

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

Michael Holzer, M.D., Universitätsklinik für Notfallmedizin, Vienna, Austria, Universitätsklinik für Notfallmedizin, Allgemeines Krankenhaus der Stadt Wien
N Engl J Med. 2002;346:549-556.

Background

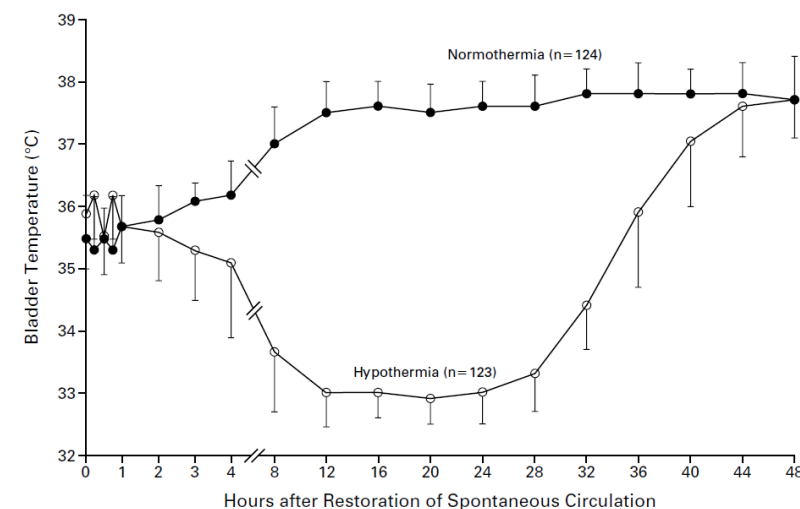
Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation.

Methods

In this multicenter trial with blinded assessment of the outcome, patients who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32°C to 34°C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia. The primary end point was a favorable neurologic outcome within six months after cardiac arrest; secondary end points were mortality within six months and the rate of complications within seven days.

Results

Seventy-five of the 136 patients in the hypothermia group for whom data were available (55 percent) had a favorable neurologic outcome (cerebral performance category, 1 [good recovery] or 2 [moderate disability]), as compared with 54 of 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81).



Mortality at six months was 41 percent in the hypothermia group (56 of 137 patients died), as compared with 55 percent in the normothermia group (76 of 138 patients; risk ratio, 0.74; 95 percent confidence interval, 0.58 to 0.95). The complication rate did not differ significantly between the two groups.

Conclusions

In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality. (*N Engl J Med* 2002;346:549-56.)

The study was carried out between March 1996 and January 2001. Since the enrollment rate was lower than expected and funding had ended by July 2000, enrollment was stopped at this date.

A total of 3551 patients were assessed for eligibility; 3246 of these patients did not meet the inclusion criteria, and 30 were not included because of logistic problems. Thus, 275 patients were enrolled.

TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

OUTCOME	NORMOTHERMIA	HYPOTHERMIA	RISK RATIO (95% CI)*	P VALUE†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson's chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.

Therapeutic Hypothermia After Cardiac Arrest

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

Writing Group

J.P. Nolan, FRCA; P.T. Morley, MD; T.L. Vanden Hoek, MD; R.W. Hickey, MD

Members of the Advanced Life Support Task Force

W.G.J. Kloeck, MBBCh, DipPEC(SA), Chair*; J. Billi, MD†; B.W. Böttiger, MD‡; P.T. Morley, MDS; J.P. Nolan, FRCA‡; K. Okada, MD¶; C. Reyes, MD#; M. Shuster, MD, FRCPC**; P.A. Steen, MD‡; M.H. Weil, MD, PhD†; V. Wenzel, MD‡

Circulation 2003;108;118-121

Selection of Patients

There seems to be good evidence 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.

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*¹. Thrombolytic therapy does not preclude the use of hypothermia; patients who received thrombolytic therapy were included in both the European and Australian studies.

1 Zwischenzeitlich (A. Janata, M. Holzer / Progress in Cardiovascular Diseases 52 (2009) 168-179) wird die therapeutische Hypothermie auch im kardiogenen Schock als möglich und sicher betrachtet.

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.

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.

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. In a recent study, intravenous infusion of 30 mL · kg⁻¹ of crystalloid at 4°C over 30 minutes reduced core temperature significantly and did not cause pulmonary edema. Cooling by peritoneal and pleural lavage is possible but not generally used. Extracorporeal cooling methods are efficient 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.

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.