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Clinical paper

Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms☆

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ABSTRACT

Background: Therapeutic hypothermia improves neurologic outcomes in patients resuscitated from cardiac arrest due to ventricular fibrillation. However, its role in patients with cardiac arrest due to non-shockable rhythms (pulseless electrical activity (PEA) and asystole) is unclear. We hypothesized that therapeutic hypothermia favorably impacts neurologic outcome and survival in patients resuscitated from cardiac arrest due to non-shockable rhythms.

Methods: Prospectively collected data on consecutive adult patients admitted to Hartford Hospital from 1/1/2004 to 11/1/2010 who survived a cardiac arrest due to PEA or asystole were analyzed. Patients who underwent therapeutic hypothermia (1/1/2007–11/1/2010) formed the hypothermia group while patients admitted prior to the institution of therapeutic hypothermia (1/1/2004–1/1/2007) at Hartford Hospital formed the control group. The primary end-point was measured using the Pittsburgh cerebral performance category (CPC) scale and patients were assessed for a good (CPC 1 and 2) or poor (CPC 3–5) neurological outcome prior to discharge from hospital. A secondary end-point was measured as survival at discharge from hospital.

Results: Of 100 post-cardiac arrest patients included in the study, 15/52 (29%) patients in the hypothermia group had a good neurologic outcome as compared to 5/43 (10%) patients in the control group ($P = 0.021$). On multivariate analysis, the odds ratio for good neurologic outcome and survival at discharge from the hospital with therapeutic hypothermia as compared to control were 4.35 (95% CI 1.10–17.24, $P = 0.04$) and 5.65 (CI 1.66–19.23, $P = 0.006$) respectively.

Conclusion: Therapeutic hypothermia is associated with favorable neurologic outcome and survival in patients resuscitated after cardiac arrest due to non-shockable rhythms.

1. Introduction

An estimated 200,000 cardiac arrests occur out-of-hospital on an annual basis in the United States,[1,2] with limited survival rates of 0–11% depending on the presenting rhythm.[3,4] The true incidence of in-hospital cardiac arrest remains less apparent, but is estimated to be 1–5 events per 1000 hospital admissions.[5]

Following a cardiac arrest, the brain tolerates anoxia up to 2–4 min[6] and thereafter irreversible neuronal damage commences in the absence of re-establishment of circulation. Re-oxygenation with successful return of spontaneous circulation (ROSC), although essential in restoring the energy charge, provokes a deleterious chemical cascade by generating free radicals and other inflammatory mediators which leads to devastating neurologic consequences and death in the form of post-resuscitation syndrome.[7] However, these harmful effects of reperfusion injury may be mitigated with the use of hypothermia as demonstrated in case reports and dog models since the 1950s.[8–15]

More recently, therapeutic hypothermia has been reported to improve neurologic outcomes and survival of out-of-hospital cardiac arrest patients who have been successfully resuscitated from ventricular fibrillation (VF).[16,17] However, this beneficial effect of hypothermia therapy on outcomes for other rhythms has not been well studied. Approximately 19–32% of patients resuscitated from cardiac arrest who survive to discharge have a poor neurological outcome.[18,19] Moreover, the survival to hospital discharge rate in these patients varies from 0 to 42%, the most common range being between 15% and 20%.[5]

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Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) and the 2010 American Heart Association guidelines for Cardiopulmonary Resuscitation And Emergency Cardiovascular Care states: "unconscious adult patients with ROSC (return of spontaneous circulation) after out-of hospital cardiac arrest should be cooled to 32–34 °C (89.6–93.2 °F) for 12–24 h when the initial rhythm was VF (Class I). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb)".[20]

The aim of the present study was to compare therapeutic hypothermia to control (normothermia) in comatose patients with cardiac arrest due to a non-shockable rhythm [pulseless electrical activity (PEA) or asystole].

2. Methods

2.1. Study population

Consecutive adult patients who were admitted to the Cardiac Intensive Care Unit (CICU) at Hartford Hospital between January 1, 2004 and November 1, 2010 after successful resuscitation from an out-of-hospital or in-hospital cardiac arrest and who met the inclusion criteria formed the study cohort. The *inclusion* criteria were:

1. PEA or asystole as the initial cardiac rhythm
2. an age of 18 to 75 years
3. Glasgow Coma Scale ≤ 8 after ROSC
4. an estimated interval of 5–15 min from the patient's collapse to the first attempt at resuscitation by emergency medical personnel
5. an interval of no more than 30 min from collapse to ROSC

Patients were *excluded* if they met any of the following criteria:

1. missing key data
2. Glasgow Coma Scale > 8 after ROSC
3. a tympanic-membrane temperature below 30 °C on admission
4. pregnancy
5. response to verbal commands after the ROSC and before initiation of hypothermia
6. evidence of hypotension (mean arterial pressure, less than 60 mm Hg) for more than 30 min after the ROSC and before initiation of hypothermia
7. evidence of hypoxemia (arterial oxygen saturation, less than 85%) for more than 15 min after the ROSC and before initiation of hypothermia
8. a terminal illness that preceded the arrest

2.2. Study design and procedures

This was a retrospective study conducted on prospectively gathered data and was approved and conducted as per guidelines of the Institutional Review Board at Hartford Hospital which also includes a formal ethical approval to conduct this study. Therapeutic hypothermia as a treatment option for cardiac arrest patients was instituted at Hartford Hospital in 2007. This provided the opportunity to study the benefits of this therapy in comparison to historical controls prior to the institution of therapeutic hypothermia at Hartford Hospital. Patients who received therapeutic hypothermia (1/1/2007–11/1/2010) formed the hypothermia group and were compared to a historical control group of patients (1/1/2004–1/1/2007) admitted to the CICU after successful resuscitation from cardiac arrest due to either PEA or asystole within the study period (Fig. 1). Patients assigned to the hypothermia group were cooled to a target temperature of 32–34 °C using a combination of an infusion of 2 L of cold normal saline at 4 °C administered via a central venous catheter during a period of 20–30 min with an intravenous pressure bag inflated to 300 mm of Hg and ice-packs, followed by use of an intracaval cooling device. Intracaval cooling was initiated as soon as feasible using an endovascular cooling catheter (Icy catheter, ZOLL Temperature management, MA, USA) which was inserted into the right or left femoral vein in the emergency department or CICU. The goal was to reach the target temperature within 4 h after return of spontaneous circulation. The target cooling temperature was defined as a core body temperature of 33 ± 1 °C. Hypothermia was maintained by endovascular cooling for 18 h and the patients were then re-warmed to a target temp. 37.0 °C set to a rate of 0.35 °C/h. Baseline vital signs, including temperature measured by rectal probe, were obtained before and during therapeutic hypothermia therapy. Temperature was measured every 15 min for the first hour followed by hourly

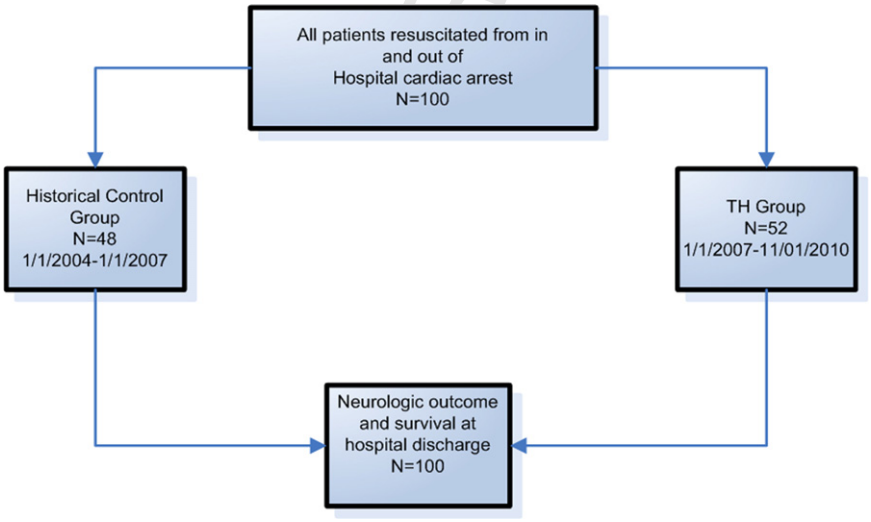

Fig. 1. Study population. The historical control group included 48 survivors of cardiac arrest from non-shockable rhythms who underwent standard post cardiac arrest care, prior to the initiation of therapeutic hypothermia (TH) at the study center. The TH group included 52 survivors of cardiac arrest from non-shockable rhythms who underwent hypothermia therapy in addition to standard post cardiac arrest care. All 100 patients were followed to hospital discharge and neurologic outcomes and survival were recorded at discharge. TH = therapeutic hypothermia.

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measurements and blood pressure as well as heart rate were measured hourly throughout the CICU stay. Baseline laboratory tests included sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, hemoglobin, white blood cell count, platelet count, international normalized ratio (INR), lactic acid and arterial blood gases which were measured every 6 h after initiation of cooling with 4 °C normal saline infusion.

Patients in the historical control group received standard care but no hypothermia in the CICU.

Patient data were obtained by systematic chart review of cardiac arrest patients admitted to Hartford Hospital during the study period. Data extracted also included location of arrest, time to ROSC, whether the arrest was witnessed, whether bystander cardiopulmonary resuscitation was provided and the presenting rhythm.

2.3. Evaluation of outcome

The primary endpoints of the study were either a good neurologic outcome, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on a five category scale, or a poor neurologic outcome defined as Pittsburgh cerebral-performance categories 3 (severe disability), 4 (a vegetative state), and 5 (death) prior to discharge from the hospital.[21–23] The secondary endpoint of the study was defined as survival at discharge from the hospital. The neurological evaluation of the patients was conducted by a consultant neurologist who examined the patient on a daily basis till discharge from hospital or death.

2.4. Statistical analysis

Continuous variables which did not have a normal distribution were expressed as median and interquartile range. Medians were evaluated for significant differences using the Mann–Whitney *U* test. Categorical variables were expressed as counts and percentages which were analyzed using the chi-square or Fisher exact test. Using the difference in risk between the two study groups (hypothermia and control), an absolute risk ratio (ARR) was calculated. A number needed to treat (NNT) was thereafter calculated using the formula NNT = 1/ARR. Cumulative survival curves were obtained using the Kaplan–Meier procedure and compared using the log-rank test.

A multivariable analysis using binomial logistic regression was performed to determine the association of therapeutic hypothermia to (1) good and poor neurologic outcomes as well as to (2) survival and death at discharge, in each instance as two separate end-points. Significant parameters obtained on univariable analysis as well as clinically significant variables regardless of their strength of univariate correlation were entered into the logistic regression model.

A forward stepwise selection procedure, based on the Wald statistic probability, was performed, with a threshold of $P \leq 0.05$ and $P \geq 0.1$ for variable entry and removal, respectively. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the model. Goodness of fit was evaluated using the Hosmer–Lemeshow test. A reasonable fit can be assumed if the result has a *P* value > 0.05.

In all statistical analyses, a $P < 0.05$ was considered significant. All statistical analyses were two-tailed and were performed using SPSS version 17.0 software (SPSS, Chicago, IL).

3. Results

A total of 100 patients were identified who met the inclusion criteria of the study and formed the study cohort. Key follow-up data were available on all of the study patients. Of these, 52 patients (52%) who received therapeutic hypothermia formed the hypothermia group, while 48 patients (48%) who did not receive therapeutic hypothermia formed the control group. Table 1 compares the demographics and clinical characteristics of patients in the hypothermia and control groups. At baseline the hypothermia and control groups were similar in demographics with regards to age, gender, ethnicity, and clinical characteristics for a history of coronary artery disease, cardiomyopathy, hypertension, end-stage renal disease and diabetes mellitus. The hypothermia group had significantly less witnessed cardiac arrests as compared to the control group (69% vs. 90%, respectively; $P = 0.015$). However, there was no significant difference in bystander performed cardiopulmonary resuscitation in the hypothermia group as compared to the control group (39% vs. 56%, respectively; $P = 0.10$). The median time to ROSC was 19 min (interquartile range 10–30) and 14 min (interquartile range 7–22) respectively for the hypothermia and normothermia groups ($P = 0.36$) (Table 1).

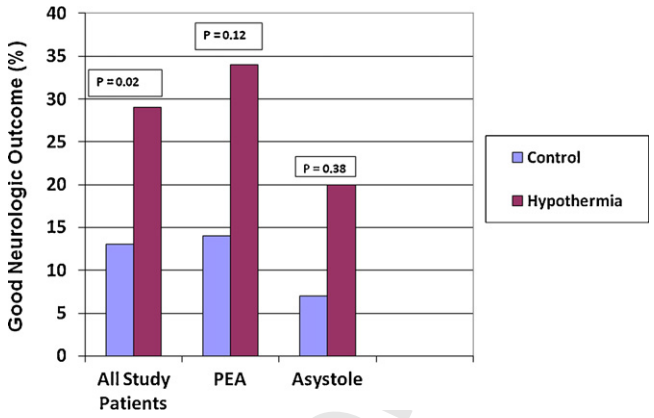

Fig. 2. Percentage of favorable neurologic outcomes at hospital discharge in the hypothermia and control groups. For the entire cohort, there was a significantly improved neurologic outcome in the hypothermia group as compared to the control group (29% vs. 13%, respectively, $P = 0.02$). There was no significant benefit of hypothermia on separate analysis of the PEA and asystole subgroups in comparison to control. PEA = pulseless electrical activity.

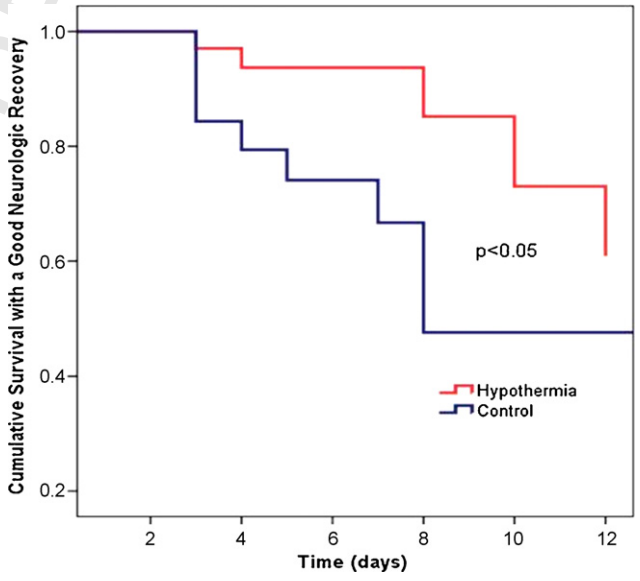

Fig. 3. Kaplan Meier survival curves demonstrating cumulative survival over time during hospital stay. Patients who underwent hypothermia were more likely to have a survival with good neurologic outcome as compared to patients who did not receive hypothermia (control) ($P < 0.05$).

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Table 1
Q4 Baseline characteristics of the study population in the hypothermia and control groups.

Characteristic	Hypothermia group ($n=52$)	Control group ($n=48$)	P value
Age			
Median	58	68	0.074
Interquartile range	50–73	52–75	
Gender, female (%)	35	48	0.22
Whites (%)	46	44	0.34
History of CAD (%)	35	27	0.52
History of CM (%)	31	35	0.67
History of HTN (%)	67	63	0.68
History of ESRD(%)	8	6	0.78
History of DM (%)	44	35	0.42
Asystole (%)	39	56	0.10
PEA (%)	62	44	0.10
In-hospital (%)	37	60	**0.017**
Time of ROSC (min)			
Median	19	14	0.36
Inter quartile range	10–30	7–22	
Witnessed arrest (%)	69	90	**0.015**
Bystander CPR (%)	39	56	0.10

SD, standard deviation; CAD, coronary artery disease; DM, diabetesm ellitus; CM, cardiom yopathy; ESRD, end-stage renal disease; HTN, hypertension; ROSC, return of speontaneous circulation; PEA, pulseless electrical activity; CPR, cardio-pulmonary resuscitation.

3.1. Neurologic outcome and survival

Fifteen of the 52 patients (29%) who underwent therapeutic hypothermia had a good neurologic outcome as compared to 6 of the 48 patients (13%) in the control group ($P=0.02$) (Fig. 2). After adjusting for age, location of arrest, witnessed arrest and time to ROSC, the hypothermia group had a significantly better neurologic outcome as compared to the control group (odds ratio 4.35; 95% CI 1.10–17.24, $P=0.04$). Using the Kaplan–Meier procedure cumulative survival curves were derived and compared using the log-rank test. The use of hypothermia therapy is associated with a significantly better survival with good neurologic outcome as compared to the control group ($P<0.05$) (Fig. 3).

Twenty of the 52 patients (38%) who underwent therapeutic hypothermia survived to hospital discharge as compared to 9 of the 48 patients (19%) in the control group ($P=0.03$). After adjusting for age, location of arrest, witnessed arrest and time to ROSC, survival at hospital discharge in the hypothermia group was significantly better when compared to the control group (odds ratio 5.65; CI 1.66–19.23, $P=0.006$).

3.2. Rhythm type

The hypothermia group was more likely to have PEA and the control group was more likely to have asystole as the presenting rhythm (Table 1). There was no significant difference in neurologic outcome in each of the PEA and asystole subgroups who received therapeutic hypothermia as compared to control (34% vs. 14%, respectively, $P=0.12$ for PEA and 20% vs. 7%, respectively, $P=0.38$ for asystole) (Fig. 2). Similarly, there was no significant difference in survival at discharge in each of the PEA and asystole subgroups who received therapeutic hypothermia as compared to control (44% vs. 24%, respectively, $P=0.14$ for PEA and 30% vs. 15%, respectively, $P=0.20$ for asystole).

3.3. Location of arrest

There were significantly more in-hospital cardiac arrests in the normothermia group as compared to the hypothermia group (60% vs. 37%, $P=0.017$) (Table 1). The most common first recorded rhythm for in-hospital cardiac arrests was PEA as compared to out-of-hospital cardiac arrests where asystole was more often the first recorded rhythm. The location of arrest (in-hospital vs. out-of-hospital) did not significantly affect neurologic outcome or survival at discharge in the hypothermia group (32% vs. 27%, respectively, $P=0.741$ for neurologic outcome and 42% vs. 36%, respectively, $P=0.68$ for survival).

4. Discussion

Prognosis after resuscitation from cardiac arrest remains poor with post-ischemic brain injury as the leading cause of death.[24] Both prospective randomized control trials and retrospective trials have shown that survival with good neurologic outcome is improved by inducing hypothermia in patients with return of spontaneous circulation after ventricular fibrillation cardiac arrest.[16,17,25] However, this benefit has not been consistently demonstrated in patients with return of spontaneous circulation from non-shockable rhythms.[20,26,27,18] For this reason the Advanced Life Support Task Force of the International Liaison committee on Resuscitation (ILCOR) and the 2010 American Heart Association guidelines for Cardiopulmonary Resuscitation And Emergency Cardiovascular Care have recommended that patients with return of spontaneous circulation from non-shockable rhythms may undergo therapeutic hypothermia as a IIb recommendation.[20]

In our study we compared consecutive patients resuscitated from cardiac arrest due to non-shockable rhythms who were treated with therapeutic hypothermia to historical controls who did not undergo similar therapy. The results demonstrate that systemic therapeutic cooling to a core body temperature between 32

Table 2
Study patients who were made DNR and comfort measures/care withrawal.

	Do-not-resuscitate (DNR)	Comfort measure/care withdrawal	Survival to discharge
Control group ($n=48$)	28 (58%)	28 (58%)	9 (19%)
Hypothermia group ($n=52$)	34 (65%)	34 (65%)	20 (38%)

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and 34 °C for a period of 18 h led to a favorable neurologic outcome and survival at hospital discharge in patients with cardiac arrest due to non-shockable rhythms. Our data demonstrates that for every 5 patients with cardiac arrests due to a non-shockable rhythm that undergo therapeutic hypothermia, one favorable neurologic outcome is gained regardless of the presenting rhythm of PEA or asystole.

In previous studies on therapeutic hypothermia performed by Don et al.[25] and Oddo et al.[27] a similar analysis was done on out-of-hospital cardiac arrest patients due to VF and non-shockable rhythms (pulseless electrical activity or asystole). Their data however failed to demonstrate a significant improvement in survival or neurologic outcome in the subgroup of patients with non-shockable rhythms who received therapeutic hypothermia as compared to historic controls. In the former study the lack of benefit is possibly due to multiple factors. First, their study patients underwent surface cooling which may be less effective in achieving target temperature when compared with intravascular cooling.[28] Second, the fact that since these were exclusively out-of-hospital cardiac arrest patients, their time to ROSC was prolonged leading to a delay in time to achieve target hypothermia. In the study performed by Oddo et al.[27] on a cohort of 23 patients with non-shockable rhythms who underwent external cooling, was perhaps underpowered to draw any meaningful conclusions.

In contrast, in an observational study by Arrich[26] where cooling was achieved mostly via an endovascular device on 197 cardiac arrest patients with pulseless electrical activity or asystole, therapeutic hypothermia showed significant mortality benefit, although there was no effect on neurologic outcome.

In a more recent observational study performed by Dumas et al.[29] on a large cohort of out-of-hospital cardiac arrest patients, 437 patients had non-shockable rhythms. Out of these, 261 patients (60%) underwent therapeutic hypothermia where cooling was achieved externally using cold air as compared to 176 patients (40%) who were not cooled. Their study showed no benefit of hypothermia therapy on neurologic outcome in patients with non-shockable rhythms. In contrast to our study, Dumas et al. also included patients who had a prolonged down time, terminal illness and hemodynamic instability in their study. Thus, the authors surmised that their results could be due to an inadequate "dose" of hypothermia in terms of degree and duration not commensurate with the circulatory status of their patients or, that patients with non-shockable rhythms were more likely to have a non-cardiac cause for cardiac arrest putting them at a higher risk-benefit ratio with use of hypothermia therapy compared to those with shockable rhythms.

To our knowledge, our study is the first to demonstrate that the use of therapeutic hypothermia in a selected group of cardiac arrest patients successfully resuscitated from non-shockable rhythms is associated with both improved neurologic outcome and survival at hospital discharge as compared to similar patients who did not receive such therapy.

5. Limitations

This is a retrospective study conducted on prospective data collected at a single large tertiary center and limits the extent to which the results can be generalized. Retrospective studies are limited by the inability to adjust for confounding factors and referral bias. Though resuscitation protocols may change over time, we do not believe that the resuscitation protocol at our institution has changed substantially during the study time period. Inspite of adjustment for the significant difference seen in number of in-hospital cardiac arrests between the two study groups, unknown confounders associated with location of cardiac arrest could have influenced the results. Patients made "do-not-resuscitate" or "comfort measures/care withdrawal" (Table 2) could have affected the survival to discharge rates in both groups.

6. Conclusions

The use of therapeutic hypothermia is associated with improved neurologic outcome and survival at discharge in patients that have been successfully resuscitated after cardiac arrest due to a non-shockable rhythm (pulseless electrical activity and asystole) and should be offered to this group of cardiac arrest survivors.

Conflict of interest statement

Financial disclosure: Speaker for ZOLL Temperature Management. Q2

Unlabeled/unapproved use disclosure: ICY Catheter© for induction of Therapeutic Hypothermia.

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