Therapeutic Hypothermia After Cardiac Arrest

An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation

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ILCOR Recommendations

On the basis of the published evidence to date, the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) made the following recommendations in October 2002:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Introduction

Induction of moderate hypothermia (28°C to 32°C) before cardiac arrest has been used successfully since the 1950s to protect the brain against the global ischemia that occurs during some open-heart surgeries. Successful use of therapeutic hypothermia after cardiac arrest in humans was also described in the late 1950s[1–3] but was subsequently abandoned because of uncertain benefit and difficulties with its use.[4] Since then, induction of hypothermia after return of spontaneous circulation (ROSC) has been associated with improved functional recovery and reduced cerebral histological deficits in various animal models of cardiac arrest.[5–8] Additional promising preliminary human studies have been completed.[9–16] At the time of publication of the *Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*, the evidence was insufficient to recommend use of therapeutic hypothermia after resuscitation from cardiac arrest.[17]

Clinical Studies

In 2002 the results of 2 prospective randomized trials were published that compared mild hypothermia with normothermia in comatose survivors of out-of-hospital cardiac arrest.[18,19] One study was undertaken in 9 centers in 5 European countries[19]; the other was conducted in 4 hospitals in Melbourne, Australia.[18]

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The criteria for entry into these trials were similar: ROSC, patients remaining intubated and ventilated, with persistent coma after out-of-hospital cardiac arrest due to VF. In the European study, the median Glasgow Coma Scale score on hospital admission in both groups was 3 with an interquartile range of 3 to 5 in the group with normothermia and 3 to 4 in the group with hypothermia.[20] Ten patients in the European study were resuscitated after in-hospital cardiac arrest (M. Holzer, written communication, October 2002). Additional criteria for entry into the European study were witnessed cardiac arrest, an estimated interval of 5 to 15 minutes from patient collapse to first resuscitation attempt by emergency medical services personnel, and an interval of ≤60 minutes from collapse to ROSC. Both studies excluded arrests that were probably of noncardiac etiology and patients with severe cardiogenic shock.

In the European study, patients randomly assigned to the hypothermia group underwent cooling to a target temperature of 32°C to 34°C by use of a mattress made specifically for this purpose (with a cover that delivered cold air) and ice packs if necessary. The aim was to reach the target temperature within 4 hours of ROSC, maintain it for 24 hours, and follow with passive rewarming. In the Australian study, patients were pseudorandomized (odd versus even days) to treatment groups that allowed cooling, by application of cold packs to the head and torso, to begin in the field before admission to the hospital. The target temperature of the hypothermia group was 33°C versus 37°C in the control group. Hypothermia was maintained for 12 hours after admission to the hospital; active rewarming started at 18 hours.

In the European study, 75 of the 136 patients (55%) in the hypothermia group for whom data were available had a favorable neurological outcome (able to live independently and work at least part-time) at 6 months compared with 54 of 137 (39%) in the normothermia group (relative risk [RR] 1.40, 95% CI 1.08 to 1.81, number needed to treat [NNT]=6].[19] At 6 months there were 56 deaths in the 137 participants (41%) in the hypothermia group versus 76 of 138 (55%) in the normothermia group (RR 0.74, 95% CI 0.58 to 0.95, NNT=7). The target temperature could not be achieved in 19 patients in the hypothermia group.

In the Australian study, 21 of 43 patients (49%) treated with hypothermia had good neurological function at discharge (to home or a rehabilitation facility) compared with 9 of 34 (26%) in the normothermia group (RR 1.85, 95% CI 0.97 to 3.49, NNT=4).[18] Mortality at discharge was 22 of 43 (51%) in the hypothermia group and 23 of 34 (68%) in the normothermia group (RR 0.76, 95% CI 0.52 to 1.10, NNT=6).

Both of these studies involved a highly selected group of patients, excluding up to 92% of patients with out-of-hospital cardiac arrest initially assessed for eligibility.[19] Those excluded had persistent hypotension (systolic blood pressure <90 mm Hg despite use of inotropes) and causes of coma other than cardiac arrest (eg, head injury, drug overdose, cerebrovascular accident). Other study limitations were that caregivers could not be blinded to treatment with hypothermia and that after ROSC, the normothermia group had an increase in core temperature of up to >38°C, as is often seen after cardiac arrest.

Some adverse events occurred more frequently in the hypothermia groups. The Australian hypothermia group had a lower cardiac index, higher systemic vascular resistance, and more hyperglycemia than patients in the control group.[18] Although not statistically significant, in the European hypothermia group there were 22% more complications; in particular, there were more cases of pneumonia (number needed to harm [NNH]=12), bleeding (NNH=14), and sepsis (NNH=16).[19]

Mechanisms of Action

There are several possible mechanisms by which mild hypothermia might improve neurological outcome when used after reperfusion. In the normal brain, hypothermia reduces the cerebral metabolic rate for oxygen ($CMRO_2$) by 6% for every 1°C reduction in brain temperature >28°C.[21] Some of this effect is due to reduced normal electrical activity,[21] however, and after cardiac arrest in dogs, $CMRO_2$ is not significantly reduced by mild hypothermia.[22] Mild hypothermia is thought to suppress many of the chemical reactions associated with reperfusion injury. These reactions include free radical production, excitatory amino acid release, and calcium shifts, which can in turn lead to mitochondrial damage and apoptosis (programmed cell death).[23–25] Despite these potential advantages, hypothermia can also produce adverse effects, including arrhythmias, infection, and coagulopathy.

Discussion

Selection of Patients

There seems to be good evidence (Level 1 [see Appendix]) to recommend the use of induced mild hypothermia in comatose survivors of out-of-hospital cardiac arrest caused by VF. Selection criteria for treatment were narrowly defined in the best evidence used and thus should be considered carefully when deciding to treat.

Several specific questions remain unanswered despite the results of these recently published controlled trials, previous clinical studies, and supporting experiments in animals. One controversial issue is whether findings from animal experiments and published clinical studies are enough to extend the use of therapeutic mild hypothermia to patients who remain comatose after cardiac arrest from any rhythm, after in-hospital cardiac arrest, and after cardiac arrest in children.

Any potentially beneficial effects of hypothermia on neuronal recovery must be counterbalanced by the known adverse effects of hypothermia. Although survivors of VF cardiac arrest have the most to gain from therapeutic hypothermia, some level 4 evidence suggests that survivors from out-of-hospital cardiac arrest of other causes may also benefit.[9] Further study is required. Many in-hospital cardiac arrests have noncardiac causes, and because the use of therapeutic hypothermia has not been studied to a significant extent in this population, its relative risks and benefits are unknown. It is possible, however, that patients who remain comatose after an in-hospital arrest of cardiac etiology will also benefit from therapeutic hypothermia.

Until further data are available, therapeutic hypothermia should not be used for patients with severe cardiogenic shock or life-threatening arrhythmias, pregnant patients, or patients with primary coagulopathy. Thrombolytic therapy does not preclude the use of hypothermia; patients who received thrombolytic therapy were included in both the European and Australian studies.

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Timing of Cooling

Cooling should probably be initiated as soon as possible after ROSC but appears to be successful even if delayed (eg, 4 to 6 hours). In the European study, the interval between ROSC and attainment of a core temperature of 32°C to 34°C had an interquartile range of 4 to 16 hours.[19]

Further research is needed to determine optimal duration of therapeutic hypothermia, optimum target temperature, and rates of cooling and rewarming. Animal data suggest that the sooner cooling is initiated after reperfusion from cardiac arrest, the better the outcome, although an impressive therapeutic benefit was seen in clinical studies when cooling was delayed for several hours. The therapeutic benefit may become much greater as better physical and pharmacological techniques to cool patients more rapidly become available. Although supporting data are limited, many critical care clinicians routinely sedate and ventilate the lungs of comatose survivors of cardiac arrest for at least 12 to 24 hours; thus, application of therapeutic hypothermia over this period would be simple. Normothermia should be restored only slowly as rebound hyperthermia is common and should be avoided.[14]

Cooling Techniques and Monitoring

A variety of cooling techniques have been described, but at this stage, none combines ease of use with high efficacy. External cooling methods are simple to use but slow in reducing core temperature. These techniques include the use of cooling blankets; application of ice packs to the groin, axillae, and neck; use of wet towels and fanning; and use of a cooling helmet.[15] In a recent study, intravenous infusion of 30 mL $\cdot$ kg^{-1} of crystalloid at 4°C over 30 minutes reduced core temperature significantly and did not cause pulmonary edema.[26] Cooling by peritoneal and pleural lavage is possible but not generally used.[27] Extracorporeal cooling methods are efficient[12] but too invasive for use in the prehospital environment or most emergency departments. An intravascular heat exchange device, which enables rapid cooling and precise temperature control, has recently become available.

Shivering during cooling leads to warming and will increase overall oxygen consumption. Shivering should be prevented by use of a neuromuscular blocker and sedation (as done in the 2 definitive trials). Careful monitoring of temperature is important during use of therapeutic hypothermia. The incidence of complications such as arrhythmias, infection, and coagulopathy is likely to increase if the core temperature falls considerably below 32°C. Continuous monitoring of temperature can be accomplished by use of a bladder temperature probe or a pulmonary artery catheter if one is in situ. Other temperature-monitoring techniques, including intermittent tympanic temperature measurements, are less reliable.

Use of Therapeutic Hypothermia in Children

There is currently insufficient evidence to make a recommendation on the use of therapeutic hypothermia in children resuscitated from cardiac arrest. The European and Australian clinical trials excluded children and cardiac arrests of noncardiac etiology (eg, respiratory failure or shock), which are typical of those in children.[18,19] In the 1970s therapeutic hypothermia was used to reduce secondary brain injury in children with severe anoxic/ischemic insults. The practice was abandoned in the 1980s after a retrospective study of near-drowning victims reported that children treated with hypothermia were at an increased risk for death, neutropenia, and sepsis compared with children treated without hypothermia.[28,29] Important limitations of this study were the limited sample size, use of historical controls, and use of a lower target temperature for a longer duration than recommended in contemporary protocols (30°C to 33°C for ≥36 hours versus 32°C to 34°C for 12 to 24 hours).

Until additional pediatric data become available, clinicians should tailor therapy for individual patients on the basis of their assessment of the risks and benefits of hypothermia. Risk-benefit assessment should take into account relevant data from laboratory models of asphyxial arrest,[8,30–32] results from trials of adult cardiac arrest,[18,19] and reports on the use of hypothermia in treatment of neonatal asphyxia.[33–38] The results of therapeutic hypothermia are generally favorable in laboratory models of hypoxic ischemic injury to immature brains of various species. Preliminary data from clinical trials of perinatal asphyxia indicate that induced hypothermia is feasible and safe, but data on long-term neurological morbidity are not yet available.[33–38] It is difficult to extrapolate from these disparate sources of information, and thus there is no consensus yet for use of therapeutic hypothermia among clinicians who care for these critically ill children.

Summary: ILCOR Recommendations

On the basis of the published evidence to date, the ILCOR ALS Task Force has made the following recommendations:

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF.
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Appendix

1998 AHA ECC Levels of Evidence Summary

Level of Evidence	Definitions
Level 1	One or more randomized clinical trials in which the lower limit of CI for treatment effect exceeds the minimal clinically important benefit
Level 2	One or more randomized clinical trials in which the lower limit of the CI for treatment effect overlaps the minimal clinically important benefit
Level 3	*Prospective* cohort of patients not randomized to an intervention; control or comparison group available
Level 4	*Historical*, nonrandomized cohort or case-control studies
Level 5	*Case series*: patients compiled in serial fashion; a control group is lacking
Level 6	An animal or mechanical model study; a *level 6A* study is well designed, shows a homogeneous pattern of results; a *level 6B* study has a less powerful design and demonstrates an equivocal or heterogeneous pattern of results
Level 7	Reasonable extrapolations from existing data; quasiexperimental designs; pathophysiological and nonquantitative reasoning
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

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