

# From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest\*

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**Objectives:** Therapeutic hypothermia has been recommended for postcardiac arrest coma due to ventricular fibrillation. However, no studies have evaluated whether therapeutic hypothermia could be effectively implemented in intensive care practice and whether it would improve the outcome of all comatose patients with cardiac arrest, including those with shock or with cardiac arrest due to nonventricular fibrillation rhythms.

**Design:** Retrospective study.

**Setting:** Fourteen-bed medical intensive care unit in a university hospital.

**Patients:** Patients were 109 comatose patients with out-of-hospital cardiac arrest due to ventricular fibrillation and nonventricular fibrillation rhythms (asystole/pulseless electrical activity).

**Interventions:** We analyzed 55 consecutive patients (June 2002 to December 2004) treated with therapeutic hypothermia (to a central target temperature of 33°C, using external cooling). Fifty-four consecutive patients (June 1999 to May 2002) treated with standard resuscitation served as controls. Efficacy, safety, and outcome at hospital discharge were assessed. Good outcome was defined as Glasgow-Pittsburgh Cerebral Performance category 1 or 2.

**Measurements and Main Results:** In patients treated with therapeutic hypothermia, the median time to reach the target

temperature was 5 hrs, with a progressive reduction over the 18 months of data collection. Therapeutic hypothermia had a major positive impact on the outcome of patients with cardiac arrest due to ventricular fibrillation (good outcome in 24 of 43 patients [55.8%] of the therapeutic hypothermia group vs. 11 of 43 patients [25.6%] of the standard resuscitation group,  $p = .004$ ). The benefit of therapeutic hypothermia was also maintained in patients with shock (good outcome in five of 17 patients of the therapeutic hypothermia group vs. zero of 14 of the standard resuscitation group,  $p = .027$ ). The outcome after cardiac arrest due to nonventricular fibrillation rhythms was poor and did not differ significantly between the two groups. Therapeutic hypothermia was of particular benefit in patients with short duration of cardiac arrest (<30 mins).

**Conclusions:** Therapeutic hypothermia for the treatment of postcardiac arrest coma can be successfully implemented in intensive care practice with a major benefit on patient outcome, which appeared to be related to the type and the duration of initial cardiac arrest and seemed maintained in patients with shock. (Crit Care Med 2006; 34:1865–1873)

**KEY WORDS:** therapeutic hypothermia; cardiac arrest; practical implementation; cytokines; outcome

Recently, therapeutic hypothermia (TH) has been shown in two randomized controlled trials to improve neurologic outcome of unconscious survivors of out-of-hospital cardiac arrest (CA) due to ventricular fibrillation (VF) and without circulatory shock (1, 2) and has therefore been recommended in this setting (3).

However, when introducing new therapeutic interventions into daily practice, major problems can arise that might potentially limit their effective clinical application, and indeed several technical difficulties have been identified with respect to the practical implementation of TH (4, 5). The duration of cooling, which varied from 12 (2) to 24 (1) hrs in the previously mentioned trials, and the optimal method to induce mild hypothermia have still to be found (6). In fact, various cooling techniques have been used, either external, such as ice bags (2) or cooling blankets (1, 7), or internal, such as specialized central venous catheters (8) or intravenous infusion of cooled fluids (9). TH may also have unwanted side effects, including reduction of cardiac index (2, 10), electrolyte disorders that might increase the risk of arrhythmias (10, 11), altered renal function with polyuria that predisposes to hypovolemia (12), and increased rate of infections (1). Furthermore, hypothermia-related side effects might cumulate with those due to post-CA cardiovascular and immune dysfunction (13, 14). The latter consideration probably explains why patients with sustained hypotension and shock were excluded from the previously mentioned trials (1, 2). For these reasons, TH has not been broadly incorporated into clinical practice (15).

We conducted a retrospective study in our intensive care unit (ICU), aiming to determine whether TH could be successfully applied in critical care practice to all comatose patients resuscitated from out-of-hospital CA, including CA due to VF and non-VF rhythms. We then assessed the potential benefit of TH on patient

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outcome, looking to the type and the duration of initial CA and the presence or absence of shock.

## METHODS

**Patients.** This retrospective study was conducted in the 14-bed medical ICU of Lausanne University Hospital, Switzerland. Full access to patient flowcharts was approved by our institutional review board. The study population consisted of 109 patients successfully resuscitated from out-of-hospital CA. The initial rhythm was VF in 86 of them and asystole or pulseless electric activity in the remaining 23. Out-of-hospital resuscitation was delivered by an emergency team, which included one trained physician, in accordance with the recommendations of the American Heart Association. Patients were initially admitted to the emergency room (where they were immediately managed by critical care physicians) and, after stabilization, were rapidly transferred to the ICU. All patients had persistent coma at admission.

**Myocardial Reperfusion Strategy.** All patients with acute ST-segment elevation myocardial infarction were immediately transferred to the cardiology catheter laboratory for primary angioplasty and stenting before being admitted to the ICU.

**Standard Resuscitation.** Comatose patients having suffered from out-of-hospital CA, admitted to our ICU from June 1999 to May 2002, served as historical controls. All patients were equipped with an intra-arterial and a central venous catheter. These patients were treated with standard resuscitation (SR), which consisted of maintaining mean arterial pressure (MAP) at 75–80 mm Hg (by the use of norepinephrine, when necessary),  $P_{aO_2}$  at 90–100 mm Hg,  $P_{aCO_2}$  at 36–40 mm Hg, and blood glucose between 6 and 8 mmol/L. Patients with sustained hypotension and shock (systolic blood arterial pressure <90 mm Hg for >60 mins, unresponsive to volume resuscitation, requiring vasopressor treatment) were equipped with a pulmonary artery catheter (Edwards LifeSciences Corporation, Irvine, CA) and treated with dobutamine, aiming at mixed venous oxygen saturation >65% and an arterial blood lactate <2.5 mmol/L, according to our local procedures for resuscitation of cardiocirculatory shock. Hemodynamic support was given at the discretion of the treating clinician.

**Therapeutic Hypothermia.** From June 2002 to September 2004, TH was implemented in our ICU for the treatment of all patients with out-of-hospital CA, including those having sustained hypotension and shock. This consisted of standard resuscitation (as previously described) plus mild hypothermia. All patients were equipped with an intra-arterial catheter and, for the continuous reliable monitoring of central temperature, with a pulmonary artery catheter. Mild hypothermia to 33°C was induced with external cooling: On

arrival to the emergency room, patients were covered with ice bags on the neck, axillae, torso, and groins. In the ICU, a cooling mattress was used (Cincinnati SubZero, Cincinnati, OH). Temperature was maintained at that level for 24 hrs. Passive rewarming was then started, with absolute avoidance in that respect of any active measure, first to a target of 35°C and then taking care not to exceed 37.5°C (using paracetamol and external cooling as necessary) until 48 hrs had elapsed from hospital admission. Patients were treated with sedation (midazolam, 0.1 mg/kg/hr intravenously), analgesia (fentanyl, 1.5  $\mu$ g/kg/hr intravenously), and paralysis (intravenous boluses of vecuronium, 0.1 mg/kg, according to nerve stimulator monitoring), which were stopped on rewarming as soon as the central temperature reached 35°C.

In addition to mild hypothermia, patients were treated, when necessary, with norepinephrine to maintain MAP between 90 and 100 mmHg, according to previous studies (2).

For both patient groups, treatment was started immediately on admission to the emergency room (= time 0).

**Data Collection and Assessment of Outcome.** Data were collected by retrospective analysis of patients' flowcharts. Patient outcome was assessed using Glasgow-Pittsburgh Cerebral Performance categories (CPC) (16). CPC 1 indicates essentially total recovery (conscious and alert patient, able to work and to lead a normal life). Patients with CPC 2 have moderate disability (conscious, able to work at least part-time, and independent for their daily life activities, with or without neurologic manifestations such as hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes). CPC 3 indicates severe disability (conscious, but fully dependent on others for daily support because of severely impaired cognitive function; these patients are discharged to institutions or long-term rehabilitation facilities). Patients with CPC 4 are in vegetative state, and CPC 5 indicates death. Outcome was assessed blindly (i.e., without knowledge of whether TH had been applied) by two physicians who independently reviewed the reports of neurologic examinations made just before hospital discharge. Good outcome was defined as CPC 1 or 2 at hospital discharge.

**Neurologic Assessment and Termination of Life Support.** Neurologic assessment and decision regarding termination of life support were based on daily examination made by the ICU physician and the consultant neurologist and, when necessary, on the results of electroencephalograph and somatosensory evoked potentials (17).

**Statistical Analysis.** Univariate comparisons between the two treatment groups (i.e., TH and SR) were carried out with Student's *t*-tests for continuous variables and with chi-square tests for categorical variables. We used multivariable binary logistic regression in order to adjust the estimated effect of TH on

outcome for possible confounders. Neurologic outcome was dichotomized as good (CPC 1 or 2) or bad (CPC 3–5). In addition to treatment group, the following potential predictors were considered: a) baseline variables: time from collapse to return of spontaneous circulation (ROSC), initial rhythm, presence of shock, and blood lactate; and b) hemodynamic status in the first 24 hrs of treatment: mean blood pressure and need for vasopressors, inotropic agents, and volume expansion. All the aforementioned covariates were entered, along with the treatment group, into an initial model without interactions. The final model was selected using backward elimination. Goodness of fit was assessed with the likelihood ratio statistic. The JMP starter software (SAS Institute, Cary, NC) was used for data analysis. We considered  $p < .05$  to be statistically significant.

## RESULTS

**Patient Characteristics.** A total of 109 patients (86 patients with CA due to VF, 23 patients with CA due to non-VF initial rhythms) were analyzed. Baseline clinical and physiologic characteristics were comparable between patients treated with TH or with SR, after CA following VF (Table 1) or non-VF rhythms (Table 2). Of note, the time from collapse to ROSC, and the values of arterial blood lactate and pH, which are major indicators of the severity of CA as well as important prognostic determinants (2, 18), did not differ between the treatment groups (Tables 1 and 2). As compared with CA following VF, CA following non-VF initial rhythms was of greater severity, as reflected by the longer time from collapse to ROSC ( $22.5 \pm 8.8$  mins vs.  $32.7 \pm 5.5$  mins,  $p < .001$ ), the higher blood lactate values at admission ( $7.7 \pm 3.3$  mmol/L vs.  $10.7 \pm 3.2$  mmol/L,  $p = .002$ ), and the higher proportion of patients with shock (23.3% vs. 45.8%,  $p = .03$ ).

**Efficiency of TH Implementation.** The median temperatures, with interquartile ranges, at each time point during the first 48 hrs are shown in Table 3 for the two treatment groups. As counted from emergency room admission (time 0), the median delay needed to reach the target central temperature of 33°C in patients receiving TH was 5 hrs (interquartile range, 3–7 hrs). There was a statistically significant trend for this delay to decrease with accruing experience (Fig. 1). Indeed, the median delay was 6 hrs for the first 20 patients treated with TH vs. 4 hrs for the last 20. Passive rewarming to a central temperature of 35°C took a median of 8 hrs (interquartile range, 6–10 hrs).

**Table 1.** Baseline characteristics of comatose patients with out-of-hospital cardiac arrest (initial rhythm: ventricular fibrillation)

	Therapeutic Hypothermia (n = 43)	Standard Resuscitation (n = 43)	p Value
Mean age, yrs	59 ± 15	63 ± 14	.22
Male gender, %	76.7	76.7	1.0
Diabetes, %	9.3	9.3	1.0
History of myocardial infarction, %	30.2	37.2	.49
History of stroke, %	9.3	7.0	.69
Acute STEMI, %	55.8	53.5	.82
Shock before starting the treatment, %	23.3	20.9	.79
Mean arterial pressure, mm Hg	91.9 ± 21.6	90.4 ± 20.6	.74
Heart rate, beats/min	103 ± 24	97 ± 26	.31
Time from collapse to ROSC, min	23.1 ± 9.0	22.7 ± 9.5	.86
Arterial lactate, mmol/L	7.9 ± 3.0	8.8 ± 4.4	.32
Arterial pH	7.16 ± 0.15	7.18 ± 0.15	.58

STEMI, ST segment elevation myocardial infarction; ROSC, return of spontaneous circulation.

Values are either mean ± SD or percentage of total number of patients in corresponding treatment group.

**Table 2.** Baseline characteristics of comatose patients with out-of-hospital cardiac arrest (initial rhythm: nonventricular fibrillation [asystole or pulseless electrical activity])

	Therapeutic Hypothermia (n = 12)	Standard Resuscitation (n = 11)	p Value
Mean age, yrs	57 ± 14	64 ± 11	.19
Asystole, <sup>a</sup> %	75.0	63.0	.65
Pulseless electrical activity, <sup>b</sup> %	25.0	36.0	.65
Shock before starting the treatment, %	50.0	45.0	.82
Mean arterial pressure, mm Hg	93.1 ± 23.7	87.0 ± 22.2	.53
Heart rate, beats/min	118 ± 31	120 ± 27	.86
Time from collapse to ROSC, mins	34.6 ± 11.9	27.5 ± 4.6	.09 <sup>c</sup>
Arterial lactate, mmol/L	9.8 ± 2.6	11.6 ± 3.8	.23
Arterial pH	7.00 ± 0.17	6.94 ± 0.21	.47

ROSC, return of spontaneous circulation.

Values are either mean ± SD or percentages of total number of patients in corresponding treatment group.

<sup>a</sup>Acute myocardial infarction n = 6, severe hypoxemia n = 3, malignant arrhythmia n = 2, toxic overdose (antiarrhythmic drugs) n = 2, severe hypovolemia n = 1, massive pulmonary embolism n = 1, anaphylaxis n = 1; <sup>b</sup>massive pulmonary embolism n = 3, acute myocardial infarction n = 2, severe hypovolemia n = 2; <sup>c</sup>p value corrected for unequal variances.

**Table 3.** Time-course of body temperature in comatose patients with out-of-hospital cardiac arrest treated with either therapeutic hypothermia or standard resuscitation

Treatment group	Temperature (°C) at Each Time-Point During the First 48 Hrs							
	0 Hrs	3 Hrs	6 Hrs	12 Hrs	18 Hrs	24 Hrs	36 Hrs	48 Hrs
Therapeutic hypothermia	35.4 (34.6–36.2)	34.4 (33.8–35.8)	33.0 (32.7–33.4)	32.9 (32.5–33.3)	33.1 (32.7–33.3)	33.2 (32.9–33.6)	36.7 (35.3–37.3)	37.7 (37.3–37.9)
Standard resuscitation	35.5 (35–36.3)	36 (35.8–36.4)	37.1 (36.4–37.4)	37.6 (37–38)	37.6 (37.2–37.8)	37.4 (36.8–37.7)	37.4 (37.1–37.8)	37.4 (36.8–37.6)

Values are median (interquartile range). 0 hr = admission at the medical emergency room.

*Impact of TH on Outcome as a Function of Initial Rhythm.* Table 4 shows the CPCs at hospital discharge in subjects who had CA with VF as initial rhythm. Good outcome (i.e., CPC 1 or CPC 2, see Methods) was observed in 24 of 43 patients (55.8%) treated with TH compared with 11 of 43 patients (25.6%) treated with SR ( $p = .004$ ). In addition, the frequency of discharge to institutions or to long-term rehabilitation facilities (CPC 3) was significantly lower among patients treated with TH (4.7%) than among those treated with SR (18.6%,  $p = .04$ ). When VF was the initial rhythm, TH was also associated with a higher hospital survival (TH 60.5% vs. SR 44.2%), a statistically nonsignificant trend (odds ratio in favor of TH 1.60; 95% confidence interval, 0.68–3.80;  $p = .28$ , binary logistic regression with treatment group as the unique predictor).

TH was safely applied to comatose patients with CA following asystole or pulseless electric activity. However, since the outcome of these patients was very poor, it was not possible, from our data, to determine whether TH was beneficial in this subgroup (Table 5).

Finally, in the TH group, the time required to reach the target temperature had no obvious relationship to outcome (median [interquartile range], 4 [3–7] hrs in the subgroup of patients with CPC 1 or 2 vs. 5.5 [3–6.8] hrs in the others,  $p = .95$ , Mann-Whitney test).

*Impact of TH on Outcome in Patients with Shock.* No studies have determined whether TH could be of benefit after CA in comatose patients with circulatory shock. We therefore analyzed the outcome of patients who were in shock before the initiation of the treatment (Table 6). On univariate analysis, TH was beneficial in these conditions, five of 17 patients who received it ending up with a good outcome, as opposed to zero of 14 patients treated with SR ( $p = .027$ ).

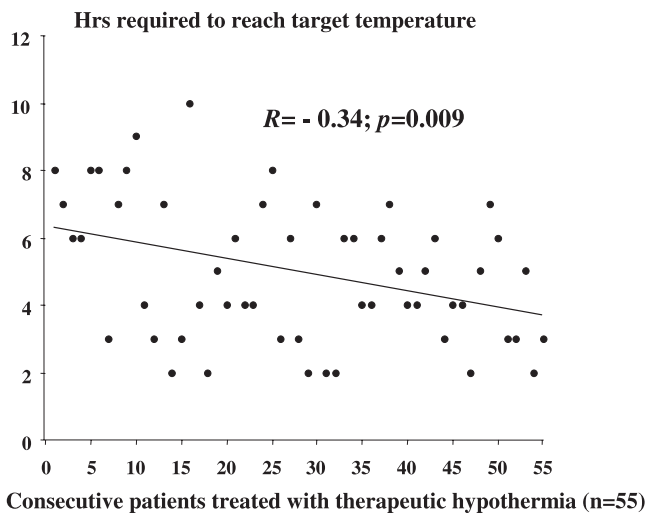


Figure 1. Time delay to reach the target temperature in 55 consecutive patients treated with therapeutic hypothermia. The delay was counted from patient's arrival into the emergency room to achievement of a central temperature of 33°C and plotted against chronological order of patient admission, showing a statistically significant decline over the 18 months required to accrue 55 cases. R, Spearman rank correlation of time delay vs. chronological order of patient admission.

Table 4. Outcome, at hospital discharge, of comatose patients with out-of-hospital cardiac arrest (initial rhythm: ventricular fibrillation)

Treatment Group	Outcome				
	CPC 1 Total Recovery	CPC 2 Moderate Disability	CPC 3 Severe Disability	CPC 4 Vegetative State	CPC 5 Death
Therapeutic hypothermia	18/43 (41.9)	6/43 (13.9)	2/43 (4.7)	0/43 (0)	17/43 (39.5)
Standard resuscitation	6/43 (14.0)	5/43 (11.6)	8/43 (18.6)	0/43 (0)	24/43 (55.8)

CPC, Glasgow-Pittsburgh Cerebral Performance categories.

Data are presented as number of patients/total number (%). Patient outcome was assessed using CPC (see also Methods). Total recovery (CPC 1), patient conscious, alert, able to work and to lead a normal life. Moderate disability (CPC 2), patient conscious, able to work at least part-time, independent for daily life activities. Severe disability (CPC 3), patient discharged to an institution for disabled or to a long-term rehabilitation facility. CPC 4 and 5 refer to a vegetative state and death, respectively. Patients with CPC 1 and 2 (i.e., those with sufficient neurologic function at hospital discharge to return home and live independently) were considered to have good outcome. With this definition, outcome was good in 55.8% of patients treated with therapeutic hypothermia compared with 25.6% of those treated with standard resuscitation ( $p = .004$ ).

Table 5. Outcome, at hospital discharge, of comatose patients with out-of-hospital cardiac arrest (initial rhythm: asystole or pulseless electrical activity)

Treatment Group	Outcome				
	CPC 1 Total Recovery	CPC 2 Moderate Disability	CPC 3 Severe Disability	CPC 4 Vegetative State	CPC 5 Death
Therapeutic hypothermia	2/12	0/12	0/12	0/12	10/12
Standard resuscitation	0/11	0/11	1/11	0/11	10/11

CPC, Glasgow-Pittsburgh Cerebral Performance categories.

Data are presented as number of patients/total number. For further definitions, see legend to Table 4.

*Termination of Life Support.* One concern with the introduction of TH in clinical practice is whether it could prolong termination of life support, potentially converting patients who would have died into a poor neurologic state. This did not seem to be the case in our study: In fact, no patient was left in vegetative state and, among nonsurvivors, the time from admission to death was comparable between the two groups (median [interquartile range], 4 [2–5] days in TH group vs. 3 [2–5] days in the SR group,  $p = .71$ ).

*Independent Predictors of Outcome: Results of Binary Logistic Regression.*

According to Tables 4–6, outcome was poorest in patients with non-VF initial rhythm or who presented with shock on emergency room admission. This fact may have depended on the higher value in these subgroups of the time interval from collapse to ROSC, a known powerful prognostic factor in CA (Table 7). Other potential confounders were hemodynamic status and management in the course of therapy, which differed between treatment groups (Figs. 2 and 3). To handle this issue, the complete dataset was reanalyzed using multivariable binary logistic regression. The variables named previously were entered along with others (complete list in Methods) into an initial model for the prediction of good outcome (i.e., CPC 1 or 2, as opposed to CPC 3–5). Following backward elimination, only two independent predictors were retained as statistically significant: the treatment group (odds ratio in favor of good outcome on application of TH, 5.56; 95% confidence interval, 2.0–16.67,  $p < .001$ ) and the time from collapse to ROSC (odds ratio for each additional 5 mins, 0.53; 95% confidence interval, 0.37–0.72,  $p < .001$ ). To express these results in more concrete form, we used the fitted model to calculate the probabilities of good outcome in each treatment group, which are plotted as a function of the time from collapse to ROSC in Figure 4. It is striking that the probability difference related to treatment group (i.e., the vertical distance between the two curves) is maximal for CA duration <30 mins. Above this time limit, the probabilities of good outcome progressively approach zero in both treatment groups and so does their difference. According to this analysis, the largest benefit of TH in terms of neurologic outcome is to be expected with relatively short duration of CA.

**Table 6.** Outcome, at hospital discharge, of comatose patients with out-of-hospital cardiac arrest; subgroup of subjects who, irrespective of initial rhythm, presented on admission with sustained hypotension and shock

Treatment Group	Outcome				
	CPC 1 Total Recovery	CPC 2 Moderate Disability	CPC 3 Severe Disability	CPC 4 Vegetative State	CPC 5 Death
Therapeutic hypothermia	3/17	2/17	0/17	0/17	12/17
Standard resuscitation	0/14	0/14	3/14	0/14	11/14

CPC, Glasgow-Pittsburgh Cerebral Performance categories.

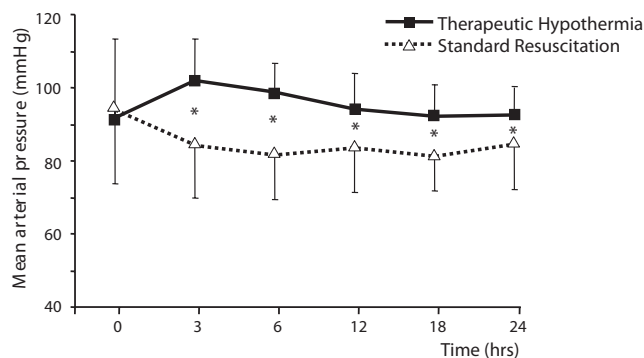
Data are presented as number of patients/total number. Sustained hypotension and shock were defined as a systolic blood arterial pressure <90 mm Hg for >60 mins, unresponsive to volume resuscitation, requiring the administration of vasopressors. For further definitions, see legend to Table 4. Outcome was good (i.e., CPC 1 or 2) in five of 17 patients who received therapeutic hypothermia, as opposed to zero of 14 who were treated with standard resuscitation ( $p = .027$ ).

**Table 7.** Time from collapse to return of spontaneous circulation in various subgroups of patients

	Patients Grouped by Initial Rhythm			
	VF		Non-VF	
	Median	IQR (No.)	Median	IQR (No.)
Therapeutic hypothermia	24	15–30 (37)	33	26–40 (11) <sup>a</sup>
Standard resuscitation	21	16–25 (39)	28	25–30 (11) <sup>b</sup>
	Patients Grouped by Presence of Shock			
	No Shock		Shock	
	Median	IQR (No.)	Median	IQR (No.)
Therapeutic hypothermia	24	15–30 (33)	32	24–35 (15) <sup>c</sup>
Standard resuscitation	22	17–26.5 (37)	28	20–32 (13)

VF, ventricular fibrillation; IQR, interquartile range.

<sup>a</sup> $p < .01$ , <sup>b</sup> $p < .05$ , non-VF vs. VF; <sup>c</sup> $p < .05$  shock vs. no shock, Mann-Whitney test. Times are in minutes. The number of patients in whom the time from collapse to return of spontaneous circulation was known is given in parentheses. This time was unknown in 11 of 109 patients.



**Figure 2.** Time-course of mean arterial pressure in comatose patients with out-of-hospital cardiac arrest treated with either standard resuscitation or therapeutic hypothermia. Data are mean and sd. \* $p < .05$ , therapeutic hypothermia vs. standard resuscitation.

**Hemodynamic Resuscitation.** As expected by our treatment protocol (see Methods), patients treated with TH had slightly higher values of MAP during the first 24 hrs of ICU treatment than those treated with SR (Fig. 2). Indeed, compared with SR, TH was associated with a higher proportion of patients who received norepinephrine (Fig. 3). Moreover, hypothermic patients were given significantly more fluids (mainly crystalloids) and dobutamine. However, multivariable logistic regression disclosed no independent effect of all these variables on patient outcome.

**Biological Variables in the First 24 hrs of Treatment.** In comparison with SR, TH was associated with higher plasma levels of myocardial creatine phosphokinase (Fig. 5). Plasma levels of total creatine kinase, glucose, creatinine, blood lactate, arterial pH,  $Paco_2$ , and  $PaO_2/FiO_2$  ratio did not differ between treatment groups (data not shown).

**Major Complications.** Infections and arrhythmias were common and of comparable frequency in both treatment groups (Table 8). No particular infection control strategy was applied during therapeutic hypothermia. A diagnosis of pneumonia was made if fever, high blood leukocyte counts, elevated plasma C reactive protein, purulent secretions, and radiologic signs of pulmonary infiltrate were present. The large majority of patients had early-onset pneumonia (i.e., occurring within 48–72 hrs after tracheal intubation), except three patients in the TH group who had late-onset pneumonia. Arrhythmias consisted of unsustained ventricular tachycardia and atrial fibrillation. No other serious adverse events were reported.

## DISCUSSION

The primary aim of this study was to assess whether TH could be implemented in critical care practice for the treatment of coma following out-of-hospital CA. Our answer to this first question is undoubtedly positive. A secondary objective was to explore the applicability of TH to patients not fulfilling the inclusion criteria of the two relevant clinical trials (1, 2), namely subjects in shock or with non-fibrillatory initial rhythm. We experienced no major difficulties and encountered no safety issue when applying TH to such patients. Furthermore, our data suggest a benefit of TH in presence of shock on admission, whereas this treat-

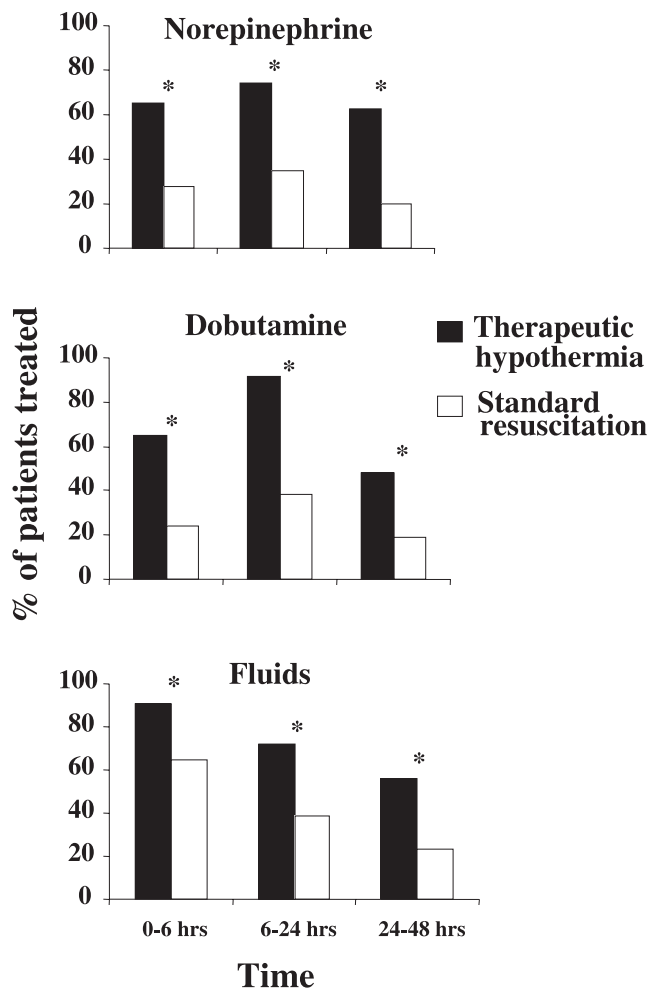


Figure 3. Adrenergic agents and fluid administration in comatose patients with out-of-hospital cardiac arrest treated with either standard resuscitation or therapeutic hypothermia. Data are percentages of patients who received the indicated agent in each treatment group. \* $p < .05$ , therapeutic hypothermia vs. standard resuscitation.

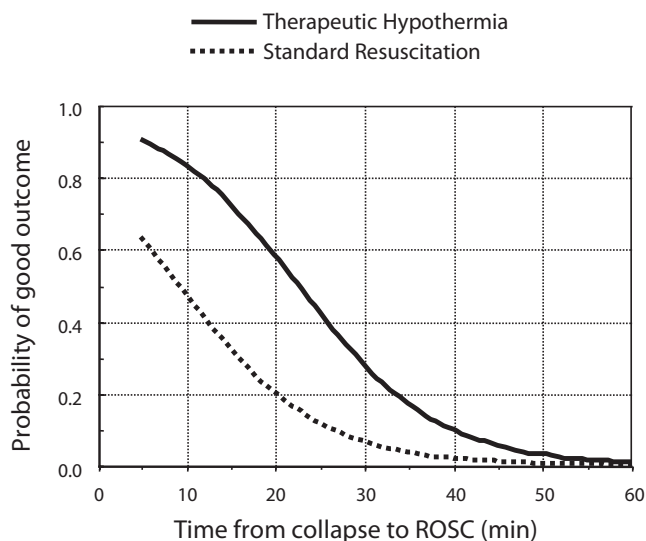


Figure 4. Impact of therapeutic hypothermia and cardiac arrest duration on probabilities of good outcome. Neurologic outcome was dichotomized as good (Glasgow-Pittsburgh Cerebral Performance categories, CPC, 1 or 2) or bad (CPC 3–5). Multivariable binary logistic regression disclosed two independent predictors of this outcome, namely the time from collapse to return of spontaneous circulation (ROSC) and the application of therapeutic hypothermia. The fitted model was used to calculate the probability of good outcome.

ment did not affect the dismal prognosis of CA associated with asystole or pulseless electrical activity.

#### Impact of TH on Neurologic Outcome.

In unconscious survivors of CA with VF as the initial rhythm, we were able to confirm the markedly favorable impact of TH on patient neurologic recovery (Table 4), as already established by two randomized controlled studies (1, 2) and a recently published systematic review and meta-analysis (19). In comparison with patients treated with SR, those who received TH more frequently returned home with the ability to lead an independent life, were less frequently discharged to long-term rehabilitation facilities, and were less likely to die. Although the impact of TH on this latter end point was not statistically significant, it was numerically quite remarkable (i.e., a 15% absolute reduction in the risk of death). Only one study tested the feasibility of TH in patients with CA and non-VF initial rhythm (20), but its benefit in such a setting is still uncertain. In our study, patients resuscitated from asystole or pulseless electrical activity fared dismally in both treatment groups (Table 5). Due to the limited number of subjects, no definitive conclusions can be made. The impact of TH on the outcome of CA associated with non-VF initial rhythm could be one focus for future large prospective studies.

Patients with shock on hospital admission appeared to benefit from TH in terms of neurologic outcome. Because shock was an exclusion criterion in the two previously mentioned trials (1, 2), we believe that these are important data with respect to the routine daily practice, suggesting that TH should also be applied to these patients.

A further important aspect of our data relates to the interaction between the duration of CA and the efficiency of TH. Specifically, the question of whether there would be a limit to this duration, beyond which TH would lack benefit, has not been handled by the available studies, at least as presented (1, 2). In these studies, the time from collapse to ROSC was only considered as a potential confounder, for which adjustment was required when assessing the global impact of TH on outcome. No attempts were made in either trial to relate the duration of CA to the therapeutic benefit of hypothermia. We show here that the positive impact of TH is most obvious with times from collapse to ROSC of  $\leq 30$  mins (Fig. 4). Although we certainly are not implying that hypo-

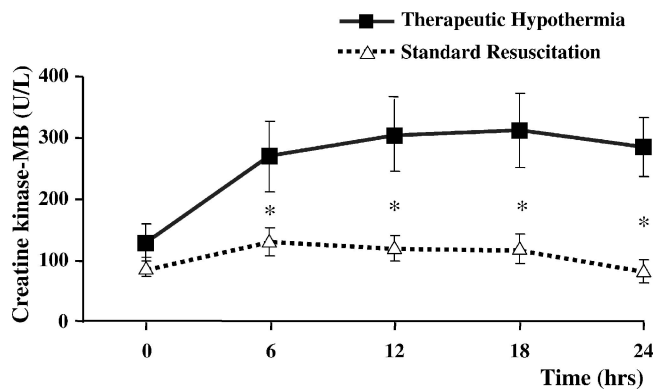


Figure 5. Plasma levels of myocardial (MB) creatine kinase in comatose patients with out-of-hospital cardiac arrest treated with either standard resuscitation or therapeutic hypothermia. Data are mean and SD. \* $p < .05$ , therapeutic hypothermia vs. standard resuscitation.

Table 8. Rate of infections and arrhythmias

	Therapeutic Hypothermia	Standard Resuscitation	<i>p</i> Value
Infection <sup>a</sup>	19/55 (34.5)	23/54 (42.6)	.38
Arrhythmia <sup>b</sup>	20/55 (36.4)	23/54 (42.6)	.51

<sup>a</sup>Therapeutic hypothermia: pneumonia  $n = 16$ , sepsis  $n = 2$ , urinary tract infection  $n = 1$ . Standard resuscitation: pneumonia  $n = 19$ , central venous catheter infections  $n = 2$ , sepsis  $n = 2$ ; <sup>b</sup>unsustained ventricular tachycardia or atrial fibrillation. Data are presented as number of patients/total with complications according to treatment group (%).

thermia should be foregone whenever this limit is exceeded, our data point to the particular importance of applying TH in patients with CA of relatively short duration, that is, those who have the best chance to survive and would then have a much higher probability to be discharged home with good neurologic recovery if treated aggressively with TH.

Finally, it is also important to note that, at least in our study, hypothermia did not prolong the decision regarding termination of life support.

**Practical Aspects Regarding the Cooling of Patients.** Regarding the practical application of TH, the type of cooling technique to be used is an important and still unresolved issue (5). In addition, the induction of an exact temperature decrease and the maintenance of this temperature within narrow limits may be difficult, particularly when using external cooling methods (19). When introducing TH in our practice, we opted for an external method, resorting to both ice packs and a cooling mattress. This method is noninvasive, was already in use to control fever in our ICU, and has been safely applied after CA in the aforementioned trials (1, 2). In our study, the median interval between admission to the hospital and achievement of the desired level of cooling was 5 hrs. Interestingly, accruing ex-

perience allowed us to progressively reduce the delay required to achieve hypothermia (Fig. 1). Following the active induction of therapeutic hypothermia, we observed a median time for passive rewarming of 8 hrs, which was comparable to that reported by the HACA trial (median time, 8 hrs) and the study from Bernard and colleagues (2) (mean time, 6 hrs). In terms of resource allocation (since we used the cooling mattress already available for the active treatment of fever in our ICU, and ice packs were handmade), the additional costs due to TH were essentially related to the systematic use of pulmonary artery catheters to monitor central temperature and the increase in ICU length of stay (median [interquartile range], 4.5 [3–6] days in TH vs. 2 [2–5] days in SR,  $p = .013$ ). We conclude from our data that TH can be effectively applied in clinical practice using external cooling techniques, without a substantial increase of usual resources. External cooling can also be safely combined with the administration of cold intravenous fluids (21). Whether the recently developed catheters for intravascular cooling (5) would offer any additional advantage remains to be determined, particularly considering the potential complications related to such an invasive approach.

**Hemodynamic Management and Cardiac Function.** Patients treated with TH received more vasopressors, particularly because we decided to maintain levels of MAP at 90–100 mm Hg, as in the study by Bernard and colleagues (2). We also observed that the required amounts of fluids and inotropic agents were higher in hypothermic than in normothermic patients. This might in part due to the direct effect of hypothermia on volemic status and cardiac function. However, the fact that the presence of a pulmonary artery catheter might induce by itself an increased use of fluids and vasoactive agents, as recently shown (22), could also partly explain these observations, particularly because the management of fluids and dobutamine was left to the discretion of the treating physician. Of note, neither the level of blood pressure nor the amount of vasopressors, fluids, or inotropic agents given had any effect on patient outcome.

Regarding the effect of TH on the heart, hypothermic patients had higher values of blood myocardial creatine phosphokinase over the first 24 hrs (Fig. 5). Because hypothermia has been shown to be protective in several experimental models of myocardial ischemia (23), it would be counterintuitive that TH, once instituted, should favor the progression of myocardial necrosis. However, the effect of mild hypothermia on myocardial tissue and function has not been studied so far in the particular context of post-CA coma. The only available data in this clinical setting are those from Bernard and colleagues (2), who also used vasopressors to maintain high levels of MAP: Indeed, these authors reported that post-CA levels of myocardial creatine phosphokinase were higher in hypothermic than in normothermic patients, as it was the case in our study. Although the interpretation of this somewhat surprising finding is unclear at present, one possible explanation could be that the combination of hypothermia and vasopressors might have induced vasoconstriction and, thereby, reduced coronary blood flow. Also, whether receiving TH or SR, approximately half of subjects had acute myocardial infarction (Table 1 and 2), raising the possibility of an imbalance between treatment groups in the extent of myocardial necrosis before initiation of treatment. Finally, in both the TH and SR groups, echocardiography (during the first 48 hrs of the treatment) was done in about 50% of the

patients: Left ventricular ejection fraction was comparable between the two groups, suggesting that hypothermia did not seem to alter cardiac function (data not shown). In absence of further evidence, we can only point to the need to evaluate, in future prospective studies, the precise effect of hypothermia on cardiac function in the setting of post-CA coma.

**Potential Complications of TH.** An important concern with TH is its potential to cause serious adverse events, in particular to predispose to infections and arrhythmia (5). This concern did not materialize in the present study. Infections were mostly related to aspiration pneumonia, not an unprecedented finding (1), and were frequent in both treatment groups, raising the question of whether prophylaxis with antibiotics and selective digestive decontamination should be systematic in coma following out-of-hospital CA (24). Despite the fact that all our patients were given both intravenous magnesium sulfate, to maintain  $Mg^{2+}$  blood values between 0.8 and 1.2 mmol/L, and potassium chloride, to maintain  $K^+$  blood values between 4.0 and 4.5 mmol/L, the incidence of cardiac arrhythmias was high in both treatment groups. Nevertheless, this type of complication appeared no more favored by TH than were infections (Table 8).

**Limitations.** Some limitations of our study deserve further discussion, first of all its retrospective nature (25). However, the two cohorts were comparable regarding baseline clinical characteristics (Table 1 and 2). In particular, the time from collapse to ROSC, a major prognostic determinant of patient outcome (2), together with baseline values of arterial blood lactate and pH, which are important indicators of the severity of CA and of the extent of tissue dysoxia (18), were similar between the two groups. These results suggest not only that treatment groups were clinically well matched but also that extrahospital resuscitation practices did not change during the study period.

It is also important to note that the introduction of a new treatment might have by itself to some extent increased the quality and intensity of intrahospital care of patients after CA (the so-called Hawthorne effect) (26, 27). We cannot exclude it but think that this factor alone could hardly account for the highly favorable impact of TH observed in this study.

## CONCLUSION

We showed that therapeutic hypothermia can be implemented with relative ease in the ICU for the treatment of all comatose patients resuscitated from out-of-hospital cardiac arrest. We confirmed a major impact of this strategy on neurologic recovery when applied to patients in whom the initial rhythm was ventricular fibrillation. Our observations further indicate that the benefit of TH extends to patients in shock and is particularly notable when the duration of cardiac arrest is short (<30 mins). In contrast, our data do not seem to support the use of therapeutic hypothermia after cardiac arrest due to asystole or pulseless electrical activity, and additional studies are required to finally establish this point.

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