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.

REFERENCES

1. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, ed. Heart disease: a textbook of cardiovascular medicine. 5th ed. Vol. 1. Philadelphia: W.B. Saunders, 1997:742-79.

2. Eisenberg MS, Horwood BT, Cummins RO, Reynolds-Haertle R, Hearne TR. Cardiac arrest and resuscitation: a tale of 29 cities. Ann Emerg Med 1990;19:179-86.

3. Bernard SA. Outcome from prehospital cardiac arrest in Melbourne, Australia. Emerg Med 1998;10:25-9.

4. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. Lancet 1994;343:1055-9.

5. Oku K, Kuboyama K, Safar P, et al. Cerebral and systemic arteriovenous oxygen monitoring after cardiac arrest: inadequate cerebral oxygen delivery. Resuscitation 1994;27:141-52.

6. Bernard S. Induced hypothermia in intensive care medicine. Anaesth Intensive Care 1996;24:382-8.

7. Sterz F, Safar P, Tisherman SA, Radovsky A, Kuboyama K, Oku K. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 1991;19:379-89.

8. Weinrauch V, Safar P, Tisherman SA, Kuboyama K, Radovsky A. Beneficial effect of mild hypothermia and detrimental effect of deep hypothermia after cardiac arrest in dogs. Stroke 1992;23:1454-62.

9. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348-58.

10. Illievich UM, Zornow MH, Choi KT, Scheller MS, Strnat MA. Effects of hypothermic metabolic suppression on hippocampal glutamate concentrations after transient global cerebral ischemia. Anaesth Analg 1994;78:905-11.

11. Colburne F, Li H, Buchan AM. Indefatigable CA1 sector neuroprotection with mild hypothermia induced 6 hours after severe forebrain ischemia in rats. J Cereb Blood Flow Metab 1999;19:742-9.

12. Hicks SD, DeFranco DB, Callaway CW. Hypothermia during reperfusion after asphyxial cardiac arrest improves functional recovery and selectively alters stress-induced protein expression. J Cereb Blood Flow Metab 2000;20:520-30.

13. Benson DW, Williams GR Jr, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. Anesth Analg 1959;38:423-8.

14. Williams GR Jr, Spencer FC. The clinical use of hypothermia following cardiac arrest. Ann Surg 1958;148:462-8.

15. Bohn DJ, Biggar WD, Smith CR, Conn AW, Barker GA. Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity and mortality after near-drowning. Crit Care Med 1986;14:529-34.

16. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 1997;30:146-53.

17. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation 1998;39:61-6.

18. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest: a clinical feasibility trial. Stroke 2000;31:86-94.

19. Adult advanced life support: the Australian Resuscitation Council guidelines. Med J Aust 1993;159:616-21.

20. Stata statistical software, version 6. College Station, Tex.: Stata, 1999.

21. White BC, Grossman LI, O'Neil BJ, et al. Global brain ischemia and reperfusion. Ann Emerg Med 1996;27:588-94.

22. Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 1986;314:397-403.

23. Jastremski M, Sutton-Tyrrell K, Vaagenes P, Abramson N, Heiselman D, Safar P. Glucocorticoid treatment does not improve neurologic recovery following cardiac arrest. JAMA 1989;262:3427-30.

24. Brain Resuscitation Clinical Trial II Study Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. N Engl J Med 1991;324:1225-31.

25. Roine RO, Kaste M, Kinnunen A, Nikki P, Sarna S, Kajaste S. Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: a placebo-controlled, double-blind, randomized trial. JAMA 1990;264:3171-7.

26. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 1989;20:904-10.

27. Morimoto Y, Kemmotsu O, Kitami K, Matsubara I, Tedo I. Acute brain swelling after out-of-hospital cardiac arrest: pathogenesis and outcome. Crit Care Med 1993;21:104-10.

28. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 1997;336:540-6.

29. Gentilello LM, Jurkovich GJ, Stark MS, Hassantash SA, O'Keefe GE. Is hypothermia in the victim of major trauma protective or harmful? A randomized, prospective study. Ann Surg 1997;226:439-47.

30. Clemmer TP, Fisher CJ Jr, Bone RC, Slotman GJ, Metz CA, Thomas FO. Hypothermia in the sepsis syndrome and clinical outcome. Crit Care Med 1992;20:1395-401.

31. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 1998;29:2461-6.

32. Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: a case-control study: the Copenhagen Stroke Study. Stroke 2000;31:2251-6.

33. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;344:556-63.

34. Bernard SA, Jones BM, Buist MD. Experience with prolonged induced hypothermia in patients with severe head injury. Crit Care (Lond) 1999;3:167-72.

35. Curry DL, Curry KP. Hypothermia and insulin secretion. Endocrinology 1970;87:750-5.

36. Hsu JWY, Madsen CD, Callaham ML. Quality-of-life and formal functional testing of survivors of out-of-hospital cardiac arrest correlates poorly with traditional neurologic outcome scales. Ann Emerg Med 1996;28:597-605.

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MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

ABSTRACT

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.)

AN estimated 375,000 people in Europe undergo sudden cardiac arrest yearly.[1] Recovery without residual neurologic damage after cardiac arrest with global cerebral ischemia is rare. After cardiac arrest with no blood flow for more than five minutes, the generation of free radicals, together with other mediators, during reperfusion creates chemical cascades that result in cerebral injury.[2] Until recently, there was no therapy with documented efficacy in preventing brain damage after cardiac arrest.

Several studies have shown that moderate systemic hypothermia (30°C)[3] or mild hypothermia (34°C)[4-8] markedly mitigates brain damage after cardiac arrest in dogs. The exact mechanism for this cerebral resuscitative effect is not clear. A reduction in cerebral oxygen consumption[9,10] and other multifactorial chemical and physical mechanisms during and after ischemia have been postulated.[11-16] These include retardation of destructive enzymatic reactions, suppression of free-radical reactions, protection of the fluidity of lipoprotein membranes, reduction of the oxygen demand in low-flow regions, reduction of intracellular acidosis, and inhibition of the biosynthesis, release, and uptake of excitatory neurotransmitters.

Preliminary clinical studies have shown that patients treated with mild hypothermia after cardiac arrest have an improved neurologic outcome, without important side effects, as compared with the outcome in historical controls.[17-20]

We compared mild hypothermia with standard normothermia in patients who had had cardiac arrest due to ventricular fibrillation. The primary end point

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was a favorable neurologic outcome within six months after cardiac arrest.[21-23] Secondary end points were mortality at six months and the incidence of complications during the first seven days. Nine centers in five European countries participated in the study.

METHODS

Patients

Patients seen consecutively in the emergency department in whom spontaneous circulation had been restored after cardiac arrest were eligible for the study. The criteria for inclusion were a witnessed cardiac arrest, ventricular fibrillation or nonperfusing ventricular tachycardia as the initial cardiac rhythm, a presumed cardiac origin of the arrest, an age of 18 to 75 years, an estimated interval of 5 to 15 minutes from the patient's collapse to the first attempt at resuscitation by emergency medical personnel, and an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation.

Patients were excluded if they met any of the following criteria: a tympanic-membrane temperature below 30°C on admission, a comatose state before the cardiac arrest due to the administration of drugs that depress the central nervous system, pregnancy, response to verbal commands after the return of spontaneous circulation and before randomization, evidence of hypotension (mean arterial pressure, less than 60 mm Hg) for more than 30 minutes after the return of spontaneous circulation and before randomization, evidence of hypoxemia (arterial oxygen saturation, less than 85 percent) for more than 15 minutes after the return of spontaneous circulation and before randomization, a terminal illness that preceded the arrest, factors that made participation in follow-up unlikely, enrollment in another study, the occurrence of cardiac arrest after the arrival of emergency medical personnel, or a known preexisting coagulopathy.

Study Design

The study was designed as a randomized, controlled trial with blinded assessment of the outcome. The protocol and consent procedure were approved by the institutional review board of each participating center. For all patients, the requirement of informed consent was waived in accordance with the ethical standards of the local institutional review board and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products.[24] The patient's family was informed about the trial, and the protocol specified that if there were any objections, the patient would be withdrawn from the study. However, there were no objections.

Treatment assignments were randomly generated by computer in blocks of 10, with stratification according to center. Sealed envelopes containing the treatment assignments were provided by the biostatistics center. Immediately after a patient had been enrolled, an envelope was opened, and the patient was assigned to the specified group.

Personnel involved in the care of patients during the first 48 hours after cardiac arrest could not be blinded with respect to treatment assignments. However, the physicians responsible for assessing the neurologic outcome within the first six months after the arrest were unaware of the treatment assignments.

Treatment

All patients received standard intensive care according to a detailed protocol. Sedation was induced by the intravenous administration of midazolam (0.125 mg per kilogram of body weight per hour initially) and fentanyl (0.002 mg per kilogram per hour initially), and the doses were adjusted as needed for 32 hours for the management of mechanical ventilation. To prevent shivering, paralysis was induced by the intravenous administration of pancuronium (0.1 mg per kilogram) every 2 hours for a total of 32 hours. Intracranial pressure was not monitored.

The temperature on admission was measured with an infrared tympanic thermometer (Ototemp LighTouch, Exergen, Watertown, Mass.). Further temperature measurements were made with a bladder-temperature probe (Foley catheter). Patients randomly assigned to the normothermia group were placed on a conventional hospital bed, and normothermia was maintained. Those randomly assigned to the hypothermia group were cooled to a target temperature of 32°C to 34°C with the use of an external cooling device (TheraKool, Kinetic Concepts, Wareham, United Kingdom). This device consists of a mattress with a cover that delivers cold air over the entire body. The goal was to reach the target bladder temperature within four hours after the return of spontaneous circulation. If this goal was not achieved, ice packs were applied. The temperature was maintained at 32°C to 34°C for 24 hours from the start of cooling, followed by passive rewarming, which we expected would occur over a period of 8 hours.

Data Collection

Data on cardiac arrest for individual patients were recorded in the Utstein style.[25] Laboratory tests were performed at base line, 12 and 48 hours after cardiac arrest, and as clinically indicated. Risk factors for an unfavorable outcome (hypotension or a nonfatal cardiac arrest after resuscitation) were documented.

Outcome

The primary outcome was a favorable neurologic outcome within six months, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on a five-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[21-23] The neurologic outcome was determined without knowledge of the patient's treatment assignment. Patients with good recovery or moderate disability had sufficient cerebral function to live independently and work at least part-time.

Secondary end points were overall mortality at six months and the rate of complications during the first seven days after cardiac arrest. Bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores were recorded. Since an individual patient might have more than one complication at a time, the occurrence of at least one complication of any kind per patient was also documented.

Statistical Analysis

Continuous variables, which were not normally distributed, are reported as medians and interquartile ranges. Categorical variables are reported as counts and percentages. Primary and secondary outcomes were binary, and the chi-square test or Fisher's exact test, as appropriate, was used to compare outcomes in the hypothermia and normothermia groups. Trends across subgroups were measured with an extension of the Wilcoxon rank-sum test.[26] The difference in risk between the two groups, with the corresponding 95 percent confidence interval, was calculated as a measure of the absolute risk, which was then used to calculate the number needed to treat. Risk ratios are reported as a measure of relative risk.

We used a multivariate logistic-regression model to determine whether the association between the intervention and the primary and secondary outcomes (neurologic recovery and mortality) was confounded by base-line differences between the study groups. All the covariables listed in Table 1 were entered into the model, except for the dose of epinephrine, which was excluded because of collinearity with the interval from the patient's collapse to the restoration of spontaneous circulation. We converted odds ratios to risk ratios using the following formula:

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	NORMOTHERMIA (N=138)	HYPOTHERMIA (N=137)
Age — yr		
Median	59	59
Interquartile range	49–67	51–69*
Female sex — no./total no. (%)	32/138 (23)	33/137 (24)
Medical history — no./total no. (%)		
Diabetes	26/138 (19)	11/135 (8)
Coronary heart disease	59/138 (43)	43/135 (32)
Cerebrovascular disease	11/138 (8)	10/135 (7)
NYHA class III or IV†	16/132 (12)	14/130 (11)
Location of cardiac arrest — no./total no. (%)		
Home	70/138 (51)	69/135 (51)
Public place	53/138 (38)	48/135 (36)
Other‡	15/138 (11)	18/135 (13)
Arrest witnessed — no./total no. (%)§	136/138 (99)	134/137 (98)
Presumed cardiac origin of arrest — no./total no. (%)§	135/138 (98)	135/137 (99)
Ventricular fibrillation or pulseless ventricular tachycardia — no./total no. (%)§	132/138 (96)	133/137 (97)
Basic life support provided by bystander — no./total no. (%)	68/138 (49)	59/137 (43)
Interval between collapse and restoration of spontaneous circulation — min¶		
Median	22	21
Interquartile range	17–33	15–28
Total epinephrine dose — mg		
Median	3	3
Interquartile range	1–6	1–5*
Hypotension after resuscitation — no./total no. (%)	68/138 (49)	75/137 (55)
Subsequent nonfatal arrest — no./total no. (%)	11/138 (8)	15/137 (11)
Thrombolysis after resuscitation — no./total no. (%)	24/133 (18)	27/135 (20)

*Data were not available for two patients.

†NYHA denotes New York Heart Association.

‡Other locations included a physician's office, the workplace, and the hospital.

§Although this was a criterion for inclusion in the study, in a few cases, the initial information was incorrect.

¶Data were not available for three patients in the normothermia group and four in the hypothermia group.

$$\text{risk ratio} = \text{odds ratio} \div ([1 - \text{incidence in normothermia group}] + \text{incidence in normothermia group} \times \text{odds ratio}).^{27}$$

Confounding can be assumed if the crude risk ratio differs from the adjusted risk ratio. Goodness of fit was assessed with the Hosmer–Lemeshow chi-square test. A reasonable fit can be assumed if the result is not significant at the 5 percent level. Analysis was carried out according to the intention-to-treat principle. Stata software (version 7, Stata, College Station, Tex.) was used to analyze the data.

RESULTS

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, with 137 patients randomly assigned to the hypothermia group and 138 to the normothermia group (i.e., the group that received standard care after resuscitation). Hypothermia was discontinued early in 14 patients for the following reasons: death (6 patients), arrhythmia and hemodynamic instability (3), technical problems with the cooling device (2), liver rupture (1), previous random assignment to the hypothermia group (1), and an error in the duration of cooling (1). All randomized patients were included in the analysis of mortality. One patient in each group was lost to follow-up for neurologic status.

At base line, the patients in the two groups were generally similar, although the patients in the normothermia group were more likely to have a history of diabetes mellitus or coronary heart disease and to have received basic life support from a bystander than were those in the hypothermia group. These differences appear to have been due to random variation (Table 1).

Cooling

In patients randomly assigned to the hypothermia group, the median interval between the restoration of spontaneous circulation and the initiation of cooling was 105 minutes (interquartile range, 61 to 192). The median interval between the restoration of spontaneous circulation and the attainment of a temperature between 32°C and 34°C was 8 hours (interquartile range, 4 to 16). In 19 patients, the target temperature could not be reached. Ice packs were required for 93 of the 132 patients for whom data were available (70 percent). The median duration of cooling was 24 hours (interquartile range, 24 to 25), and among patients in whom the target temperature was reached, it was maintained for a median of 24 hours (interquartile range, 12 to 29). Passive rewarming to a temperature above 36°C lasted for a median of 8 hours (interquartile range, 8 to 12). The temperature curves for the normothermia and hypothermia groups are shown in Figure 1.

Outcome at Six Months

A total of 75 of the 136 patients (55 percent) in the hypothermia group had a favorable neurologic outcome, as compared with 54 of the 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81) (Table 2). To prevent one unfavorable neurologic outcome, 6 patients would need to be treated with hypothermia (95 percent confidence interval, 4 to 25 patients). After adjustment for a history of diabetes mellitus, a history of coronary heart disease, and receipt of basic life support from a bystander, the risk ratio changed only marginally (data not shown). After adjustment for all the base-line variables shown in Table 1, the risk ratio increased slightly, to 1.47 (95 percent confidence interval, 1.09 to 1.82).

The rate of death six months after cardiac arrest was 14 percentage points lower in the hypothermia group than in the normothermia group (risk ratio for the hypothermia group, 0.74 [95 percent confidence interval, 0.58 to 0.95]) (Table 2 and Fig. 2). On the basis of the difference in the risk of death between the two groups, 7 patients would need to be treated with hypothermia (95 percent confidence interval, 4 to 33 patients) to prevent 1 death. After adjustment for base-line differences in the proportions of patients with a history of diabetes mellitus, a history of coronary heart disease, and receipt of basic life support from a bystander, the risk ratio changed only minimally (data not shown). After adjustment for all the base-line variables shown in Table 1, the effect

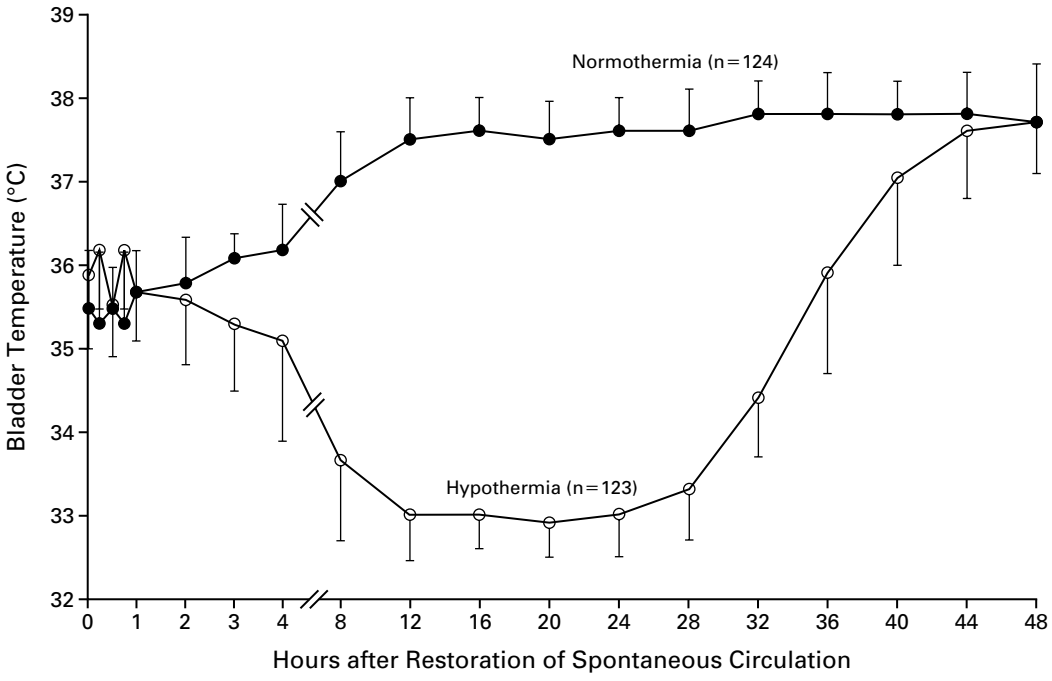


Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups.

The T bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.

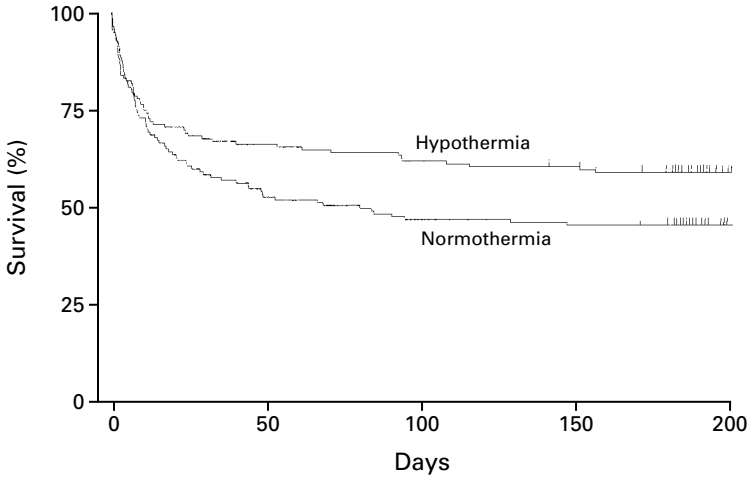
TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

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.



NO. AT RISK					
Hypothermia	137	92	86	83	11
Normothermia	138	74	66	64	9

Figure 2. Cumulative Survival in the Normothermia and Hypothermia Groups. Censored data are indicated by tick marks.

of hypothermia on mortality was slightly stronger (risk ratio, 0.62; 95 percent confidence interval, 0.36 to 0.95).

Most of the patients with unfavorable neurologic outcomes died within six months after discharge from the hospital. In this subgroup of patients, mortality after discharge did not differ significantly according to the assigned treatment (Table 3).

Complications

The proportion of patients with any complication did not differ significantly between the two groups (93 of 132 patients in the normothermia group [70 percent] and 98 of 135 in the hypothermia group [73 percent], P=0.70). Sepsis was more likely to develop in the patients with hypothermia than in those with normothermia, although this difference was not statistically significant (Table 4). The total number of complications was not significantly higher in the hypothermia group than in the normothermia group (P=0.09).

DISCUSSION

Our results show that among patients in whom spontaneous circulation had been restored after cardiac arrest due to ventricular fibrillation, systemic cool-

TABLE 3. DEATHS BEFORE DISCHARGE AND DEATHS AFTER DISCHARGE ACCORDING TO THE CEREBRAL-PERFORMANCE CATEGORY.

OUTCOME	NORMOTHERMIA	HYPOTHERMIA
Death in hospital — no.	69	50
Not discharged — no.	2	2
Death after discharge — no./ total no. discharged*		
CPC 1	0/30	1/45
CPC 2	0/12	0/19
CPC 3	1/16	1/14
CPC 4	6/8	4/6

*One patient in the normothermia group and one in the hypothermia group were lost to follow-up. There were no significant differences between the two groups (chi-square = 0.30, with 3 df; P = 0.96). A cerebral-performance category (CPC) of 1 indicates good cerebral performance (the patient is alert and has normal cerebral function). CPC 2 indicates moderate disability (the patient is alert and has sufficient cerebral function to live independently and work part-time). Such patients might have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory loss or other mental changes. CPC 3 indicates severe cerebral disability (the patient is conscious but dependent on others for daily support because of impaired brain function). CPC 4 indicates a vegetative state.

TABLE 4. COMPLICATIONS DURING THE FIRST SEVEN DAYS AFTER CARDIAC ARREST.*

COMPLICATION	NORMOTHERMIA	HYPOTHERMIA
	no./total no. (%)	
Bleeding of any severity†	26/138 (19)	35/135 (26)
Need for platelet transfusion	0/138	2/135 (1)
Pneumonia	40/137 (29)	50/135 (37)
Sepsis	9/138 (7)	17/135 (13)
Pancreatitis	2/138 (1)	1/135 (1)
Renal failure	14/138 (10)	13/135 (10)
Hemodialysis	6/138 (4)	6/135 (4)
Pulmonary edema	5/133 (4)	9/136 (7)
Seizures	11/133 (8)	10/136 (7)
Lethal or long-lasting arrhythmia	44/138 (32)	49/135 (36)
Pressure sores	0/133	0/136

*None of the comparisons between the two groups, performed with the use of Pearson's chi-square test, indicated significant differences.

†The sites of bleeding were mucous membranes, the nose, the urinary tract, the gastrointestinal tract, subcutaneous tissue, and skin, as well as intracerebral and intraabdominal sites.

ing to a bladder temperature between 32°C and 34°C for 24 hours increased the chance of survival and of a favorable neurologic outcome (a cerebral-performance category of 1 or 2), as compared with standard normothermic life support.

The use of moderate hypothermia after cardiac arrest was initially reported in the late 1950s and early 1960s.[28-30] Although the target temperature was lower in these studies than in ours and the method and duration of cooling also differed from those in our study, the results were similar. However, the findings were inconclusive, and the rate of complications was higher than that observed with the mild hypothermia used in our study. There were no further investigations of hypothermia as a resuscitative measure until the 1990s, when laboratory studies demonstrated the benefit of mild hypothermia.[4-8,16] These studies led to preliminary clinical studies of mild hypothermia.

In the study by Bernard et al.,[17] cooling was induced more rapidly (with ice packs) and for a shorter period than in our study. Nevertheless, the results were similar to ours. The neurologic outcome has also been consistently favorable in studies of mild hypothermia in animals.[31-34] In the pilot studies by Yanagawa et al.[18] and Nagao et al.,[19] the frequency of a favorable neurologic outcome was similar to that in our study, although the method and duration of cooling in these studies differed from those in our study. In contrast to these encouraging findings, a study of hypothermia in patients with traumatic brain injury[35] showed no improvement in the neurologic outcome. The reasons for this discrepancy are thought to include the different pathogenesis of direct central nervous system injury, as well as the late initiation of cooling in some of the patients and variations in intensive care and life support among participating hospitals.[35,36]

Although the proportions of patients with any complication did not differ significantly between the two treatment groups in our study, a detailed analysis of the complications and an analysis of the total number of complications revealed a trend toward a higher rate of infectious problems in the hypothermia group. Nevertheless, the benefit of hypothermia exceeded its possible adverse effects.

One limitation of our study was the fact that the attending physicians could not be blinded to the treatment assignments. The relative risk may be slightly exaggerated in studies that are not double blind.[37] Although the outcome was assessed without knowledge of the treatment assignments, we did not verify that the blinding was successful. Even if it was not successful in a few cases, we do not believe that any bias that might have been introduced would have been strong enough to invalidate our findings.

The study population was restricted to a group of patients with a high risk of brain damage because of the specified interval between the patient's collapse and the first attempt at resuscitation by emergency

medical personnel, as well as other factors, so only 8 percent of the patients assessed for eligibility were included in the trial. Further studies are warranted to determine whether our findings apply to patients at lower risk for brain damage and to those with cardiac arrest due to causes other than ventricular fibrillation.

Treatment with hypothermia may be of value in terms of public health. Each year, cardiac arrest occurs in approximately 375,000 people in Europe,[1] about 30,000 of whom would meet our inclusion criteria. We can be 95 percent confident that treatment with hypothermia would prevent an unfavorable neurologic outcome in 1200 to 7500 of these patients.

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APPENDIX

The following investigators participated in the Hypothermia after Cardiac Arrest Study Group (the number of patients enrolled at each center is shown): **Chair, Central Coordinating Office** —M. Holzer (Universitätsklinik für Notfallmedizin, Vienna, Austria); **Steering Committee** — E. Cerchiari (Ospedale Niguarda Ca'Granda, Milan, Italy), P. Martens (A.Z. Sint Jan, Bruges, Belgium), R. Roine (Helsinki University Hospital, Helsinki, Finland), F. Sterz (Universitätsklinik für Notfallmedizin, Vienna, Austria); **Central Coordinating Office** — P. Eisenburger, C. Havel, J. Kofler, E. Oschatz, K. Rohrbach, W. Scheinecker, W. Schörkhuber; **hospital investigators** — W. Behringer, A. Zeiner (Universitätsklinik für Notfallmedizin, Vienna, Austria; 88 patients); A. Valentin (Krankenhaus Rudolfstiftung, Vienna, Austria; 2 patients); M. De Meyer (A.Z. Sint Jan, Bruges, Belgium; 35 patients); O. Takunen, M. Tiainen (Helsingin Yliopistollisen Keskussairaalan, Helsinki, Finland; 71 patients); S. Hachimi-Idrissi, L. Huyghens (Academisch Ziekenhuis van de Vrije Universiteit Brussel, Brussels, Belgium; 25 patients); M. Fischer, P. Walger (Medizinische Fakultat der Rheinischen Friedrich-Wilhems-Universitat Bonn, Bonn, Germany; 15 patients); A. Bartsch, M. Foedisch (Evangelisches Waldkrankenhaus Bonn, Bonn, Germany; 15 patients); E. Cerchiari (Ospedale Niguarda Ca'Granda, Milan, Italy; 12 patients); M. Bonizzoli, E. Pagni (Azienda Ospedalieria Careggi, Florence, Italy; 12 patients); **Monitoring Committee** — A.N. Laggner (Universitätsklinik für Notfallmedizin, Vienna, Austria), A. Kaff (Rettungs- und Krankenbeförderungsdienst der Stadt Wien, Vienna, Austria), B. Schneider (randomization procedure) (Institut für Medizinische Statistik, Universität Wien, Vienna, Austria); **Data Analysis** — M. Müllner (Universitätsklinik für Notfallmedizin, Vienna, Austria).

REFERENCES

1. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997;30:1500-5.
2. Negovsky VA. Postresuscitation disease. Crit Care Med 1988;16:942-6.
3. Leonov Y, Sterz F, Safar P, Radovsky A. Moderate hypothermia after cardiac arrest of 17 minutes in dogs: effect on cerebral and cardiac outcome. Stroke 1990;21:1600-6.
4. Leonov Y, Sterz F, Safar P, et al. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 1990;10:57-70.
5. Sterz F, Safar P, Tisherman S, Radovsky A, Kuboyama K, Oku K. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 1991;19:379-89.
6. Weinrauch V, Safar P, Tisherman S, Kuboyama K, Radovsky A. Beneficial effect of mild hypothermia and detrimental effect of deep hypothermia after cardiac arrest in dogs. Stroke 1992;23:1454-62.
7. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348-58.
8. Safar P, Xiao F, Radovsky A, et al. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. Stroke 1996;27:105-13.
9. Hegnauer AH, D'Amato HE. Oxygen consumption and cardiac output in the hypothermic dog. Am J Physiol 1954;178:138-42.
10. Mezrow CK, Sadeghi AM, Gandsas A, et al. Cerebral blood flow and metabolism in hypothermic circulatory arrest. Ann Thorac Surg 1992;54:609-15.
11. Chopp M, Knight R, Tidwell CD, Helpern JA, Brown E, Welch KM. The metabolic effects of mild hypothermia on global cerebral ischemia and recirculation in the cat: comparison to normothermia and hyperthermia. J Cereb Blood Flow Metab 1989;9:141-8.
12. Dempsey RJ, Combs DJ, Maley ME, Cowen DE, Roy MW, Donaldson DL. Moderate hypothermia reduces postischemic edema development and leukotriene production. Neurosurgery 1987;21:177-81.
13. Kramer RS, Sanders AP, Lesage AM, Woodhall B, Sealy WC. The effect of profound hypothermia on preservation of cerebral ATP content during circulatory arrest. J Thorac Cardiovasc Surg 1968;56:699-709.
14. Natale JA, D'Alecy LG. Protection from cerebral ischemia by brain cooling without reduced lactate accumulation in dogs. Stroke 1989;20:770-7.
15. Sterz F, Leonov Y, Safar P, et al. Multifocal cerebral blood flow by Xe-CT and global cerebral metabolism after prolonged cardiac arrest in dogs: reperfusion with open-chest CPR or cardiopulmonary bypass. Resuscitation 1992;24:27-47.
16. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 1989;20:904-10.
17. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 1997;30:146-53.
18. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation 1998;39:61-6.
19. Nagao K, Hayashi N, Kanmatsuse K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. J Am Coll Cardiol 2000;36:776-83.
20. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest: a clinical feasibility trial. Stroke 2000;31:86-94.
21. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4.
22. Brain Resuscitation Clinical Trial II Study Group. A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. N Engl J Med 1991;324:1225-31.
23. Safar P, Bircher NG. Cardiopulmonary cerebral resuscitation: basic and advanced cardiac and trauma life support: an introduction to resuscitation medicine. 3rd ed. London: W.B. Saunders, 1988:267.
24. Human Medicines Evaluation Unit. Note for guidance on good clinical practice (clinical practice medicinal products [CPMP]/International Conference of Harmonization [ICH]/135/95). Guidelines for good clinical practice. ICH topic E6. London: European Agency for the Evaluation of Medicinal Products, 1995:1-58. (Also available at http://www.eudra.org/emca.html.)
25. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style: a statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 1991;84:960-75.
26. Cuzick J. A Wilcoxon-type test for trend. Stat Med 1985;4:87-90.
27. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.
28. Benson DW, Williams GR Jr, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. Anesth Analg 1958;38:423-8.
29. Williams GR Jr, Spencer FC. The clinical use of hypothermia following cardiac arrest. Ann Surg 1959;148:462-8.

30. Ravitch MM, Lane R, Safar P, Steichen FM, Knowles P. Lightning stroke: report of a case with recovery after cardiac massage and prolonged artificial respiration. N Engl J Med 1961;264:36-8.
31. Markarian GZ, Lee JH, Stein DJ, Hong SC. Mild hypothermia: therapeutic window after experimental cerebral ischemia. Neurosurgery 1996; 38:542-50.
32. Coimbra C, Wieloch T. Hypothermia ameliorates neuronal survival when induced 2 hours after ischaemia in the rat. Acta Physiol Scand 1992; 146:543-4.
33. Colbourne F, Li H, Buchan AM. Indefatigable CA1 sector neuroprotection with mild hypothermia induced 6 hours after severe forebrain ischemia in rats. J Cereb Blood Flow Metab 1999;19:742-9.
34. Hickey RW, Ferimer H, Alexander HL, et al. Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats. Crit Care Med 2000;28:3511-6.
35. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;344:556-63.
36. Safar P, Kochanek PM. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;345:66.
37. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.