TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

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ABSTRACT

Background Cardiac arrest outside the hospital is common and has a poor outcome. Studies in laboratory animals suggest that hypothermia induced shortly after the restoration of spontaneous circulation may improve neurologic outcome, but there have been no conclusive studies in humans. In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest.

Methods The study subjects were 77 patients who were randomly assigned to treatment with hypothermia (with the core body temperature reduced to 33°C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility.

Results The demographic characteristics of the patients were similar in the hypothermia and normothermia groups. Twenty-one of the 43 patients treated with hypothermia (49 percent) survived and had a good outcome — that is, they were discharged home or to a rehabilitation facility — as compared with 9 of the 34 treated with normothermia (26 percent, P=0.046). After adjustment for base-line differences in age and time from collapse to the return of spontaneous circulation, the odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011). Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia. There was no difference in the frequency of adverse events.

Conclusions Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest. (N Engl J Med 2002;346:557-63.)

CARDIAC arrest outside the hospital is a major cause of unexpected death in developed countries, with survival rates ranging from less than 5 percent to 35 percent.[1-3] In patients who are initially resuscitated, anoxic neurologic injury is an important cause of morbidity and mortality.[4]

Currently, the treatment of patients with coma after resuscitation from out-of-hospital cardiac arrest is largely supportive. Because cerebral ischemia may persist for some hours after resuscitation,[5] the use of induced hypothermia to decrease cerebral oxygen demand has been proposed as a treatment option.[6] Although this suggestion has been supported by studies in animal models,[7-12] the studies in humans that have been reported to date have been uncontrolled or retrospective.[13-18]

After a pilot study that suggested the feasibility, safety, and possible efficacy of this treatment,[16] we conducted a prospective, controlled trial comparing moderate induced hypothermia with normothermia in comatose survivors of out-of-hospital cardiac arrest.

METHODS

Study Design

The study was performed in Melbourne, Australia, between September 1996 and June 1999. The ambulance service has treatment protocols that follow the recommendations of the Australian Resuscitation Council.[19] Patients were enrolled in the study when the following criteria were fulfilled: an initial cardiac rhythm of ventricular fibrillation at the time of arrival of the ambulance, successful return of spontaneous circulation, persistent coma after the return of spontaneous circulation, and transfer to one of four participating emergency departments. The exclusion criteria were an age of less than 18 years for men, an age of less than 50 years for women (because of the possibility of pregnancy), cardiogenic shock (a systolic blood pressure of less than 90 mm Hg despite epinephrine infusion), or possible causes of coma other than cardiac arrest (drug overdose, head trauma, or cerebrovascular accident). Patients were also excluded if an intensive care bed was not available at a participating institution.

After the return of spontaneous circulation had been accomplished outside the hospital, eligible patients were randomly assigned to hypothermia or normothermia according to the day of the month, with patients assigned to hypothermia on odd-numbered days. For these patients, the paramedics began measures in the field to initiate hypothermia by removing the patient's clothing and applying cold packs (CoolCare, Cheltenham, Victoria, Australia) to the patient's head and torso. The treatment of patients assigned to normothermia followed usual prehospital treatment protocols.

On arrival at a participating emergency department, the patients underwent routine initial assessment and treatment, includ-

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ing mechanical ventilation and correction of cardiovascular instability. After an evaluation of neurologic status, all patients were given intravenous midazolam (2 to 5 mg) and vecuronium (8 to 12 mg). Arterial blood gas values, corrected for temperature, were used to adjust the ventilator to maintain a partial pressure of arterial oxygen of 100 mm Hg and a partial pressure of arterial carbon dioxide of 40 mm Hg. The mean arterial blood pressure was maintained between 90 and 100 mm Hg by infusion of epinephrine or nitroglycerin, as indicated. Thrombolytic therapy was administered to patients with electrocardiographic changes suggestive of acute myocardial infarction, unless it was contraindicated. Intravenous heparin was administered if the history, electrocardiogram, or both suggested an ischemic coronary syndrome without infarction. All patients were given a lidocaine bolus (1 mg per kilogram of body weight) followed by an infusion (2 mg per minute for 24 hours) in an attempt to prevent recurrent ventricular tachyarrhythmias. Potassium was given intravenously to maintain a serum level of 4.0 mmol per liter, and insulin was administered subcutaneously to maintain a blood glucose level of 180 mg per deciliter (10 mmol per liter) or less. Aspirin was administered to all patients.

Core body temperature was monitored by reading the tympanic temperature or bladder temperature until a pulmonary-artery catheter was placed. Initial investigations in the emergency department included 12-lead electrocardiography and measurement of arterial blood gases, electrolytes, glucose, creatine kinase (total and MB fractions), and lactate. These measurements were repeated at 1 to 3 hours (on admission to the intensive care unit) and at 6, 12, 18, and 24 hours after arrival at the hospital. Complete blood counts were performed on arrival and repeated at 12 and 24 hours.

After the admission of the patient to the intensive care unit, a pulmonary-artery catheter was inserted, and hemodynamic data were obtained 1 to 3, 6, 12, 18, and 24 hours after arrival at the hospital. Some patients (7 of 39 undergoing hypothermia and 11 of 33 undergoing normothermia) were treated without the use of a pulmonary-artery catheter, as requested by the attending physician in the intensive care unit.

The study was approved by the Medical Standards Committee of the Metropolitan Ambulance Service and the institutional ethics committee at each participating hospital. Because of the emergency conditions under which this study was performed, written informed consent for participation in the study was sought from the next of kin as soon as possible after the arrival of the patient at the hospital.

Treatment Protocol

Patients assigned to hypothermia underwent initial basic cooling measures in the ambulance. After arrival at the hospital, they underwent vigorous cooling in the emergency department (or the intensive care unit if a bed was immediately available), as soon as possible after the initial assessment, by means of extensive application of ice packs around the head, neck, torso, and limbs. When the core temperature reached 33°C, the ice packs were removed, and this temperature was maintained until 12 hours after arrival at the hospital while the patient continued to be sedated and paralyzed with small doses of midazolam and vecuronium, as required, to prevent shivering that might lead to warming. Beginning at 18 hours, the patients were actively rewarmed for the next 6 hours by external warming with a heated-air blanket, with continued sedation and neuromuscular blockade to suppress shivering. Patients assigned to normothermia were also sedated and paralyzed initially, but the target core temperature was 37°C. Passive rewarming was used in these patients if there was mild spontaneous hypothermia on arrival.

After 24 hours, patient care followed the usual intensive care unit protocols. Patients who had regained consciousness underwent extubation and were transferred to a coronary care unit. Active life support was withdrawn from most patients who remained deeply comatose at 72 hours. Patients with an uncertain prognosis underwent tracheostomy and were discharged from the intensive care unit.

Assessment of Outcome

When the patients were ready for discharge from the hospital, they were assessed by a specialist in rehabilitation medicine who was unaware of the treatment group. On the basis of this evaluation, patients were discharged to home, to a rehabilitation facility, or to a long-term nursing facility. Discharge home or to a rehabilitation facility was regarded as a good outcome, whereas death in the hospital or discharge to a long-term nursing facility, whether the patient was conscious or unconscious, was regarded as a poor outcome.

Statistical Analysis

The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be sent home or to a rehabilitation facility. Secondary outcome measures included the hemodynamic, biochemical, and hematologic effects of hypothermia. Statistical analysis was performed with the Stata statistical package.[20] Continuous variables, such as vital signs and biochemical results, were analyzed by repeated-measures analysis of variance, which was modeled by generalized estimating equations with unstructured correlation and robust standard errors. Data for some variables were insufficient at certain time points, and for these a first-order autoregression correlation structure with robust standard errors was used. Base-line data (measurements on arrival at the hospital) were compared by t-tests for continuous variables and by the chi-square test or Fisher's exact test for categorical variables. An adjusted odds ratio for a good outcome as compared with a bad outcome was calculated by multivariate logistic regression.

On the basis of our previous study,[16] it was determined that a sample of 62 patients (31 in each group) would be required to show a change in the rate of a good outcome (discharge to home or to a rehabilitation facility) from 14 percent to 50 percent, with a power of 80 percent and a significance level of 0.05. An analysis of results from 62 eligible patients found that the outcome in the control group was better than our previously published rate,[16] but that there was a strong trend toward improved outcome in the hypothermia group. The study was continued for a further 12 months, at which time 84 patients had been eligible for enrollment, 77 had been enrolled, and 72 had been treated according to the correct treatment assignment.

RESULTS

Characteristics of the Patients

Eighty-four patients were eligible for enrollment in the study over a period of 33 months. Data on seven of these patients were excluded from the analysis (five because they were transferred from the initial hospital to a nonparticipating intensive care unit and two because the next of kin refused consent for data collection). Of the remaining 77 patients, 43 were assigned to hypothermia and 34 to normothermia.

The clinical characteristics of the 77 patients are shown in Table 1. Four patients assigned to hypothermia did not receive this treatment because the emergency physician erred by not initiating cooling (three patients) or because the patient was inadvertently rewarmed shortly after admission to the intensive care unit (one patient). One patient who was assigned to normothermia became moderately hypothermic

TABLE 1. CLINICAL CHARACTERISTICS OF THE 77 PATIENTS WITH ANOXIC BRAIN INJURY WHO WERE ELIGIBLE FOR RANDOMIZATION.*

CHARACTERISTIC	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)	P VALUE
Age (yr)			0.55
Median	66.8	65.0	
Range	49–89	41–85	
Male sex (%)	58	79	0.05
Arrest witnessed (%)	95	94	0.81
Bystander performed cardiopulmonary resuscitation (%)	49	71	0.05
Time from collapse to emergency-medical-services call (min)	2.1±1.9	2.7±3.0	0.32
Time from call to emergency-medical-services arrival (min)	7.9±3.1	8.3±2.8	0.60
Time from arrival to first DC shock (min)	2.5±2.2	2.0±1.2	0.22
Time from first shock to return of spontaneous circulation (min)	13.6±11.2	12.1±7.9	0.48
Time from collapse to return of spontaneous circulation (min)	26.5±12.9	25.0±8.9	0.54
Number of DC shocks	4.2±3.0	4.1±3.2	0.87
Dose of epinephrine (mg)	2.2±2.1	2.2±1.9	0.97

*Plus–minus values are means ±SD. DC denotes direct current.

(33°C) for a prolonged period (four hours) during emergency angioplasty. We analyzed data for these patients on arrival at the emergency department but not on admission to the intensive care unit or at 6, 12, 18, and 24 hours. Outcomes for all patients were analyzed.

Systemic and Cerebral Characteristics

The hemodynamic data for the first 24 hours are shown in Table 2. In the hypothermia group, the core temperature decreased from 34.9°C 30 minutes after return of spontaneous circulation to 33.5°C 120 minutes after the return of spontaneous circulation, a decrease of 0.9°C per hour. In the hypothermia group, 59 percent required an infusion of epinephrine during the first 24 hours, as compared with 49 percent of the normothermia group. Two patients, both in the normothermia group, had cardiac complications in the first 24 hours. One patient had cardiogenic shock and died at two hours, and another had complete heart block at eight hours, which was treated with transvenous cardiac pacing.

The biochemical data during the first 24 hours are shown in Table 3. Three patients with chronic renal failure who were undergoing long-term dialysis were enrolled in the study (two treated with hypothermia and one with normothermia); however, the creatinine levels of these patients (7.9 to 11.3 mg per deciliter [700 to 1000 μmol per liter]) are not included. These patients underwent dialysis after admission. No other patient required renal support.

The hematologic data are shown in Table 4. Because many patients were treated with anticoagulants and clotting times were adjusted to the therapeutic range, it was not possible to compare coagulation times between the two groups. Three patients (one undergoing hypothermia and two undergoing normothermia) received thrombolytic therapy, and three (two undergoing hypothermia and one undergoing normothermia) underwent urgent angioplasty. There were no significant hemorrhagic complications in either group.

Outcomes

The outcomes of the patients at discharge from the hospital are shown in Table 5. Twenty-one of 43 patients in the hypothermia group (49 percent) were considered to have a good outcome (discharged to home or to a rehabilitation facility), as compared with 9 of 34 in the normothermia group (26 percent, P=0.046). Univariate analysis revealed that the patient's age and the time from collapse to return of spontaneous circulation significantly affected the outcome. For each two-year increase in age, there was a 9 percent decrease in the likelihood of a good outcome (odds ratio, 0.91; 95 percent confidence interval, 0.84 to 0.98; P=0.014), and each additional 1.5 minutes in the time from collapse to return of spontaneous circulation was associated with a 14 percent decrease in the likelihood of a good outcome (odds ratio, 0.86; 95 percent confidence interval, 0.78 to 0.94; P=0.001). Cardiopulmonary resuscitation administered by a bystander was associated with a nonsignificant improvement in outcome (odds ratio, 1.40; 95 percent confidence interval, 0.55 to 3.57; P=0.49). According to multivariate logistic-regression analysis with adjustment for base-line differences in age and in time from collapse to return of spontaneous circulation, the odds ratio for good outcome in the hypothermia group as compared with the normothermia group was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011).

The primary cause of death was considered to be cardiac failure in 5 of the 22 patients in the hypothermia group who died (these deaths occurred between 18 and 48 hours after collapse) and 4 of 23 in the normothermia group (these deaths occurred between 2 and 50 hours after collapse). One patient each in the hypothermia and normothermia groups was diagnosed as brain-dead, on day 2 and day 4, respectively. The remaining deaths in both groups re-

TABLE 2. PHYSIOLOGICAL AND HEMODYNAMIC VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	ADMISSION TO ICU	6 HR	12 HR	18 HR	24 HR
Number of patients	Hypothermia	43	39	39	39	39	38
	Normothermia	34	33	32	32	32	31
Temperature (°C)	Hypothermia	35.0±1.18	33.3±0.98†	32.7±1.19†	33.1±0.89†	36.0±1.24†	37.4±0.85†
	Normothermia	35.5±0.90	36.0±0.76†	37.1±0.75	37.4±0.58†	37.3±0.56†	37.3±0.59†
	P value‡	0.02	<0.001	<0.001	<0.001	<0.001	0.60
Mean arterial blood pressure (mm Hg)	Hypothermia	90.4±18.89	108.7±20.89†	97.0±14.92	89.5±13.16	88.8±9.17	89.1±12.9
	Normothermia	87.2±21.46	94.4±18.80	92.2±13.00	90.8±14.16	91.3±12.96	92.1±11.76
	P value‡	0.51	0.02	0.16	0.82§	0.38	0.24
Pulse (per minute)	Hypothermia	97±22.5	82±21.6§	72±17.1§	70±17.6	80±18.2§	89±17.9†
	Normothermia	105±30.4	100±17.0	100±21.9	94±17.9	97±16.8	99±15.5
	P value‡	0.18	0.001	<0.001	<0.001	<0.001	0.02
Cardiac index (liters/min/m² of body-surface area)¶	Hypothermia		2.0 (1.2–4.4)	2.1 (0.9–4.2)	2.4 (0.8–4.9)	2.9 (1.5–7.3)§	3.4 (1.6–6.8)§
	Normothermia		2.6 (1.4–5.5)	2.7 (1.4–6.1)	3.2 (1.2–6.1)	3.3 (1.5–5.8)	3.0 (1.8–5.7)
	P value‡		0.01	0.16	0.10	0.12	0.54
Systemic vascular resistance (dyn-sec·cm⁻⁵)¶	Hypothermia		2213 (599–4645)	1808 (836–4531)	1564 (439–4280)	1198 (402–2833)§	987 (551–2500)§
	Normothermia		1356 (481–2545)	1278.5 (346–2841)	1056 (340–3163)	964 (479–2204)†	1072 (591–1998)
	P value‡		0.02	<0.001	0.002	0.23	0.50

*Plus–minus values are means ±SD. Medians and ranges (in parentheses) are given for the cardiac index and systemic vascular resistance, which were log-transformed before analysis of variance was performed, because of nonparametric distribution. One patient in the hypothermia group and two in the normothermia group died during the first 24 hours. ED denotes emergency department, and ICU intensive care unit.

†P<0.05 for the comparison with the value on admission to the emergency department.

‡P values are for the differences between the hypothermia and the normothermia groups.

§P<0.01 for the comparison with the value on admission to the emergency department.

¶Cardiac index and systemic vascular resistance values are given for the 32 patients treated with hypothermia and the 22 patients treated with normothermia who had a pulmonary-artery catheter.

sulted primarily from severe neurologic injury and withdrawal of all active therapy. These deaths occurred between days 2 and 30. The difference in mortality rates between the hypothermia group (51 percent) and the normothermia group (68 percent) did not reach statistical significance (P=0.145).

DISCUSSION

Cerebral reperfusion injury occurs when cerebral blood flow is restored after cardiac arrest and resuscitation.[21] Increased intracellular levels of glutamate, an excitatory neurotransmitter released from presynaptic terminals, activate ion-channel complexes that cause calcium to shift from the extracellular to the intracellular fluid, leading to the accumulation of oxygen free radicals and the activation of degradative enzymes. In addition, cerebral hemodynamics may remain abnormal after resuscitation from cardiac arrest.[5]

Randomized, controlled studies of pharmacologic interventions to improve patients' neurologic outcome after cardiac arrest have tested thiopental,[22] corticosteroids,[23] lidoflazine,[24] and nimodipine[25] but have found no benefit. The use of hypothermia after resuscitation from cardiac arrest has been studied in laboratory animals.[7-12] These studies demonstrated significantly improved outcome when moderate hypothermia was induced after resuscitation. However, the mechanism by which hypothermia may be beneficial is uncertain. Hypothermia decreases cerebral oxygen demand and may thus provide protection from ongoing cerebral ischemia. Hypothermia also reduces the glutamate level and the subsequent production of oxygen free radicals.[26] Moreover, hypothermia decreases intracranial pressure,[27] which may be raised in some patients after resuscitation from cardiac arrest.[28]

There is concern that hypothermia may have adverse effects on cardiac function, coagulation, the immune system, and acid–base status. Accidental hypothermia is associated with increased mortality in patients with major trauma[29] or sepsis syndrome.[30] On the other hand, induced hypothermia has been studied with promising results in patients with severe stroke[31,32] and with variable results in patients with severe head injury.[27,33,34]

TABLE 3. BIOCHEMICAL VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	ADMISSION TO ICU	6 Hr	12 Hr	18 Hr	24 Hr
Number of patients	Hypothermia	43	39	39	39	39	38
	Normothermia	34	33	32	32	32	31
Potassium (mmol/liter)	Hypothermia	3.8 (2.5–7.8)	3.6 (2.6–6.9)	3.6 (2.7–6.3)	4.1 (2.6–7.6)	4.3 (3.1–5.6)†	4.5 (2.9–7.1)‡
	Normothermia	3.9 (2.2–6.4)	3.9 (2.5–5.1)	4.0 (2.7–5.7)	4.2 (3.3–5.7)	4.1 (3.1–6.0)	3.9 (3.9–4.6)
	P value§	0.84	0.98	0.06	0.52	0.05	<0.001
Lactate (mmol/liter)	Hypothermia	8.3 (2.2–14.9)	2.7 (0.9–11.6)‡	3.7 (1.2–11.8)‡	4.4 (1–11.1)‡	3.4 (0.5–10.3)‡	2.5 (0.7–11.4)‡
	Normothermia	7.5 (2–14)	2.6 (0.9–8.4)‡	3.3 (1.1–9.3)‡	3.5 (1–12.4)‡	2.6 (0.7–11)‡	1.6 (0.6–11)‡
	P value§	0.75	0.46	0.79	0.67	0.18	0.08
Glucose (mmol/liter)¶	Hypothermia	13.3 (9.0–33.0)	16.2 (7.4–26.8)	16.0 (7.1–36.7)	16.1 (4.2–28)	10.5 (4.2–25)‡	8.0 (1.6–27.8)‡
	Normothermia	12.6 (4.8–22.7)	10.5 (6.6–17.9)	12.1 (5.8–25)	11.6 (6.2–28)	10.7 (5.3–21)	7.5 (3.5–15.1)‡
	P value§	0.13	0.002	0.02	0.14	0.97	0.92
Creatine kinase (mmol/liter)	Hypothermia	149 (25–3295)	261 (85–3061)‡	635 (95–6068)‡	1544 (110–9795)‡	2221 (95–7590)‡	1079 (85–8670)‡.
	Normothermia	111 (67–635)	525 (69–2949)‡	651 (79–5306)‡	1205 (90–5750)‡	1295 (85–6794)‡	1274 (95–11,061)‡
	P value§	0.32	0.99	0.72	0.76	0.93	0.49
Creatine kinase MB (mmol/liter)	Hypothermia	21 (4–120)	27 (8–133)	50 (5–247)†	39 (5–559)‡	66 (5–432)‡	57 (4–321)‡
	Normothermia	21 (10–117)	40 (5–224)	27 (5–259)	31 (5–875)	25 (5–190)	33 (6–423)†
	P value§	0.35	0.80	0.23	0.22	0.05	0.28
Creatinine (μmol/liter)‖	Hypothermia	140 (38–211)	122 (62–215)‡	110 (50–220)‡	108 (35–345)‡	104 (35–270)‡	109 (47–310)‡
	Normothermia	125 (75–297)	120 (72–311)†	110 (66–260)	127 (55–354)	95 (45–375)	111 (50–394)†
	P value§	0.78	0.86	0.11	0.10	0.23	0.96
Arterial pH	Hypothermia	7.29±0.11	7.35±0.11‡	7.33±0.08	7.31±0.11	7.33±0.11	7.37±0.10‡
	Normothermia	7.27±0.09	7.37±0.06‡	7.36±0.07‡	7.36±0.09‡	7.37±0.06‡	7.40±0.06‡
	P value§	0.78	0.87	0.15	0.04	0.05	0.07

*Plus–minus values are means ±SD. Medians and ranges (in parentheses) are given for other variables, which were log-transformed before analysis of variance was performed, because of nonparametric distribution. One patient in the hypothermia group and two in the normothermia group died during the first 24 hours. ED denotes emergency department, and ICU intensive care unit.

†$P<0.05$ for the comparison with the value on admission to the emergency department.

‡$P<0.01$ for the comparison with the value on admission to the emergency department.

§P values are for the differences between the hypothermia and the normothermia groups.

¶To convert the values for glucose to milligrams per deciliter, divide by 0.05551.

‖To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

TABLE 4. HEMATOLOGIC VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	12 HR	24 HR
Number of patients	Hypothermia	43	39	38
	Normothermia	34	32	31
Platelet count ($\times 10^{-3}$/mm^3)	Hypothermia	209±65.7	193±60.2†	190±63.3†
	Normothermia	221±63.4	217±63.0	199±54.2†
	P value‡	0.46	0.24	0.82
White-cell count ($\times 10^{-3}$/mm^3)	Hypothermia	10.9 (5.7–21.5)	14.5 (5.5–30.4)§	14.6 (7.1–35.3)§
	Normothermia	11.1 (6.3–25.3)	14.6 (8.5–29)§	15.8 (9.8–25.3)§
	P value‡	0.46	0.12	0.34

*Values for platelet counts are means ±SD. Medians and ranges (in parentheses) are given for white-cell counts, which were log-transformed before analysis of variance was performed, because of nonparametric distribution. One patient in the hypothermia group and two in the normothermia group died during the first 24 hours. ED denotes emergency department.

†$P<0.05$ for the comparison with the value on admission to the emergency department.

‡P values are for the differences between the hypothermia and the normothermia groups.

§$P<0.01$ for the comparison with the value on admission to the emergency department.

The results of our study suggest that moderate induced hypothermia lasting for 12 hours is not associated with clinically significant adverse effects. Although hypothermia decreased the pulse rate and increased systemic vascular resistance, there were no clinically significant cardiac arrhythmias in the hypothermia group. The levels of creatine kinase (both the total and the MB fractions) were similar in both groups, suggesting that hypothermia does not increase the extent of myocardial damage in patients resuscitated after cardiac arrest. The increase in potassium at 24 hours in the hypothermia group has been previously observed during rewarming[15] and was not considered to be clinically important. The increase in blood glucose has also been previously described in patients with hypothermia.[35]

Although previous studies have shown adverse effects on platelet and white-cell counts when hypothermia is used for more prolonged periods,[14,34] we found no statistically significant differences between the two groups when hypothermia was used for 12 hours. Although we did not specifically test immune function, no clinically significant infections were noted in either group.

There are several limitations to this study. Because it was not feasible to blind clinicians to the patients' treatment-group assignments, there is a possibility that bias affected patient care and outcome. However, we attempted to treat all patients according to a protocol that minimized individual variation among physicians. It is unlikely that therapy was withdrawn from any patient inappropriately, since this was always a consensus decision of the treating medical and nursing staff, made in consultation with the family of the patient.

TABLE 5. OUTCOME OF PATIENTS AT DISCHARGE FROM THE HOSPITAL.

OUTCOME*	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

*The difference between the rates of a good outcome (normal or with minimal or moderate disability) in the hypothermia and the normothermia groups (49 percent and 26 percent, respectively) was 23 percentage points (95 percent confidence interval, 13 to 43 percentage points; P=0.046). The unadjusted odds ratio for a good outcome in the hypothermia group as compared with the normothermia group was 2.65 (95 percent confidence interval, 1.02 to 6.88; P=0.046). The odds ratio for a good outcome in the hypothermia group as compared with the normothermia group, after adjustment by logistic regression for age and time from collapse to return of spontaneous circulation, was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011).

Out-of-hospital randomization of patients in emergency medical systems is problematic. We used the method of odd and even days because it was the only one feasible for immediate use by large numbers of

ambulance officers and by the physicians in four emergency departments. Despite the potential for bias in randomization, it appears that the two patient groups were comparable. In particular, the degree of anoxic neurologic insult, as indicated by the duration of cardiac arrest, was similar in both groups. In fact, the higher rate of bystander cardiopulmonary resuscitation among the patients treated with normothermia would be expected to improve the outcome in this group. Improved outcome in the group treated with hypothermia might be explained by the exclusion of patients with a poor prognosis; however, we are not aware of eligible patients who were not included in the outcome analysis.

The assessment of outcome after cardiac arrest has been debated.[36] In this study, we considered the place to which the patient was discharged by a rehabilitation physician who was unaware of initial treatment protocols (home, rehabilitation facility, or long-term nursing facility) to be an important outcome measure. Although a patient may be discharged to a long-term nursing facility because of a lack of social support, this was not the case in the one conscious patient (in the normothermia group) who was discharged to a long-term nursing facility.

We conclude that induced hypothermia improves outcomes in patients who are comatose after resuscitation from out-of-hospital cardiac arrest. However, treatment assignment was not blinded, and there is the possibility that some aspects of care differed between the groups. Therefore, further studies are required to confirm these findings and determine the optimal duration of hypothermia.

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