Hypothermia After Cardiac Arrest
Feasibility and Safety of an External Cooling Protocol

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Background—No proven neuroprotective treatment exists for ischemic brain injury after cardiac arrest. Mild-to-moderate induced hypothermia (MIH) is effective in animal models.

Methods and Results—A safety and feasibility trial was designed to evaluate mild-to-moderate induced hypothermia by use of external cooling blankets after cardiac arrest. Inclusion criteria were return of spontaneous circulation within 60 minutes of advanced cardiac life support, hypothermia initiated within 90 minutes, persistent coma, and lack of acute myocardial infarction or unstable dysrhythmia. Hypothermia to 33°C was maintained for 24 hours followed by passive rewarming. Nine patients were prospectively enrolled. Mean time from advanced cardiac life support to return of spontaneous circulation was 11 minutes (range 3 to 30); advanced cardiac life support to initiation of hypothermia was 78 minutes (range 40 to 109); achieving 33°C took 301 minutes (range 90 to 690). Three patients completely recovered, and 1 had partial neurological recovery. One patient developed unstable cardiac dysrhythmia. No other unexpected complications occurred.

Conclusions—Mild-to-moderate induced hypothermia after cardiac arrest is feasible and safe. However, external cooling is slow and imprecise. Efforts to speed the start of cooling and to improve the cooling process are needed. **(*Circulation*. 2001;104:1799-1804.)**

Key Words: cardiopulmonary resuscitation ■ cerebral ischemia ■ death, sudden ■ hypothermia ■ resuscitation, brain

Many patients who have return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest (CA) eventually have a poor neurological outcome due to hypoxic-ischemic brain injury. Some studies report survival rates ≤42%,[1,2] but 1% to 20% is more normal.[1–6] Many surviving patients are left with significant neurological disabilities.[7,8]

Although general supportive measures such as avoiding hypotension, hypovolemia, and hypoxemia and supporting cardiac function are important, no neuroprotective treatment exists that targets specifically the cytotoxic events that occur during CA.[9] Results from animal models of diffuse forebrain ischemia[10] and human studies of global ischemia after CA[11,12] suggest that neuronal death is delayed, especially in the hippocampus. In these animal models, hypothermia consistently has reduced neuronal damage.[13,14] The earlier hypothermia begins and the longer into reperfusion it lasts, the greater and more permanent is the protection,[15,16] especially in models that most closely simulate CA.[14,17–19] Translation of results from these animal models, including depth of hypothermia and time window of efficacy, to human clinical trials is still unproven.

The mechanism by which hypothermia conveys its neuroprotective effects is unclear, but hypothermia decreases metabolic demand,[20] decreases release of extracellular glutamate and other neurotoxic transmitters,[21] suppresses inflammation,[22] and stabilizes cell membranes.[23] To date, few preliminary reports have evaluated post-CA neuroprotective hypothermia in humans.[24–26] Several large studies are ongoing. One recent report in which 27 patients were cooled externally to 32°C to 34°C for 24 hours described encouraging results, although achievement of target temperature took an average of 287 minutes from CA.[27]

Several theoretical impediments exist to inducement of mild-to-moderate hypothermia in human CA patients, including logistics of rapid patient access and quick inducement of the cooling algorithm. Furthermore, safety of mild-to-moderate induced hypothermia (MIH) may be problematic in patients with unstable postarrest cardiac status. We studied

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TABLE 1. Inclusion Criteria

Documented out-of-hospital CA
ROSC with systolic blood pressure ≥90 within 60 min of initiation of ACLS
Enrollment and initiation of hypothermia within 90 min of initiation of ACLS
Age 18 to 85
Comatose upon enrollment (Glasgow Coma Scale ≤8)
Informed consent obtained

feasibility and safety of MIH (32°C to 34°C) in patients who had suffered CA and had ROSC after resuscitation.

Methods

The University of Texas Committee for the Protection of Human Subjects approved the present trial. Because this was a preliminary feasibility and safety study, the committee would not consider "waived" consent. Patients who experienced CA and had ROSC were screened for inclusion. Houston Fire Department–Emergency Medical Services activated our stroke team pager for out-of-hospital CA patients. A member of the stroke team enrolled patients who met inclusion (Table 1) and exclusion (Table 2) criteria. We used time of initiation of advanced cardiac life support (ACLS) as time zero. Patients were required to have ROSC within 60 minutes of ACLS and initiation of hypothermia within 90 minutes of ACLS. Prearrest characteristics were recorded and baseline cardiological and neurological assessment performed.

For each patient, after informed consent was obtained, hypothermia was instituted. The patient was sedated with a propofol drip and paralyzed to suppress shivering. A temperature-sensing thermistor bladder catheter was placed to assess core temperature. The patient was wrapped in 2 cooling blankets (Baxter Corp, RK-2000K-Thermia). The patient was "log rolled," with 1 blanket wrapped around the torso and the other around the pelvis and legs. Until blankets were placed, ice packs were placed on the patient's axilla and groin. Iced saline gastric lavage was performed. The goal was to achieve 33°C within 120 minutes.

All patients were intubated endotracheally in the field and mechanically ventilated on arrival. Mechanical ventilation was managed in accordance with predefined parameters. Acetylsalicylic acid (aspirin) and subcutaneous heparin were prescribed, but intravenous heparin or glycoprotein IIb/IIIa inhibitors were not allowed. Continuous pulse oximetry and cardiac rhythm telemetry were used on each patient. Arterial and central lines were placed for continuous blood pressure and central venous pressure monitoring. At the discretion of the treating physician, a pulmonary artery catheter also was inserted.

Once hypothermia was achieved, 33°C was maintained for 24 hours. Sedation was maintained by use of continuous propofol infusion. Vecuronium infusion was titrated to suppress shivering. After the maintenance period, the patient was passively rewarmed to 36.5°C by setting the cooling blankets for a 1° increase every 4 hours. MIH was stopped for any of the following; sepsis, significant dysrhythmia, clinically significant congestive heart failure, shock, thrombocytopenia, coagulopathy, intracerebral hemorrhage, and clinically significant extracranial hemorrhage. All patients were included in analysis, even if therapy was halted.

TABLE 2. Exclusion Criteria

Significant cardiac dysrrhythmias or cardiac instability
ECG evidence of continuing acute myocardial ischemia
Evidence of sepsis
Vasoactive drugs required to maintain adequate perfusion
Cardiogenic shock (systolic blood pressure ≤90)
Coagulopathy or thrombocytopenia
QT_c interval >470 ms
In-hospital CA
Any conditions precluding treatment in the opinion of the primary physician

Patients were monitored for 48 hours after rewarming. Neurological assessments were performed every 24 hours for 3 days and at discharge. Noncontrast computed tomographic scans of the brain and electroencephalogram were performed after rewarming.

Our primary objective was to determine feasibility as defined by ability to achieve and maintain hypothermia and safety of MIH. Secondary analysis of outcome was assessed by use of discharge disposition, modified Rankin score, and the Mini Mental Status Examination. At 30 days, poor outcome was predefined as death, need for institutionalization, or modified Rankin score of ≥4 (which suggests functional dependence). Good outcome was predefined as discharge to home or to an acute rehabilitation facility and a modified Rankin score of ≤3.

To predict and analyze enrollment rates, a retrospective chart review was performed by searching medical records from July 1, 1998, through November 30, 1999, for a diagnosis code of 427.5 (CA) or procedure code of 99.60 (cardiopulmonary resuscitation). These charts were reviewed for eligibility for the present study.

Results

We enrolled 9 patients from July 1998 through October 1999. CA origin was ventricular fibrillation in 7, asphyxiation due to carbon dioxide displacement of oxygen in an industrial accident in 1, and sudden unexplained death in epilepsy in 1. Concurrent morbidities included hypertension in 5, diabetes mellitus in 4, coronary artery disease in 3, congestive heart failure in 2, tobacco use in 1, epilepsy in 1, renal failure in 1, and previous malignant arrhythmia in 1.

Table 3 provides the patients' presenting evaluations and an overview of treatment parameters. Information is subdivided further to compare patients with good and poor outcomes. All poor outcomes resulted in death. Basic life support in the form of bystander cardiopulmonary resuscitation was performed in 1 patient 4 minutes into CA. Time of onset of CA was estimated by witness recollection. Average time from CA to ACLS was 13±8 minutes (range 0 to 25). Average time from ACLS to ROSC was 11±9 minutes (range 3 to 30).

Four of the 9 patients survived; 3 survivors were discharged home on returning completely to baseline with a Rankin score of 0 (no disability) and a Mini Mental Status Examination of 30 (normal cognitive functions). The remaining survivor (1 of 4) was discharged home but had significant memory deficits that required 24-hour supervision (Rankin score 3, Mini Mental Status Examination 20). Of the 4 survivors, 2 emerged from coma within 24 hours of achieving normothermia and 2 within 48 hours. All surviving patients made neurological progress over a period of 5 to 7 days before reaching a functional plateau.

Five patients died. All remained comatose 72 hours after achieving normothermia. Families of all 5 patients had a consultation with an independent neurologist before withdrawal of care.

MIH was feasible but slow. ACLS to initiation of hypothermia took 78±20 minutes (range 40 to 109; Table 3). Emergency department presentation to initiation of MIH took 46 minutes (range 10 to 70 minutes). Much of this time was spent obtaining informed consent. From time of CA to achievement of goal temperature took 391 minutes (range

TABLE 3. Characteristics of Enrolled Cohort Further Divided Into Good- and Poor-Outcome Patients

		Outcome	
	All Patients (n=9)	Good (n=4)	Poor (n=5)
Mean age, y	59±13 (40–77)	61±2.8 (59–65)	58±18 (40–77)
Men, n	6/9	3/4	3/5
Race			
Black	4/9	2/4	2/5
White	5/9	2/4	3/5
Temperature on admission	36°C±1.4 (33.2°C–37.5°C)	36.6°C±1.0 (35.5°C–37.5°C)	35.6°C±1.6 (33.2°C–37.5°C)
Glasgow Coma Scale score	3.6±0.9 (3–5)	3.8±1.0 (3–5)	3.4±0.9 (3–5)
Time from CA to ROSC, min	24±9 (10–35)	15±5 (10–20)	31±4 (25–35)
Time from initiation of ACLS to ROSC, min	11±9 (3–30)	5±2 (3–8)	16±9 (7–30)
Time from CA to initiation of MIH, min	91±18 (65–117)	99±15 (80–117)	84±18 (65–114)
Time from ACLS to initiation of MIH, min	78±20 (40–109)	90±13 (78–109)	69±20 (40–96)
Time from emergency department admission to initiation of MIH, min	46±22 (10–70)	61±4 (55–65)	33±23 (10–70)
Time from CA to achieving goal temperature, min	391±177 (167–770)	499±218 (307–770)	305±79 (167–367)
Time from ACLS to achieving goal temperature, min	378±178 (167–765)	489±219 (298–765)	290±71 (167–346)
Time from initiation of MIH to achieving goal temperature, min	301±178 (90–690)	400±231 (190–690)	221±74 (90–265)

All numbers are mean±SD (range) unless otherwise noted.

167 to 770); initiation of MIH to goal temperature took 301 minutes (range 90 to 690 minutes). Figure 1 indicates rate of cooling in each patient.

Hypothermia was maintained adequately. Temperature was kept 32°C to 34°C for 91.7% of the 24-hour maintenance phase. Rewarming occurred more quickly than the desired 1°C every 4 hours. Normothermia was achieved at an average of 645 minutes (range 330 to 990 minutes) rather than the expected 840 minutes. Postrewarming rebound hyperthermia (≥38°C) occurred in all 9 patients.

The patient whose CA was caused by sudden unexplained death in epilepsy experienced significant cardiac dysrhythmia during the maintenance portion of MIH. Despite being given an intravenous phenytoin load, the patient had a second seizure. Immediately after this seizure, he experienced a brief run of self-limited ventricular tachycardia without change in clinical status. On the decision of the primary treatment team, hypothermia was discontinued 4 hours into maintenance. This patient eventually had a poor neurological outcome. No other patient had any cardiac complications that could be directly attributed to hypothermia, and all others received the full course of MIH.

Table 4 lists complications experienced by our patients. Status epilepticus occurred in 4 of 9 patients, attributed to hypoxic-ischemic brain injury in all. These attacks began with myoclonic movements of the face and arms during rewarming, which progressed to generalized seizures. Status epilepticus was treated with standard protocols, including intravenous phenytoin, continuous electroencephalographic monitoring, and intravenous barbiturates. Despite aggressive measures, all status epilepticus patients died. One other patient who survived and did not experience status epilepticus developed a generalized seizure disorder that responded to valproate.

Other complications included pneumonia (in 5 patients) that required use of intravenous antibiotics. Sputum culture from all 5 affected patients indicated aspiration pneumonia. One patient who was taking oral warfarin before enrollment developed coagulopathy with a maximum international normalized ratio of 4.9. This occurrence did not result in hemorrhagic complications, treatment was not required, and the patient eventually had good outcome. We did not note any

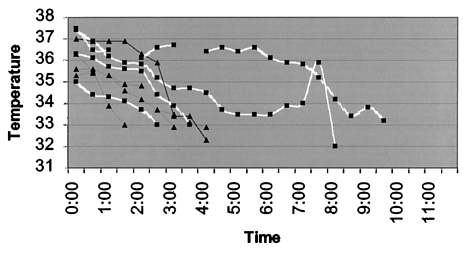

Figure 1. Temperature (in °C) and time (in h:min) are shown. ■ indicates patients with good outcome; ▲, poor outcome.

TABLE 4. Complications

		Outcome	
Adverse Event	Total Incidence	Good	Poor
Death	5/9	0/4	5/5
Pneumonia	5/9	3/4	2/5
Status epilepticus	4/9	0/4	4/5
Increased serum lipase or amylase	4/9	0/4	4/5
Electrolyte abnormalities	3/9	1/4	2/5
Increased serum creatinine	3/9	1/4	2/5
Cardiac dysrrhythmia	1/9	0/4	1/5
Epilepsy	1/9	1/4	0/5
Coagulopathy	1/9	1/4	0/5
Transient horizontal diplopia	1/9	1/4	0/5

All values are No. of patients.

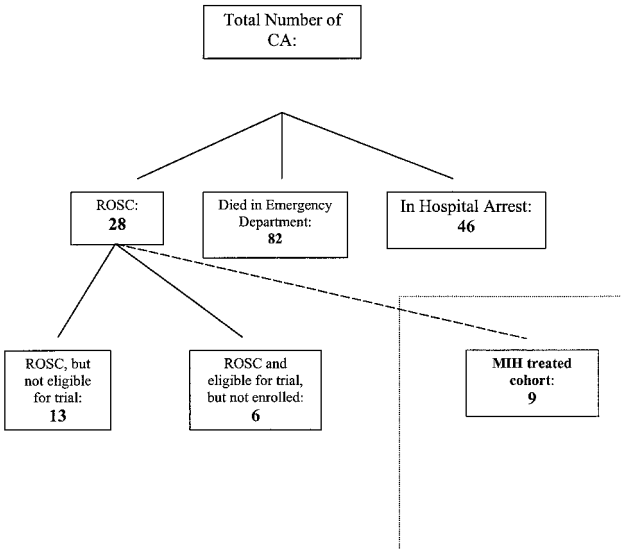

Figure 2. Comparison of retrospective natural history group to hypothermia cohort.

significant fluctuation of international normalized ratio or evidence of coagulopathy in other patients. Transient electrolyte abnormalities were present in 3 patients but did not affect outcome. Mild transient increases in serum creatinine and blood urea nitrogen occurred in 3 patients. These increases were attributed to ischemic acute tubular necrosis. Transient increases in lipase and amylase occurred in 4. No changes were noted in hemoglobin, platelet count, white blood cell count, liver enzymes, and fibrinogen levels, or on ECG (data not shown).

No patient experienced significant hypotension or cardiac failure, uncontrollable hypertension, or hypoxemia (data not shown). Dehydration that required aggressive fluid resuscitation occurred in 2 patients. Eight received computer-assisted tomography of the brain after MIH therapy. None of the tomographic scans revealed significant abnormalities.

Figure 2 shows outcome in 156 patients (both those who were and were not included in the present trial) discharged after CA between July 1998 and November 1999. Patients with in-hospital CA were not eligible for our protocol. Thirteen patients did not meet inclusion criteria because of time constraints or cardiac instability. Six remaining patients were eligible but could not be enrolled because informed consent could not be obtained. Average age of these 6 patients was 65±10 years, time from CA to ROSC was 32±20 minutes, and time from ACLS to ROSC was 20±14 minutes. Outcome of these patients was uniformly poor.

Discussion

Feasibility

Results of the present study demonstrate that MIH after CA is feasible. We used existing practice patterns and technology in the present study but were unable to achieve MIH within a time window likely to be most beneficial on the basis of preclinical animal models. In our present study, achieving MIH took an average 6.5 hours after CA, whereas in animal studies, hypothermia is most effective if begun within the first few minutes after CA.

Our data can be compared with recently published results from a similar protocol in Europe.[27] In 27 patients (average interval from CA to ROSC 21 minutes), MIH was achieved slightly faster (287 minutes, versus 301 minutes in our cohort) by use of a different external cooling methodology but still was not achieved within the desired therapeutic time window.

In the present study, average time from starting MIH to goal temperature was 301 minutes, far longer than our goal of 120 minutes. Only 1 patient reached goal temperature within the desired time frame. Other trials in which external cooling blankets were used also have reported this difficulty.[28] MIH might be reached more quickly by use of endovascular cooling catheters or more sophisticated external cooling devices.

Our passive rewarming protocol also was unsatisfactory. Attainment of normothermia occurred in a rapid and minimally controlled fashion. All 9 patients experienced rebound hyperthermia of >38°C after rewarming. The cause of this phenomenon is unclear. No direct link existed to infection or agitation. This occurrence may represent a resetting of the hypothalamic "thermometer" in the setting of extended hypothermia. Regardless of the cause, hyperthermia exacerbates neurological damage[29] and should be controlled in future studies.

Eligibility

On the basis of our present experience, 15 of 156 (9.6%) CA patients would have been eligible for the present study. These data should help to determine resources needed for future efficacy trials. However, our data also suggest that a greater proportion of CA patients might be eligible for MIH than were included in our trial.

The main reason for exclusion was failure to achieve stable cardiac status (82 of 156 patients); ECG evidence of ischemia was the second most common reason. These patients were excluded because deeper hypothermia causes malignant ventricular arrhythmia. Although MIH has not been shown to cause dysrhythmia, we were concerned that patients with acute myocardial ischemia might be more predisposed to this complication.[30] Because the patients in our cohort tolerated MIH with only 1 episode of ventricular tachycardia, patients with ECG evidence of acute myocardial injury might be safely included in future studies.

Another 46 were excluded because CA occurred in hospital. We reasoned that this group of patients was more likely to harbor associated medical (especially cardiac) conditions that might complicate hypothermia. However, absence of significant medical complications in our patients implies that many patients with in-hospital CA might tolerate MIH. The final major reason for exclusion (in 6 of 156 patients total or 6 of 15 otherwise eligible) was failure to obtain informed consent from relatives within the protocol-specified time window.

Speed

Among patients whom we enrolled, an average of 46 minutes was required to obtain informed consent. Strong human data

suggest that time to therapy is one of the best indicators of outcome.[31] Difficulties obtaining consent suggest the advisability of considering waiver of consent in future studies. Another reason for delay is that current guidelines dictate that ACLS be performed at the site of CA as opposed to use of the "load-and-go" process common in trauma and ischemic stroke. A diversion strategy also may help to hasten enrollment in future studies. Finally, delay occurred in some patients in that hypothermia was deferred until after a pulmonary artery catheter was placed. Although placement of such catheters may induce arrhythmia, the cardiac stability of our MIH patients argues that pulmonary artery catheter placement, if needed, may be done safely after MIH is initiated.

Safety

Many medical problems occurred in our MIH patients, but they were common to patients who survive CA. Resistant status epilepticus occurred during rewarming in 4 of 9 patients. This complication has not been reported in other pilot safety studies of hypothermia[25–27] but is common after anoxic brain injury. Other complications, such as pneumonia, potassium disturbances, and elevated levels of creatinine and pancreatic enzymes, were similar to complications described in trials of hypothermia for head injury[28] but were less severe. None of these complications resulted in worsened outcome, and all were easy to manage. Although hypothermia is theorized to suppress immune response,[22] the rate of patients with pneumonia (5 of 9) was not higher than expected in comatose CA patients.

Outcome

Survival rate among MIH patients (4 of 9) in the present study is somewhat higher than in several large series.[1–4] Factors besides hypothermia may account for the good outcome in the present study. All patients were sedated with propofol during MIH. Like some other anesthetic agents, propofol is neuroprotective.[32] However, a trial in which barbiturates were administered after CA showed no benefit in their use.[33] Patients with good outcome experienced less total time in anoxia than in the poor outcome group. Good outcome might be explained by a less severe ischemic insult rather than by any effect of hypothermia. A "breaking point" appears to occur around the 20-minute range of CA to ROSC, at which the likelihood of recovery is hopelessly small. Because CA-to-ROSC duration is such an important predictor of outcome, any imbalance in this variable must be avoided in future therapeutic trials.

A trend toward lower temperature on arrival occurred in patients who did not survive. Poor-outcome patients also achieved the hypothermic goal quicker (Figure 1). Extensive neuronal damage probably occurred, which caused inability of the hypothalamus to regulate body temperature and mount a shiver response. No other factors predicted good outcome, including initial physical examination and Glasgow Coma Scale scores.

MIH is a labor-intensive procedure. The main drivers of cost are intravenous paralytic agents and anesthetics, cooling-blanket rental, and nursing services for 24 to 48 hours. Recognition of clinical, laboratory, electrophysiological, and imaging modalities that can predict which patients will be more likely to respond to MIH would be of important clinical use.[34]

In conclusion, MIH after CA appears feasible and safe, especially when poor prognosis after CA is taken into account.[35] Our present cohort tolerated MIH without significant cardiac adverse events. However, with external cooling blankets and current practice patterns, MIH could not be accomplished within a time likely to be most effective based on preclinical data. MIH warrants further study, but controlling for duration of ischemia and shortening of the time to achievement of hypothermia will be important to future evaluations.

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