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Impact of time to cooling initiation and time to target temperature in patients treated with hypothermia after cardiac arrest

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Abstract

Purpose: Little is known about the role of time to initiation of therapeutic hypothermia and time to target temperature (TTT) in the prognosis of patients resuscitated from cardiac arrest.

Methods: A retrospective analysis was performed in 145 survivors of cardiac arrest who underwent therapeutic hypothermia between January 2003 and January 2013. The objective was to identify predictors of survival free from significant neurological sequelae (Cerebral Performance Categories Scale (CPC): >2) six months after cardiac arrest. We evaluated the effect of faster and earlier cooling.

Results: Overall survival at six months was 42.1% (61 patients); 59 of these were considered to have a good neurological status (CPC≤2), and in whom therapeutic hypothermia was initiated earlier (87±17 min *vs.* 111±14 min; p=0.042), and the target temperature was reached at an earlier time (TTT: 316 ± 30 min *vs.* 365 ± 27 min; p=0.017). Multivariate analysis selected longer duration of cardiac arrest (odds ratio (OR) =1.06 per min), a non-shockable initial rhythm (OR=13.8), severe acidosis (OR=0.009 per 0.01 unit), older age (OR=1.04 per year) and longer TTT (OR=1.005 per min) as associated with poor prognosis.

Conclusion: The most important prognostic factors for death or lack of neurological recovery in patients with cardiac arrest treated with therapeutic hypothermia are initial-rhythm, time from cardiac arrest to return of spontaneous circulation and arterial-pH at admission. Although the speed of cooling initiation and the time to reach target temperature may play a role, its influence on prognosis seems to be less important.

Keywords

Cardiopulmonary resuscitation, heart arrest, induced mild hypothermia, neurological outcome, intensive care

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Introduction

Sudden cardiac death is a major public health issue. Between 40 and 54 patients per 100,000 inhabitants per year suffer out-of-hospital cardiac arrest with cardiopulmonary resuscitation being attempted.[1] Return of spontaneous circulation (ROSC) is achieved in only 25–40% of these patients.[2] Of those admitted to the hospital, only between 7% and 30% are discharged with a favourable neurological outcome.[3] Poor prognosis in patients in whom ROSC has

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been initially achieved is largely attributed to post-cardiac arrest syndrome, which involves a combination of post-anoxic brain injury, circulatory dysfunction and systemic ischaemia-reperfusion response.[4]

Experimental and clinical evidence confirms the neuroprotective effects of targeted temperature management using either mild therapeutic hypothermia or temperature up to 36ºC.[5,6] Thus, therapeutic hypothermia is now recommended by international resuscitation guidelines.[7] Although various studies have shown that early initiation of therapeutic hypothermia and rapid achievement of target temperature were key factors for improving neurological outcome and survival,[8,9] others have showed contradictory results.[10-12]

Literature on prognostic factors predicting improved survival after resuscitation remains limited, especially in those undergoing therapeutic hypothermia, therefore, further research is warranted in order to provide physicians with finer prognostic evaluation tools that may help them in decision making. Furthermore, evaluating the effects of rapid and earlier cooling in these patients is also a relevant objective. In order to address these issues we retrospectively reviewed all patients admitted to our department in the past 10 years for cardiac arrest in whom therapeutic hypothermia had been performed.

Methods

We conducted a retrospective cohort study of consecutive adult patients with ROSC after cardiac arrest who had been admitted to the intensive cardiac care unit (ICCU) of Hospital General Universitario Gregorio Marañón, Madrid, Spain, between 1 January 2003 and 1 January 2013 and treated with therapeutic hypothermia.

Therapeutic hypothermia

All comatose patients with a Glasgow Coma Scale (GCS)≤8 after cardiac arrest were admitted to the ICCU and monitored and treated according to international clinical standards and the institutional protocol. All patients were cooled on admission with an intravenous infusion of 4°C cold saline at a rate of 30 ml/kg in the first 30 min. We aimed for a target temperature of 32–34ºC, which was subsequently maintained for 24h. Before 2008 thermal blankets and ice were used to maintain target temperature; after 2008 the Arctic-Sun® device (a noninvasive surface cooling device with self-adhesive, hydrogel-coated pads) was the preferred method for target temperature maintenance. All patients were sedated with midazolam and received analgesia using morphine. To prevent shivering, paralysis was induced by the intravenous administration of cisatracurium for the duration of therapeutic hypothermia. Continuous sedation was stopped at normothermia. If necessary, vasoactive or inotropic support was administered to maintain a mean arterial blood pressure >80 mmHg.

Data collection

Data were collected prospectively using Utstein-style recommendations.[13] Time from collapse to return of spontaneous circulation (T-ROSC), time from collapse to the first visit by emergency medical technician (EMT) (Time to arrival of ALS), time from collapse to first cardiopulmonary resuscitation (CPR) (T-CPR), time Bystander-CPR, advanced life support time (T-ALS), time from ROSC to initiation of therapeutic hypothermia (TIH) and time from ROSC to target temperature (TTT) were determined independently by two physicians. Although during the study period two different target temperatures (32°C and 33°C) were used, TTT for the study was defined as the time to reach 33ºC. Arterial blood sampling was performed on admission. Cardiac arrest was dichotomized as shockable rhythms (ventricular fibrillation (VF) and ventricular tachycardia (VT) and non-shockable rhythms (including asystole and pulseless electrical activity. Post-resuscitation circulatory shock was defined as the occurrence of arterial hypotension (mean arterial pressure <60 mmHg or systolic blood pressure <90 mmHg) sustained for more than 60 min following hospital admission, despite fluid resuscitation, leading to the administration of norepinephrine.

Objectives

Our primary objective was to identify predictors of survival with favourable neurological outcome in patients admitted after cardiac arrest and in whom therapeutic hypothermia was used, as well as determining the effects of rapid and earlier cooling in this population. Vital and neurological status were assessed six months after admission by a telephone interview. Where necessary, we request the help of our primary care physician or social worker to complete the information.

In patients with successful resuscitation, neurological outcome was determined using the Glasgow–Pittsburgh cerebral performance category (CPC), consisting of five strata. In the present study, a favourable neurological outcome was defined as CPC 1 or 2.

Statistical analysis

Patients were retrospectively divided into two groups: those with favourable outcome (alive and free from significant neurological sequelae (CPC ≤ 2) at six months) and those with unfavourable outcome (dead or with significant neurological sequelae (CPC > 2)). Continuous variables are presented as mean± 95% confidence interval (CI) and were compared with Student's *t* test. Variables that were not normally distributed were described as medians and interquartile ranges, and differences were analysed with the Mann–Whitney *U* test. Categorical variables were compared by the chi-square test or Fisher's exact test.

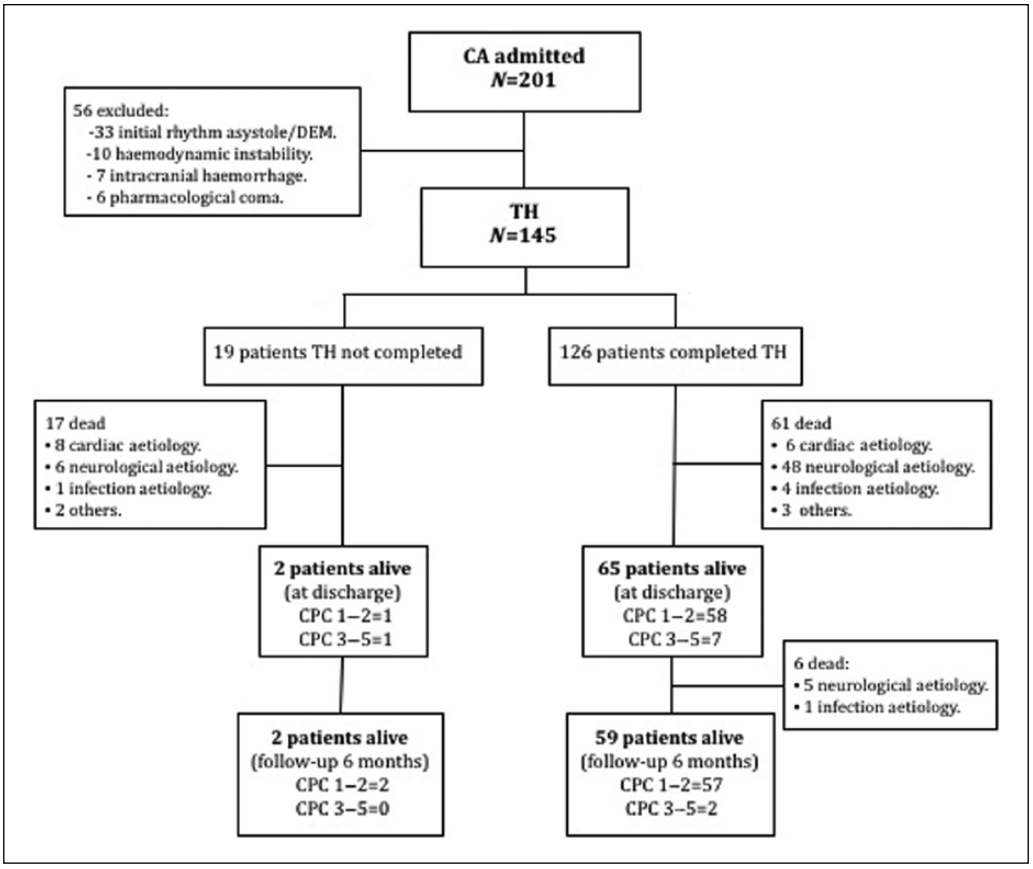

Figure 1. Flow chart for patients admitted in our unit, who were comatose survivors of a cardiac arrest during the study period. CA: cardiac arrest; TH: therapeutic hypothermia; CPC: Cerebral Performance Categories Scale.

Logistic regression models were constructed with backward stepwise variable selection. We tried both forward and backward selection with both leading to the same models. Variables with a p-value of <0.02 in univariate analyses were considered as candidates for inclusion in the multivariate model. We forced into the model three variables with a p-value >0.02 (TIH, Time to arrival of ALS, and target temperature) as these have been found to be associated with prognosis in previous studies. Goodness of fit for the logistic regression model was verified by the Hosmer–Lemeshow test. Linearity in the log-odds ratio for continuous explanatory variables was verified by adding smooth spline terms. Possible medical relevant interaction terms between variables were tested.

The final model was evaluated both in those patients in whom hypothermia was initiated and in those who had to cancel for various reasons without significant changes. The model was also evaluated at discharge and at six months with no differences being observed.

The data were entered into a Microsoft® Access database and Microsoft® Office Excel. SPSS 20.0 (SPSS, Inc., USA) and R 2.15.0 2 (r-project, USA) were used for statistical analyses. Two-sided p-values less than 0.05 were considered statistically significant.

Results

Study population

Between 1 January 2003 and 1 January 2013, 201 patients were admitted to our unit with a diagnosis of cardiac arrest with a persistent GCS <8. Until 2007 patients with asystole or pulseless electrical activity (PEA) as initial rhythm were not considered candidates for therapeutic hypothermia. Thus, 33 such patients were excluded. Ten additional patients in refractory shock, seven patients with haemorrhagic stroke and six patients with pharmacological coma, who regained consciousness after reversal of sedation, were also excluded (Figure 1).

As a result, therapeutic hypothermia was initiated in 145 patients, 126 of whom underwent therapy for 24 h. Nineteen patients were unable to complete the desired 24 h under therapeutic hypothermia (seven died during therapy and 12 had the therapy reversed due to haemodynamic instability, of which 10 died during admission and two were still alive at the end of follow-up).

Patient and hospital characteristics

The general and clinical features of the entire patient cohort are outlined in Table 1. Univariate analysis showed

Table 1. Characteristics of patients with good and poor prognosis.

	Total (*n*=145)	Alive and CPC≤2 (*n*=59)	Dead or CPC>2 (*n*= 86)	*p* value
Age	62.2 (59.8–64.6)	57.9 (54.0–61.8)	65.1 (62.3–68.0)	**0.003**
Sex, male	113 (77.9%)	47 (79.7%)	66 (76.7%)	0.677
Previous heart disease	76 (52.4%)	24 (40.7%)	45 (52.3%)	0.168
BMI, kg/m²	27.2 (26.2–28.3)	26.1 (25.2–27.1)	28.1 (26.5–29.8)	0.052
Hypertension	80 (55.2%)	30 (50.8%)	50 (58.1%)	0.386
Dyslipidaemia	56 (38.6%)	16 (27.1%)	40 (46.5%)	**0.018**
Diabetes mellitus	30 (20.7%)	6 (10.2%)	24 (27.9%)	**0.010**
Non-smoking	61 (42.1%)	23 (39.0%)	38 (44.2%)	0.433
Shock on admission	66 (45.5%)	15 (25.4%)	51 (59.3%)	**<0.001**
Creatinine clearance, ml/min per 1.73 m²	74 (68–79)	83 (75–91)	67 (60.7–74.2)	**0.004**
Glycaemia, mg/dl	237 (221–254)	210 (185–235)	257 (235–280)	**0.005**
Arterial blood pH	7.19 (7.16–7.21)	7.26 (7.22–7.29)	7.14 (7.11–7.17)	**<0.001**

Continuous variables are presented as mean ± 95% CI confidence interval and categorical variables are presented as counts and percentages.
CPC: Cerebral Performance Categories Scale; BMI: body mass index.

that patients with good prognosis tended to be younger and have a lower incidence of dyslipidaemia and diabetes mellitus. They were also less frequently in shock. Furthermore, their blood test showed that they tended to have lower glycaemia, higher creatinine clearance and higher arterial pH.

Characteristics of cardiac arrest

The characteristics of cardiac arrest are shown in Table 2. Univariate analysis showed that patients with good prognosis had shorter T-ROSC (19.4 min, 95% CI: 16.9–22.0 *vs*. 28.2 min, 95% CI: 25.6–30.9; $p < 0.001$), T-CPR (3.4 min, 95% CI: 2.2–4.6 *vs*. 5.6 min, 95% CI: 4.2–7.0; $p = 0.022$), Time to arrival of ALS (8.3 min, 95% CI: 6.5–10 *vs*. 11.0 min, 95% CI: 9.4–12.6; $p=0.025$), Time Bystander-CPR (4.9 min, 95% CI: 3.4–6.5; *vs*. 5.4 min, 95% CI: 4.0–6.8; $p = 0.656$) and T-ALS (10.8 min, 95% CI: 8.9–12.7 *vs*. 16.9 min, 95% CI: 14.9–18.9; $p <0.001$). Also, they had more often received bystander resuscitation (63.6% *vs*. 51.3%; $p = 0.174$). In patients with good prognosis, therapeutic hypothermia was initiated earlier (TIH: 87 min, 95% CI: 70–104 *vs*. 111 min, 95% CI: 96–125; $p = 0.042$), and the target temperature was reached at an earlier time (TTT: 316 min, 95% CI: 286–346 *vs*. 365 min, 95% CI: 338–392; $p = 0.017$). Likewise, these patients more often presented with shockable rhythms (94.9% *vs*. 52.3%; $p < 0.001$) and cardiac arrest was more often of cardiac aetiology (89.8% *vs*. 68.6%; $p = 0.015$). Among patients with favourable outcome, the Artic-Sun® was the most common method for target temperature maintenance (57.7% *vs*. 39.6%; $p = 0.020$). No differences were observed with regards to target temperature and the rebound hyperthermia during rewarming. Figure 2 shows the timings related to therapeutic hypothermia.

Outcomes

Therapeutic hypothermia could not be completed in 19 patients (seven died during therapy and 12 had to be suspended because of haemodynamic instability). During admission, 78 out of the 145 patients (53.8%) died. The most common cause of death was post-anoxic brain injury (54 patients, 69.2% of all deaths). Other common causes of death were cardiac (14 patients, 17.9%), infection (five patients, 6.4%) and other causes (five patients, 6.4%). During the six-month follow-up period, six additional patients died (five due to neurological sequelae and one due to infection). Overall survival at six months was 42.1% (61 patients).

Regarding neurological outcome, 59 of the 67 hospital survivors (88.1%) had no significant neurological sequelae (42 patients with CPC= 1 and 17 with CPC = 2), and eight had significant neurological damage (six patients with CPC = 3 and two patients with CPC = 4). At six months, 59 out of the 61 survivors (96.7%) had a good neurological outcome (46 patients with CPC = 1 and 13 with CPC = 2) and two had CPC = 3.

Predictors of survival free from significant neurological sequelae

Multivariate analysis showed that several variables were independently associated with unfavourable outcome (death or CPC > 2) at six months (Table 3). These included: asystole/electric-mechanical dissociation as presenting rhythm (odds ratio (OR) 13.775), and lower pH in the blood test on admission (OR 0.009). Although in univariate analyses also T-CPR and T-ALS were both significant predictors of poor prognosis, in multivariate models only T-ROSC was significantly associated with outcome (OR 1.063 per min). Age (OR 1.04 per year) and TTT (OR 1.005 per min)

Table 2. Characteristics of cardiac arrest and intervention times.

	Total (*n*=145)	Alive and CPC≤2 (*n*=59)	Death or CPC>2 (*n*= 86)	*p* value
Out-of-hospital cardiac arrest	131 (90.3%)	52 (88.1%)	79 (91.8%)	0.456
Initial rhythm, VF/VT	101 (69.7%)	56 (94.9%)	45 (52.3%)	**<0.001**
Witnessed cardiac arrest	129 (89.0%)	55 (93.2%)	74 (86.0%)	0.287
Bystander CPR[a]	86 (65.6%)	33 (63.6%)	39 (51.3%)	0.174
T-CPR, min	4.7 (3.7–5.7)	3.4 (2.2–4.6)	5.6 (4.2–7.0)	**0.022**
Time Bystander-CPR, min	5.2 (4.2–6.2)	4.9 (3.4–6.5)	5.4 (4.0–6.8)	0.656
Time to arrival of ALS	9.9 (8.7–11.0)	8.3 (6.5–10.0)	11.0 (9.4–12.6)	**0.025**
T-ALS, min	14.4 (12.9–15.8)	10.8 (8.9–12.7)	16.9 (14.9–18.9)	**<0.001**
T-ROSC, min	24.6 (22.7–26.6)	19.4 (16.9–22.0)	28.2 (25.6–30.9)	**<0.001**
Out-of-hospital TH[a]	33 (25.2%)	18 (32.7%)	15 (19.7%)	0.091
TIH, min	101 (90–112)	87 (70–104)	111 (96–125)	**0.042**
TTT, min	345 (325–365)	316 (286–346)	365 (338–392)	**0.017**
Hyperthermia during rewarming	44 (30.3%)	14 (25.5%)	30 (34.9%)	0.144
Hypothermia protocol				**0.020**
Ice packs and cold fluid infusions	77 (53.1%)	25 (42.3%)	52 (60.4%)	
Arctic-Sun®	68 (46.9%)	34 (57.7%)	34 (39.6%)	
Target temperature				0.309
32°C	24 (16.6%)	12 (20.3%)	12 (14%)	
33°C	121 (83.4%)	47 (79.7%)	74 (86%)	
Aetiology of cardiac arrest				**0.015**
Cardiac	112 (77.2%)	53 (89.8%)	59 (68.6%)	
Respiratory	6 (4.1%)	2 (3.4%)	4 (4.7%)	
Neurological	4 (2.8%)	0 (0%)	4 (4.7%)	
Metabolic/toxic	13 (9%)	4 (6.8%)	9 (10.5%)	
Unknown	10 (6.9%)	0 (0%)	10 (11.6%)	

Continuous variables are presented as mean± 95% CI confidence interval and categorical variables are presented as counts and percentages.
CPC: Cerebral Performance Categories Scale; VF: ventricular fibrillation; VT: ventricular tachycardia; CPR: cardiopulmonary resuscitation; Time to arrival of ALS: time of onset of cardiac arrest to the first visit by emergency medical technician; T-ALS: advanced life support time; T-ROSC: time from collapse to return of spontaneous circulation; TH: therapeutic hypothermia; TIH: time from return of spontaneous circulation to initiation of therapeutic hypothermia; TTT: time from return of spontaneous circulation to target temperature.
[a]Excluded intrahospital cardiac arrest.

were also associated with a worse prognosis but less decisively so. The remaining variables were statistically rejected.

Discussion

Our data underline the importance of the first recorded rhythm during cardiac arrest as the most significant predictor of survival and neurological outcome in patients admitted after cardiac arrest undergoing therapeutic hypothermia. In our cohort, of 44 subjects with asystole or PEA as the presenting rhythm, only three survived with CPC ≤ 2 at six months (6.8%), whereas of the 101 patients presenting with a shockable rhythm, 56 survived with good neurological outcome (OR 13.78, p <0.001). Sasson et al. observed in a meta-analysis that the pooled OR for survival to hospital discharge among patients found in VF/VT compared with those found in non-shockable rhythms ranged from 2.9 to 20.6 depending on the overall baseline rates of survival of the study.[14]

Several reasons may account for these differences. Asystole can be both a primary arrhythmia or the final result of a VF that has degenerated to imperceptible amplitude due to the time elapsed from the time of initial cardiac arrest until such time that first rhythm is monitored.[15] In our cohort, there is a tendency for patients with non-shockable rhythms to remain in cardiac arrest for a longer period of time before rhythm monitoring is performed than patients with shockable rhythms (12.2 ± 2.3 min PEA/asystole group *vs*. 8.8 ± 1.3 min VF/VT group; p = 0.164), although these differences did not reach statistical significance. Moreover, patients with cardiac arrest of non-cardiac aetiologies (stroke, respiratory failure, etc.) are known to present predominantly with non-shockable rhythms, with survival in these patients generally being worse.[16] In our series, patients with cardiac arrest of cardiac aetiology more often presented with a shockable rhythm (77.7% cardiac aetiology group *vs*. 42.4% non-cardiac aetiology group; p<0.001).

Another prognostic factor was the time from collapse to ROSC. In our cohort the delay in achieving ROSC involves a significant worsening of prognosis with an OR (per min) of 1.063 (95% CI: 1.013–1.116; $p = 0.013$). These differences are influenced mainly by a delay in starting CPR (3.4 ± 1.2 min *vs*. 5.6 ± 1.4 min; $p = 0.022$) and a longer T-ALS (10.8 ± 1.9 min *vs*. 16.9 ± 2 min; $p < 0.001$). The initiation of CPR by witnesses is associated with better outcomes (63.6% *vs*. 51.3%; $p = 0.174$). These data confirm the importance of initiating resuscitation measures as quickly as possible, and the critical importance of early defibrillation. Several studies have documented the effects of time to defibrillation and of bystander CPR on survival in cardiac arrest. When bystander CPR is provided, the decrease in survival rates is more gradual and averages 3%–4% per minute from collapse to defibrillation.[17] CPR prolongs VF, delays the onset of asystole and extends the window of time during which defibrillation can successfully occur.[18] Prolonged CPR can lead to dynamic or fixed failure of cerebral microcirculatory reperfusion despite adequate cerebral perfusion pressure and cause ischaemia and microinfarcts.[19]

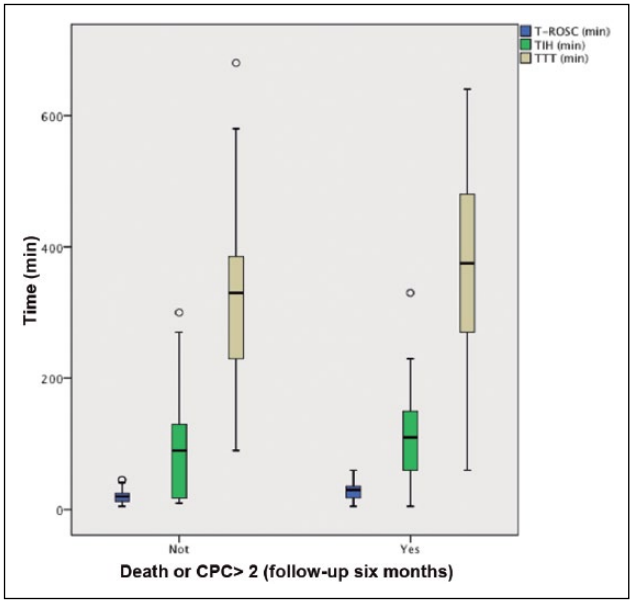

Figure 2. Differences between good prognosis (alive and CPC≤2) and poor prognosis (death and/or CPC>2) in terms of duration of cardiac arrest and hypothermia timing.
T-ROSC: time from collapse to return of spontaneous circulation; TIH: time from return of spontaneous circulation to initiation of therapeutic hypothermia; TTT: time from return of spontaneous circulation to target temperature; CPC: Cerebral Performance Categories Scale.

The pH value at the time of admission was also associated with prognosis. As pH at admission becomes lower survival free from neurological sequelae is reduced. Previous studies have reported that pH may be an independent prognostic factor.[20] There are several mechanisms of acidosis-related brain damage. Damage to inhibitory GABAergic cells and free radical reactions are among the previously described hypotheses.[21] Interruption of adequate blood flow due to cardiac arrest causes a shift from aerobic to anaerobic metabolism, and accumulation of CO_2, lactate and hydrogen ions. The end result of this perfusion deficit is a severe metabolic and hypercarbic acidosis at the tissue level. Even when conventional closed-chest resuscitation is applied, the systemic and regional blood flow generated rarely exceeds one-quarter of the normal, thus failing to fully meet tissue metabolic demands.[22] It is also known that pH is an indirect indicator of the patient's haemodynamic status, so those who are in shock tend to have lower pH values.[23]

Little is known about the long-term outcome of elderly survivors of cardiac arrest. In a recent study Chan et al. reported that mortality increases with age, but survival rates are not very different from other serious conditions such as heart failure,[24] therefore, these patients may benefit from more aggressive treatment. Our study supports the idea that age is an independent predictor of recovery without sequelae.

Studies in animals have reported that early initiation of therapeutic hypothermia and increased cooling rate improves prognosis.[25,26] However, human studies have reported mixed results.[9,11,12] Recently, Kim et al. reported that use of prehospital cooling reduced core temperature by hospital arrival and reduced the time to reach a temperature of 34ºC; it did not improve survival or neurological status,

Table 3. Predictors of survival free from significant neurological sequelae to six months.

Variables	Adjusted OR	95% IC (OR)	*p*-value
Age (one additional year)	1.04	1.005–1.076	0.024
T-ROSC (one additional minute)	1.063	1.013–1.116	0.013
TTT (one additional minute)	1.005	1.002–1.009	0.006
Non-shockable rhythm	13.775	3.384–56.065	<0.001
Arterial blood pH	0.009	0.001–0.382	0.014

Logistic regression model included the following variables: age, dyslipidaemia, diabetes mellitus, shock on admission, creatinine clearance, glycaemia, arterial blood pH on admission, lactate on admission, initial rhythm, time from collapse to first CPR (T-CPR), advanced life support time (T-ALS), time to arrival of advanced life support (Time to arrival of ALS), time from collapse to return of spontaneous circulation (T-ROSC), time from return of spontaneous circulation to initiation of therapeutic hypothermia (TIH), time from return of spontaneous circulation to target temperature (TTT), hypothermia protocol, aetiology of cardiac arrest, hyperthermia during rewarming and target temperature. *n*=145. Missing data: 0.

although this study has several limitations such that only 74% of the patients with a shockable rhythm and 59% with non-shockable rhythm eventually reached the target temperature.[11] Previously, Bernard et al. published the result that use of prehospital therapeutic hypothermia did not show improvement of neurological status at hospital discharge;[12] however, this study has a important limitation in lack of continuity of cooling in the emergency department (although the cooling by paramedics during transport was superior for the prehospital hypothermia group, the effectiveness of cooling in the emergency department for the first hour was far superior in the control group, with no temperature differences observed between the groups beyond the first hour). In our study, we observed that patients in whom less time was consumed in attaining target temperature had a better prognosis than those who required a longer time to reach target temperature (OR 1.005, 95% CI 1.002–1.009; p= 0.006), and this itself was influenced by prompt initiation of therapeutic hypothermia, as patients in whom therapy was initiated earlier achieved target temperature in a shorter time. In contrast to the study by Bernard et al.,[12] patients that had received prehospital therapeutic hypothermia had lower TTT (259+39 min *vs*. 372+22 min; p<0.001). Therefore, it is not only early initiation of therapeutic hypothermia that is important, but also rapid cooling. The theoretical advantages of early initiation of therapeutic hypothermia may include decreasing reperfusion-related injury. Protective cellular mechanisms consistent with this concept include attenuation of the oxidant burst seen within minutes of normothermic reperfusion or the inhibition of reperfusion-activated apoptotic pathways.[27] Although the speed of cooling initiation and the time to reach target temperature might play a role, its influence on prognosis appears to be less important than other factors previously explained (OR 1.005).

Limitations

The study was conducted at a single large tertiary referral centre and so the results may not be generalizable. This was a retrospective study conducted on prospectively gathered data, which implies inherent limitations such as an inability to adjust for unknown confounding factors and referral bias. Probably the most important limitation of our study is the number of variables included in the model, due to the sample size seeming too small to support so much adjustment, therefore this model will need to be prospectively validated. Another important limitation is the difficulty in getting precise information regarding the time of cardiac arrest, initiation of CPR and its duration, with this information being obtained by means of reports from prehospital emergency services and questioning of witnesses. In survivors of witnessed cardiac arrest, T- ROSC is a good estimate of the duration of circulatory arrest while in those with unwitnessed cardiac arrest it may underestimate the actual duration of circulatory collapse. In our study, among the 16 patients with unwitnessed cardiac arrest treated with therapeutic hypothermia, the mean time without CPR was 14.7 min; in only four survivors, duration of cardiac arrest was estimated at less than 30 min based on the Utstein style recommendations. Being a retrospective study we have not included other prognostic factors such as the presence of minimal responsiveness or seizures, because these date were not collected from our database.

Conclusion

In conclusion, our study shows that the most important factors influencing the prognosis of patients who suffer cardiac arrest are presenting rhythm, time from collapse to ROSC and arterial pH at admission, reflecting the haemodynamic status of the patient. Although the speed of cooling initiation and the time to reach target temperature might play a role, their influence on prognosis seems to be less important.

Conflicts of interest

None of the authors declares any conflicts of interest nor has financial disclosures.

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