Earlier Hypothermia Attainment is Associated with Improved Outcomes after Cardiac Arrest

Abstract

Introduction: Therapeutic hypothermia (TH, 32-34ºC) reduces mortality and improves neurologic outcomes after ventricular fibrillation cardiac arrest (CA). The relationship between time to achieve TH and outcomes remains undefined. We hypothesized that a shorter interval from CA to achieve TH would be associated with improved neurologic outcome.

Methods: We retrospectively reviewed subjects within or out-of-hospital CA treated with TH between November 2006 and April 2009 at our institution. The time to target temperature was defined as the interval between witnessed CA and first measurement of hypothermia (≤ 34 ºC) and further categorized as early (< 6 hours) or delayed (> 6 hours). Outcomes were assessed at the time of death or discharge using Cerebral Performance Category Score (CPC); good outcome was defined as CPC ≤ 2. Fisher's Exact test was used to assess the univariate relationship between time to TH and outcome.

Results: 26 patients achieved TH after in-hospital (39%) and out-of-hospital (61%) CA. Five patients (5/26) reached early target temperature; 80% (4/5) of those had a good neurological outcome. 24% (5/21) of subjects with delayed target temperature achieved a good neurological outcome. The univariate relationship between time to target temperature and neurological outcome was statistically significant (p=0.034).

Conclusion: Attaining TH within 6 hours of in or out-of-hospital CA was associated with a greater likelihood of a good neurological outcome at discharge. Time from CA to achieved TH should be included as a clinically important covariate in future studies of predictors of outcome after CA.

Keywords: Hypothermia, cardiac arrest, hypoxic-ischemic brain injury.

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Introduction

Mild therapeutic hypothermia (TH, 32-34ºC) reduces mortality and improves neurologic outcomes in patients that are successfully resuscitated after ventricular fibrillation (VF) cardiac arrest.[1-3] In a recent study,[3] there was an association of positive outcomes when therapeutic hypothermia was combined with the return of spontaneous circulation (ROSC) within 25 minutes of cardiac arrest (CA). There remains an undefined relationship between the time to achieve therapeutic hypothermia after cardiac arrest and neurologic outcomes. We hypothesized that a shorter interval from CA to achieve mild TH would be associated with improved neurologic outcome.

Methods

After obtaining approval of the Mayo Clinic Institutional Review Board, we retrospectively reviewed the electronic medical record of all patients treated with therapeutic hypothermia at Mayo Clinic Florida between November 2006 and April 2009. Subjects within or out-of-hospital CA due to witnessed VF or other non-perfusing rhythm (pulse-less electrical activity, asystole) that were treated with TH per ILCOR/AHA recommendations[4] for 12 to 24 hours were included. The time of CA, time of ROSC, and time from CA to achieve therapeutic hypothermia were abstracted from the medical record. Time from CA to therapeutic hypothermia was categorized as rapid (< 6 hours) or delayed (> 6 hours). Outcomes were assessed at the time of death or hospital discharge, quantified by the Pittsburgh CPC[5] score (1 = good recovery, 2 = moderate disability, 3 = severe disability, 4 = vegetative state, 5 = death). Good outcome was defined as CPC score of 1 or 2. Fisher's Exact test was used to assess the univariate relationship between time from cardiac arrest to target temperature and the neurological outcome.

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Table 1: Characteristics of early vs. delayed groups. The univariate relationship between time from cardiac arrest to target temperature (≤ 34 degrees centigrade) and CPC score at discharge was statistically significant (p = 0.034).

	Early Attained Hypothermia (< 6 hours to target temp) n = 5	Delayed Attained Hypothermia (> 6 hours to target temp) n = 21
Median Age	75 (range 26-93)	63 (range 19-86)
Gender	60% female (n = 3/5) 40% male (n = 2/5)	43% female (n = 9/21) 57% male (n = 12/21)
Presenting Rhythm	60% V- fib arrest (n = 3/5) 40% PEA / asystole (n = 2/5)	19% V- fib arrest (n = 4/21) 81% PEA / asystole (n = 17/21)
Good Outcome (CPC 1-2) at Discharge	80% (n = 4/5)	24% (n = 5/21)
Poor Outcome (CPC 3-5) at Discharge	20% (n = 1/5)	76% (n = 16/21)

Results

Thirty-three patients were treated with mild TH after witnessed in-hospital (39%) and out-of-hospital (61%) CA. Subjects were excluded if they did not reach target temperature or had an unwitnessed CA (n = 7/33). Of the remaining 26 patients, 42% (11/26) survived to hospital discharge, and 35% (9/26) achieved a good neurologic outcome at discharge (CPC 1 or 2).

The "early group" consisted of five patients that reached target temperature within six hours of cardiac arrest. The median age among these patients was 75 (range 26-93 years of age), and three of the five (60%) were female. Three of these five patients (60%) presented with ventricular fibrillation arrests. Eighty percent (80%, n =4/5) of patients in this group achieved a good neurological outcome at the time of discharge. One patient, age 93, suffered a pulse-less electrical activity (PEA) arrest after choking and remained comatose; care was subsequently withdrawn.

Twenty-one patients achieved target temperature beyond six hours, constituting the "delayed group." The median age among these patients was 63 (range 19-86 years of age), and nine of the twenty-one (43%) were female. Nineteen percent (19%, n = 4/21) of patients in the delayed group presented with ventricular fibrillation arrest. Only 24% (5/21) of patients with delayed induced hypothermia achieved a good neurological outcome at the time of discharge.

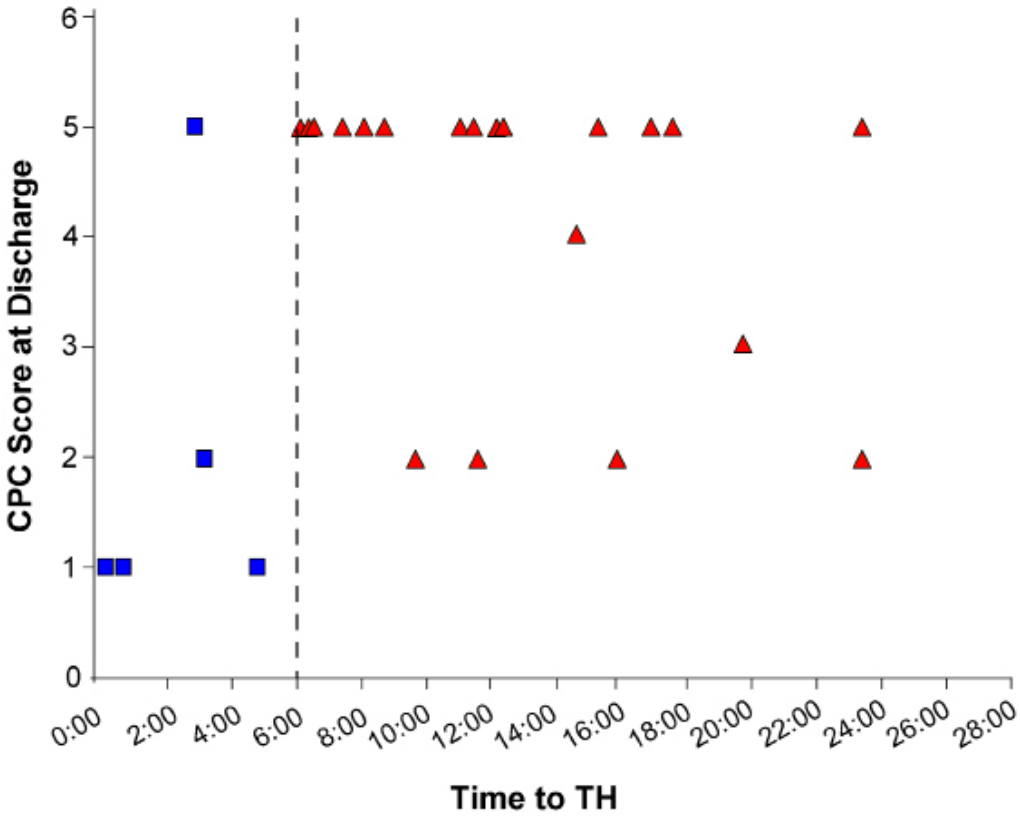
Table 1 compares the characteristics and outcomes between the early and delayed hypothermia groups. The univariate relationship between the time from cardiac arrest to target temperature and neurological outcome was statistically significant (p=0.034) between groups.

Discussion

Therapeutic hypothermia (defined as core body temperature of 32 to 34 degrees C) has been well established as a means of improving neurologic outcome after ventricular fibrillation cardiac arrest.[1,2] However, the optimal time to reach hypothermia, as well as the optimal duration and means to achieve hypothermia, remains unclear. Current guidelines are derived from two landmark studies published in 2002 which demonstrated the efficacy of therapeutic hypothermia in reducing neurologic morbidity after cardiac arrest. The Bernard Australian group[1] used ice packs in the field and attained cooling between 2 and 6 hours after ventricular fibrillation arrest, but maintained hypothermia for only 12 hours. The European Hypothermia after Cardiac Arrest group,[2] which cooled patients for 24 hours, attained hypothermia on average 8 hours (inter-quartile range 4-16 hours) after ROSC with surface cooling devices applied upon arrival to the hospital. Both studies reported a number needed to treat (NNT) of 6-7 patients in order to prevent one death and improve neurologic outcome with hypothermia.

Current research is investigating the means by which hypothermia provides its neuro-protective benefit. It is believed that hypothermia impacts at least two major physiologic factors: 1) reduction in brain metabolism (CMRO2 = cerebral metabolic rate of oxygen consumption), thereby reducing cerebral oxygen demand in the setting of reduced cardiac output,[6] and 2) reduction in cellular excitotoxic cascade and inflammation.[4] Faster attainment of hypothermia, therefore, makes sense physiologically to reduce the mismatch between cardiac output, cerebral blood flow and CMRO2, as well as in reducing the cellular excitotoxic cascade. Recent animal models of induced cardiac arrest and hypothermia induction demonstrate shorter times to reach hypothermia improve outcome.[7,8] To our knowledge, however, no study has correlated shorter time to

Figure 1: X axis displays time to reach therapeutic hypothermia (TH, 32-34 degrees centigrade). Y-axis displays CPC clinical outcomes. All but one patient who was cooled within six hours (threshold) appeared to have a better outcome (CPC 1-2) compared to those patients reaching TH after six hours, (p=0.034)



attainment of hypothermia with improved clinical outcomes in human subjects. Rather, there has been a suggestion in one prior study that the time to reach target temperature in fact does not have a relationship to outcomes in patients treated with therapeutic hypothermia.[9] This retrospective review of 55 patients treated with hypothermia demonstrates great efficiency of the institution's ability to achieve hypothermia. The median time to attainment of hypothermia in that study was 5 hours, with a statistically significant trend for the delay to decrease as experience with inducing hypothermia accrued. Patients were divided into good outcome (CPC 1-2) and poor outcome (CPC 3-5) at the time of discharge, and time to achieve hypothermia compared between groups. Those with a good outcome achieved target temperature within 4 hours (median) vs. 5.5 hours in the group with poor outcome; the result was not statistically significant (p = 0.95, Mann-Whitney test).[9] We acknowledge the limitations of our small sample size, collected from a single academic center; however, there did appear to be a "threshold" that attainment of hypothermia within 6 hours was associated with improved outcome. The result suggests that time to attainment of hypothermia should be further studied as a potentially important clinical variable affecting outcomes after cardiac arrest, much as the time from CA to ROSC is known to affect survival.[3]

Admittedly, there are confounding factors that make it difficult to determine if time to attain hypothermia is an independent predictor of outcome. In our population, the 4 of 5 patients with early hypothermia and good outcome also had CA to ROSC times less than 20 minutes, and 3 of these patients presented with VF arrests. The delayed hypothermia group had a significant percentage (81%) of patients presenting with PEA or asystolic arrests, typically requiring longer resuscitation efforts and ultimately delaying the induction of therapeutic hypothermia. To further assess the validity of time to attain hypothermia as an independent predictor of outcome, multivariate analysis of a much larger, multi-center population is necessary.

Nonetheless, as institutions implement therapeutic hypothermia as standard treatment following cardiac arrest, we suggest that attaining hypothermia within six hours may be a threshold of therapeutic effect. It may be that a linear or exponential loss of benefit is incurred with delays in achieving target temperature, however our small sample size of patients who achieved hypothermia within six hours (n = 5) precludes a sub-analysis of earlier time windows. The delay in achieving target temperature has diminished within our own institution as experience accrues, and some have even called for hypothermia to be implemented in a cardiac arrest "bundle"[10] to routinely achieve target temperatures as quickly as possible. Further investigations are needed to determine if time to attain therapeutic hypothermia is an independent predictor of outcome, but in any case, it may be a marker of other outcome predictors, such as presenting rhythm, and time from CA to ROSC, both of which can influence the rapidity of inducing and achieving core temperature less than 34 degrees C. Indeed, cardiac arrest represents a disease in

which there is an integrated "chain of survival" in which multiple components are inherently linked to improved outcomes.

Conclusions

Attaining therapeutic hypothermia within 6 hours of in or out-of-hospital CA is associated with a greater likelihood of achieving a good neurological outcome at discharge. Time from cardiac arrest to achieved hypothermia should be included as a clinically important covariate in future studies of predictors of outcome after cardiac arrest.

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