Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: A prospective study*

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Objectives: **Current indications for therapeutic hypothermia (TH) are restricted to comatose patients with cardiac arrest (CA) due to ventricular fibrillation (VF) and without circulatory shock. Additional studies are needed to evaluate the benefit of this treatment in more heterogeneous groups of patients, including those with non-VF rhythms and/or shock and to identify early predictors of outcome in this setting.**

Design: **Prospective study, from December 2004 to October 2006.**

Setting: **32-bed medico-surgical intensive care unit, university hospital.**

Patients: **Comatose patients with out-of-hospital CA.**

Interventions: **TH to 33 ± 1°C (external cooling, 24 hrs) was administered to patients resuscitated from CA due to VF and non-VF (including asystole or pulseless electrical activity), independently from the presence of shock.**

Measurements and Main Results: **We hypothesized that simple clinical criteria available on hospital admission (initial arrest rhythm, duration of CA, and presence of shock) might help to identify patients who eventually survive and might most benefit from TH. For this purpose, outcome was related to these predefined variables. Seventy-four patients (VF 38, non-VF 36) were included; 46% had circulatory shock. Median duration of CA (time from collapse to return of spontaneous circulation [ROSC]) was 25 mins. Overall survival was 39.2%. However, only 3.1% of patients with time to ROSC >25 mins survived, as compared to 65.7% with time to ROSC ≤25 mins. Using a logistic regression analysis, time from collapse to ROSC, but not initial arrest rhythm or presence of shock, independently predicted survival at hospital discharge.**

Conclusions: **Time from collapse to ROSC is strongly associated with outcome following VF and non-VF cardiac arrest treated with therapeutic hypothermia and could therefore be helpful to identify patients who benefit most from active induced cooling. (Crit Care Med 2008; 36:2296–2301)**

KEY WORDS: hypothermia; cardiac arrest; indications; predictors; outcome

Therapeutic hypothermia (TH) has been convincingly shown to improve outcome in a selected subset of patients with cardiac arrest (CA) due to ventricular fibrillation (VF) and without sustained postresuscitation circulatory shock (1–4). However, in clinical practice, these represent a minority of patients and indeed indications for TH are narrowly defined (5–7). This might at least in part contribute to explain why TH is still underused (8). In order to better define the role of TH in general clinical setting and to expand its appropriate utilization to a larger proportion of patients, additional studies including unselected heterogeneous cohorts of comatose survivors of CA of various etiologies are needed. We therefore designed a prospective study including all patients admitted to our intensive care unit (ICU) for post-CA coma. All patients were treated with a uniform protocol of TH. Several predefined clinical variables obtained at admission, including duration of CA (defined as the time from collapse to return of spontaneous circulation), initial arrest rhythm (VF or non-VF) and hemodynamic status (presence or absence of postresuscitation circulatory shock), were analyzed and their potential correlation with clinical outcome at hospital discharge was evaluated.

***See also p. 2456.**

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METHODS

Patient Population

This prospective study was conducted between December 2004 and October 2006, in a 32-bed adult medico-surgical ICU of a university hospital. Full approval was given by our institutional ethic committee. Patient population consisted of all consecutive subjects, aged <80 yrs admitted for persistent coma following out-of-hospital cardiac arrest (OHCA). Out-of-hospital resuscitation was delivered by an emergency medical team, which included one trained physician, according to the American Heart Association guidelines published in 2000 (9) and, since January 2006, to the 2005 revised version of these guidelines (10). Patients were initially treated in the emergency room and, after stabilization, were rapidly transferred to the ICU.

Therapeutic Hypothermia

TH was started immediately on admission to the emergency room and was administered according to our local, previously described protocol (11). Mild hypothermia, to a central temperature of 33 ± 1°C, was maintained for 24 hrs with the use of an external cooling technique, combining the use of ice packs and a cooling mattress (Cincinnati SubZero, Cincinnati, OH). Sedation (midazolam, 0.1 mg/kg/hr intravenous [IV]), analgesia (fentanyl, 1.5 μg/kg/hr IV) and neuromuscular blockade (IV vecuronium, boluses of 0.1 mg/kg, according to nerve stimulator monitoring) were applied in the course of cooling induction and maintenance, and were stopped after passive rewarming to a central temperature of 35°C. All patients were equipped with an intra-arterial catheter and a pulmonary-artery catheter for hemodynamic and central temperature monitoring. Crystalloids were used for volume resuscitation. Norepinephrine was used to maintain mean arterial blood pressure >70 mm Hg. Inotropic support consisted of dobutamine, aiming at mixed venous oxygen saturation (Svo_2) >65% and an arterial blood lactate <2.5 mmol/L, according to our local procedures for resuscitation of cardio-circulatory shock.

Myocardial Reperfusion

Following placement of ice packs, all patients with acute ST-segment elevation myocardial infarction (STEMI) were immediately transferred to the cardiology catheter laboratory for primary angioplasty and stenting before ICU admission.

Data Collection and Assessment of Outcome

Data were collected prospectively using Utstein style recommendations (12). Duration of CA was assessed by calculating the time from collapse to return of spontaneous circulation (ROSC) and was determined independently by two physicians. As a marker of global tissue ischemia, blood lactate was measured on admission to the emergency room. The type of CA was dichotomized as ventricular fibrillation (VF) and non-VF (including asystole and pulseless electrical activity). Postresuscitation circulatory shock was defined as the occurrence of arterial hypotension (mean arterial pressure <60 mm Hg or systolic blood pressure <90 mm Hg) sustained for more than 60 mins following hospital admission, despite fluid resuscitation, leading to the administration of norepinephrine (3,4). In patients fulfilling the criteria of postresuscitation circulatory shock, those with a cardiac index <2.2 $L/min^{-1}/m^{-2}$ and requiring inotropic support with dobutamine were considered as having cardiogenic shock, according to standard definitions (13).

Outcome was recorded as survival and degree of neurologic recovery at hospital discharge. Neurologic recovery was assessed using Glasgow-Pittsburgh Cerebral Performance categories (CPC) (14,15). CPC 1 indicates full 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 persistent vegetative state and CPC 5 indicates death. Outcome was assessed blindly by two physicians, who independently reviewed the reports of neurologic examinations made just before hospital discharge. Good neurologic outcome was defined as CPC 1 (full recovery) or 2 (moderate disability).

Neurologic Assessment and Termination of Life Support

Decision regarding termination of life support was based on daily clinical and neurologic assessment made by the ICU physician and the consultant neurologist. Electroencephalography and somato-sensory evoked potentials were obtained whenever deemed necessary to the decision making (16).

Statistical Analysis

Univariate comparisons between dichotomous subgroups were carried out with Wilcoxon's rank test for continuous variables and with chi-square tests for categorical variables. Multivariable logistic regression was used to evaluate a potential association between clinical variables obtained at admission and hospital survival. As the time from collapse to ROSC was not found to be a linear variable, it was entered as a categorical variable in the model. For the purpose of the analysis, the median time from collapse to ROSC of the total cohort was selected and dichotomized as ≤25 or >25 mins. The following variables were also analyzed for a possible association with outcome: age, sex, initial arrest rhythm (VF or non-VF), arterial lactate on admission to the emergency room, and presence of circulatory shock on admission to the ICU. A stepwise forward algorithm was used, with variables entered or removed one at a time based on the p values associated with likelihood ratio tests (p to enter = 0.15, p to remove = 0.20). Before accepting the final model, continuous covariates were checked for linearity in the logit, using fractional polynomials (17). Goodness of fit of the final model was evaluated with the Hosmer-Lemeshow test, using deciles of risk. The predictive ability of the final model was evaluated by calculating the area under the receiver operator characteristics (ROC) curve. All calculations were carried out with release 9 of the STATA software (College Station, TX). A p value <0.05 was considered statistically significant. Descriptive data regarding continuous variables are reported as the median and interquartile range (IQR).

RESULTS

Patient Characteristics and Outcome

During the study period, 88 patients were admitted to the ICU for coma after CA. Fourteen patients were not given TH because of age >80 yrs (n = 11) and underlying terminal disease (n = 3). Seventy-four patients treated with TH for persistent coma after CA were included in the study. Hospital admission data are shown in Table 1. Thirty-four patients (46% of total cohort) met the criteria for postresuscitation circulatory shock. Among these patients, 14 (41% of patients with shock, 19% of the entire cohort) fulfilled the criteria of cardiogenic shock (cardiac index <2.2 $L/min^{-1}/m^{-2}$ and requirement of inotropic support with dobutamine). Among those without shock, CA was related to non-VF rhythms in 17 (23% of total cohort, data not shown in Table 1). Thus, 51 of the 74 patients (69%) did not meet current indications for TH (5–7). Table 2 shows the outcome of the entire cohort at hospital discharge.

Outcome by Duration of Cardiac Arrest

As shown in Figure 1, time from collapse to ROSC was significantly lower in survivors (median 15.5, IQR 10–21 mins) than in nonsurvivors (median 32, IQR 25–39 mins, $p < 0.0001$). This was also the case of plasma levels of lactate on admission to the emergency room (median 8.1, IQR 4.7–10 mmol/L in survivors vs. 11, IQR 7.9–14 mmol/L in nonsurvivors, $p = 0.0008$). Time from collapse to ROSC was strongly associated with neurologic outcome. The latter was good (i.e., CPC 1 or 2) in 22 of 38 patients (57.9%) with a time to ROSC ≤25 mins, but in none of the patients in whom time to ROSC was >25 mins (Table 3).

Outcome by Initial Arrest Rhythm

Survival and neurologic recovery at hospital discharge were significantly better in patients with CA due to VF rhythms, as compared to those with asystole or pulse-

Table 1. Patients' baseline characteristics

Number of patients	74
Median age, years	61
Interquartile range	51–68
Female sex	14 (19%)
Etiology of cardiac arrest	
Cardiac	
STEMI	37 (50%)
Malignant ventricular fibrillation[a]	12 (16%)
Idiopathic ventricular fibrillation	5 (7%)
NSTEMI	4 (5%)
Noncardiac	
Severe airway obstruction	8 (11%)
Drug toxicity	4 (5%)
Massive pulmonary embolism	3 (4%)
Hyperkalemia	1 (1%)
Bystander cardiopulmonary resuscitation	35 (47%)
Witnessed cardiac arrest	58 (78%)
Duration of cardiac arrest	
Time from collapse to ROSC, mins	25
Interquartile range	15–34
Initial arrest rhythm	
Ventricular fibrillation	38 (51%)
Nonventricular fibrillation	36 (49%)
Asystole	24 (32%)
Pulseless electrical activity	12 (17%)
Postresuscitation circulatory shock	
Yes	34 (46%)
Cardiogenic	14 (19%)
Noncardiogenic	20 (27%)
No	40 (54%)
Median blood lactate, mmol/L	10.0
Interquartile range	7.4–13.1

Data indicate number of patients, with percentage in brackets, unless otherwise noted.

[a]Previous history of coronary artery disease or chronic heart dysfunction. NSTEMI, non-ST elevation myocardial infarction; ROSC, return of spontaneous circulation; STEMI, ST elevation myocardial infarction.

Table 2. Outcome at hospital discharge of the entire cohort

Outcome	Number of patients/total number (%)
Survival	29/74 (39.2)
Good neurological outcome	24/74 (32.4)
Poor neurological outcome	5/74 (6.8)[a]

Neurological recovery was assessed using Glasgow-Pittsburgh Cerebral Performance categories (CPC). CPC 1 = full recovery; CPC 2 = moderate disability (conscious, able to work at least part-time, and independent for daily life activities, with or without neurological manifestations such as hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes); CPC 3 = severe disability (conscious, but fully dependent on others for daily support because of severely impaired cognitive function, requiring long-term rehabilitation); CPC 4 = vegetative state; CPC 5 = death. Good neurologic outcome = CPC 1–2; Poor neurologic outcome = CPC 3–5.

[a]At hospital discharge, all five patients had severe neurologic disability. No patient was in a vegetative state.

less electrical activity (Table 3). However, the duration of CA was significantly shorter in patients with coma after CA due to VF (median 20, IQR 12–25 mins), than in those with CA due to non-VF rhythms (32 mins, IQR 25–40 mins, $p < 0.0001$). Twenty-nine percent of patients with non-VF CA had a time from collapse to ROSC ≤25 mins, as compared to 78% of those with VF CA ($p < 0.001$). Six of 36 (17%) patients with non-VF rhythms survived, and three had eventually a good neurologic outcome at hospital discharge (one with asystole due to severe hyperkalemia, two with pulseless electrical activity due to severe airway obstruction). These three patients had a time to ROSC ≤25 mins.

Outcome by Presence or Absence of Postresuscitation Circulatory Shock

Survival and neurologic recovery at hospital discharge did not differ in patients with or without postresuscitation circulatory shock (Table 3). Of note, there were no statistically significant differences between these two subgroups in terms of time from collapse to ROSC, lactate levels or proportion of non-VF rhythms (not shown).

Multivariable Analysis

In multivariable analysis, only time from collapse to ROSC and blood lactate levels, were significantly associated with survival (Table 4), whereas initial arrest rhythm was not ($p = 0.16$). Circulatory shock, age and sex were all rejected at a statistical level ≥0.2 at the conclusion of the stepwise procedure for variable selection. The selected model achieved an area under the ROC curve of 0.93, indicating an outstanding ability to discriminate between survivors and nonsurvivors (17).

When this same model was applied to our previous cohort of comatose CA patients treated with TH (11), the area under the ROC curve was 0.83, indicating substantial similarity of outcome determinants in both cohorts. Moreover, applying the 25-min cutoff for duration of CA (derived from the present data, see Table 3) to the complete dataset of our previous study (which included data from 48 patients treated prospectively from June 2002 to December 2004 with TH, and 50 historical controls treated from October 1999 to May 2002 with standard resuscitation and normothermia) shows that TH, in our system, has the greatest benefit in comatose patients with relatively short duration of CA (Table 5).

DISCUSSION

The main result of this prospective study is that, in our system, a strong correlation was found between the time from collapse to ROSC and the outcome of all comatose survivors of CA treated with TH, including non-VF patients with or without the presence of postresuscitation circulatory shock. Our results are consistent with those of several recent studies that reported an association between longer duration of CA and poor outcome in patients with OHCA (18–20), which points to the crucial role of the quality of out-of-hospital cardiopulmonary resuscitation in this setting. In our study, when time to ROSC was ≤25 mins, hospital survival rate was high (65.7%), with predominantly good neurologic outcome (57.9%, see Table 3). In contrast, prognosis was dismal when return of

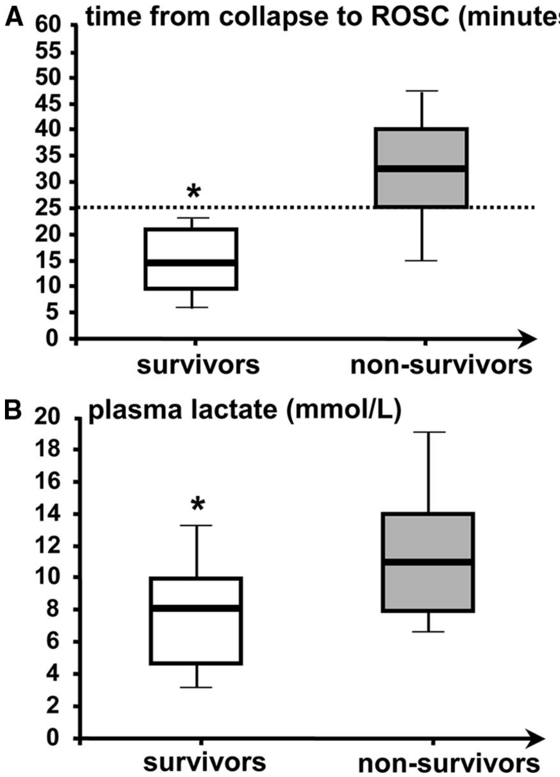

Figure 1. Differences, between survivors and nonsurvivors of post-cardiac arrest coma, in terms of duration of cardiac arrest (time from collapse to return of spontaneous circulation (*ROSC*) (*A*) and plasma levels of lactate on admission to the emergency room (*B*). Box-plots represent median and interquartile ranges (25th and 75th percentiles), and error bars the 10th and 90th percentiles. The hatched line in *A* shows the median duration of cardiac arrest of the total cohort (25 mins).

Table 3. Outcome based on the time from collapse to ROSC, initial arrest rhythm, and post-resuscitation circulatory shock

Variable		Survival	Good neurologic outcome
Time from collapse to ROSC[a]	≤25 mins	25/38 (65.7%)	22/38 (57.9%)
	>25 mins	1/32 (3.1%)	0/32 (0%)
p value		**<0.001**	**<0.001**
Initial arrest rhythm	VF	23/38 (60.5%)	21/38 (55.3%)
	Non-VF	6/36 (16.7%)[b]	3/36 (8.3%)
p value		**<0.001**	**<0.001**
Circulatory shock[c]	No	17/40 (42.5%)	15/40 (37.5%)
	Yes	12/34 (35.3%)	9/34 (26.5%)
p value		0.53	0.31

Data represent number of patients with indicated outcome/total patients in category, with percentage in brackets.

[a]Undetermined in four patients; [b]four patients with asystole, two with pulseless electrical activity. [c]Post-resuscitation circulatory shock was defined as the occurrence of arterial hypotension (mean arterial pressure <60 mm Hg or systolic blood pressure <90 mm Hg) sustained for more than 60 minutes following hospital admission, in spite of fluid resuscitation, leading to the administration of norepinephrine.

ROSC, return of spontaneous circulation; VF, ventricular fibrillation.

Table 4. Multivariable analysis of early independent predictors of survival in patients with coma after ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with mild hypothermia

Variable	Odds ratio	Confidence interval	*p* Value
Time from collapse to ROSC ≤25 mins	45.10	4.64–408.60	**<0.001**
Lactate level at hospital admission	0.79	0.64–0.97	**0.02**
Initial arrest rhythm ventricular fibrillation	3.23	0.64–16.28	0.16

ROSC, return of spontaneous circulation.

spontaneous circulation took longer than 25 mins. The only other variable associated with survival independent of time from collapse to ROSC was blood lactate level at admission, pointing to the extent of global ischemia as the major pathophysiological determinant of outcome. These results indicate that benefits of TH should be expected mostly in subjects with "reversible" global brain anoxo-ischemic injury, represented by comatose patients with a relatively short duration of CA who eventually have the greatest chance to survive with good neurologic recovery at hospital discharge. This conclusion is further supported by the reanalysis of our previous cohort of post-CA comatose patients (Table 5) (11). It is worth noting that the percentages of patients with a time to ROSC ≤25 mins who received TH and came out of the hospital in good neurologic condition were quite similar in our present cohort (57.9%, Table 3) and in our previous one (67.9%, Table 5). It must also be underlined that the benefit of TH indicated by our previous study in this subgroup of patients was impressive, since neurologic outcome was good in only 21.2% of the corresponding subgroup not treated with TH (Table 5).

Second, our study gives important information about the relevance of initial arrest rhythm for the clinical decision making process after coma due to CA. Non-VF rhythms (asystole and pulseless electrical activity) are associated with poor outcome after CA (21, 22), but the role of TH in comatose patients with non-VF rhythms is still unknown (7). In our study, patients with initial non-VF rhythm treated with TH had significantly worse outcome than those with VF rhythms (Table 3). However, initial arrest rhythm, in contrast to time from collapse to ROSC, was not significantly associated with outcome in multivariable analysis (Table 4). Of note, while 78% of subjects with VF CA had a time to ROSC ≤25 mins, this was only the case in 29% of patients with non-VF CA. Six patients with non-VF rhythms survived and three had eventually good neurologic outcome at hospital discharge: these three patients had a time from collapse to ROSC ≤25 mins. Taken together, our findings suggest that comatose survivors of CA with an initial non-VF rhythm and a short duration of CA (represented by 29% of patients with time to ROSC ≤25 mins in our cohort) may also benefit from TH. However, given the limited number of

Table 5. Outcome by duration of cardiac arrest: comparison between therapeutic hypothermia and normothermia

	Good Neurologic Outcome	
Time from Collapse to ROSC	Normothermia	Hypothermia
≤25 mins	7/33 (21.2%)	19/28 (67.9%)
>25 mins	2/17 (11.8%)	2/20 (10%)

Data represent number of patients with indicated outcome/total patients in category, with percentage in brackets.

ROSC, return of spontaneous circulation.

survivors in the non-VF group, no definite recommendations can be derived from our data and additional studies using larger number of patients are needed to further evaluate the impact of TH on the outcome of patients with non-VF OHCA.

The third important finding of our study is that the presence of postresuscitation circulatory shock does not have a negative impact on outcome. Recent studies have shown that, apart from the primary brain insult directly related to the extent of global ischemia, many of these patients experience a variable degree of the so-called "postresuscitation disease" (23–25). This is characterized by a circulatory shock with multiple mechanisms (hypovolemic, cardiogenic, and vasodilatory), its occurrence and severity being dependent on the degree and duration of initial organ ischemia (26, 27). In our study, as in our previous one (11), we applied the criteria for postresuscitation circulatory shock according to those published by the American Heart Association (7). Based on these criteria, we found a relatively high incidence of shock in our study (46%) that may be explained at least in part by the large number of patients with non-VF rhythms and with long duration of circulatory arrest. Among patients with postresuscitation shock, 14 of 34 fulfilled the criteria of cardiogenic shock. Although circulatory shock is still considered a contraindication for TH (5,7), several recent studies have reported its successful application in this setting (11, 20, 28, 29). In a recent study by Hovdenes et al., TH was initiated in patients with OHCA and cardiogenic shock (of whom 23 of 50 were treated with intra-aortic balloon pump) and a 61% survival with good neurologic recovery (CPC 1 and 2) was observed (30). Our data are in line with these findings and further indicate that patients with postresuscitation circulatory shock (cardiogenic and noncardiogenic) did not fare significantly worse than those without shock. Accordingly, we contend that postresuscitation shock might be removed from the contraindication list of TH.

One limitation of our study relates to the rather restricted number of included patients. We may incidentally point out that one of the relevant studies in the field was not of much larger size (3). This is counterbalanced by the fact that the present data, collected prospectively, are quite clear-cut and in close agreement with the observations made in our previous study. Further, they are supported by the good performance of the model shown in Table 3 (derived from the present data) for survival prediction in our previous series of patients treated with TH (area under the curve of ROC 0.83).

A second limitation is represented by the actual accuracy of the time from collapse to ROSC in estimating the duration of global ischemia. Time from collapse to ROSC is an important admission variable that is generally reported in CA studies. In survivors of witnessed CA (i.e., the majority of our patient cohort), time to ROSC is a good estimate of the duration of circulatory arrest while in those with unwitnessed CA it may underestimate the actual duration of circulatory collapse (12). Interestingly, in our study, among the 16 patients with unwitnessed CA treated with TH, in the only two survivors, duration of CA was estimated at less than 25 mins based on the Utstein style recommendations.

As a third limitation, we must also emphasize that the current results apply to our system of management of patients with OHCA, but they may not necessarily be generalized to all systems. Finally, while time from collapse to ROSC was found to be associated with outcome in patients with post-CA coma treated with TH, it is important to underline that other important parameters must be considered when applying this treatment in clinical practice, mainly the quality of out-of-hospital cardiopulmonary resuscitation, patient's comorbid condition, as well as previous mental status and underlying terminal disease.

CONCLUSION

Taken together, the present data suggest that the time from collapse to ROSC is a major determinant of outcome in comatose survivors of CA treated with TH. In contrast, initial arrest rhythm and presence of circulatory shock do not appear to independently predict survival at hospital discharge. Our findings seem to support a broader application of TH than heretofore recommended, provided a strict protocol is followed for induced cooling and controlled rewarming, as has been the case in our ICU now for more than four years.

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