placed between the bagged ice and the skin to prevent tissue damage. Other options include fan and mist techniques, cold saline infusions, invasive cooling catheters and cooling blankets. Poor response to initial cooling suggests the need to add and combine cooling techniques. Overcooling is potentially harmful and is best avoided by using continuous core temperature monitoring and by moderating cooling as the target temperature range approaches. Once the target temperature is attained, an external cooling blanket should be applied to maintain hypothermia.
Therapeutic Hypothermia for Survivors of Cardiac Arrest

A) Cardiac Arrest (pre-hospital and ED)
- Resuscitate as per ACLS guidelines
- Remove clothing: expose patient to ambient air while maintaining privacy and dignity
- Pre-hospital: notification and transfer to receiving ED

Is there return of spontaneous circulation?

- No
  - Continue ACLS
  - Search for reversible causes of cardiac arrest
  - Consider termination of resuscitation

- Yes
  - Eligible for hypothermia
  - Not eligible
    - Continue standard care

B) Survivor: Assess Eligibility for hypothermia

Inclusion Criteria
1. Primary cardiac arrhythmia*
2. Collapse to ACLS <15 min
3. Collapse to ROSC ≤ 60 min
4. Persistent coma (GCS <10)
5. Adult victim (>18)

Exclusion Criteria
1. Improving neurological status
2. Coma secondary to non-cardiac factors
3. Arrest secondary to non-cardiac factors
4. Persistent hypoxia: \(O_2\) sat <85% for >15 min
5. Hemodynamic instability despite vasopressors
   - SBP < 90 mm Hg for >30 min
   - MAP < 60 mm Hg for >30 min
6. Coagulopathy
7. History of terminal illness

* Best evidence of benefit is in survivors of VF/VT cardiac arrest. There is theoretical benefit in survivors of other primary cardiac arrest rhythms (non VF/VT rhythms) if they meet other eligibility criteria. The decision to initiate hypothermia in the non-VF/VT patient should be made in consultation with receiving ED or ICU.

C) Post-Arrest Care of the Cardiac Arrest Survivor (first 15 minutes)

- Stabilize cardio-respiratory system
- Goal MAP > 75 mm Hg (vasopressor use recommended if required)
- Goal oxygen saturation > 98%
- Baseline neurological exam (see I)
- Baseline vital signs and temperature
- Communicate induction of hypothermia with accepting ED/ICU
- Sedation and paralysis (see II)

D) Initiate Therapeutic Hypothermia

**Fig. 1. Algorithm for hypothermic modulation of anoxic brain injury. ED = emergency department; ACLS = advanced cardiac life support; ROSC = return of spontaneous circulation; GCS = Glasgow Coma Scale; SBP = systolic blood pressure; MAP = mean arterial pressure; VF = ventricular fibrillation; VT = ventricular tachycardia; ICU = intensive care unit; NS = normal saline solution**
Issues in the care of the hypothermic patient

Sepsis, hemodynamic instability and coagulopathy are the most common adverse effects of induced hypothermia, although these rarely occur at core temperatures of 32°–34°C or when hypothermia is maintained for less than 24 hours. Moderate to severe hypothermia (<32°C) may increase systemic vascular resistance and cause relative bradycardia, but the clinical significance of these effects is unknown. Ventricular fibrillation is a recognized risk of severe hypothermia (core temperature <28°C), but mild hypothermia may actually protect against ventricular fibrillation. Hypothermia has a variable effect on fluid and electrolyte balance, therefore patients undergoing HMABI require tight serum glucose control, close electrolyte monitoring, and the maintenance of optimal intravascular fluid status.

Induced hypothermia may modify the choice of reperfusion modality for patients with acute myocardial infarction. Although hypothermia is not a contraindication to thrombolysis, plasminogen activators may be less effective because of reduced enzyme activity at low temperature. Efficacy and complication rates have not been established in this population, so the management of cardiac arrest patients with acute myocardial infarction will depend on local resources and transport times.

Implementation into current practice

Hypothermic modulation of anoxic brain injury is a promising therapeutic modality, but implementation in the prehospital and emergency medicine realms will require collaboration between emergency medical services providers, emergency physicians and nurses, critical care services and various other medical services and specialties. Protocol development should proceed with local needs, skills and resources in mind. Ongoing education, quality monitoring and continuous outcome evaluation are important to ensure optimal care.

Acknowledgement: We acknowledge the contribution of Dr. David Easton in the development of the algorithm for hypothermic modulation of anoxic brain injury (Fig. 1).

Competing interests: None declared.

References


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