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Clinical paper

Time to awakening and neurologic outcome in therapeutic hypothermia-treated cardiac arrest patients☆,☆☆

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ABSTRACT

Introduction: Therapeutic hypothermia (TH) has been shown to improve outcomes in comatose Post-Cardiac Arrest Syndrome (PCAS) patients. It is unclear how long it takes these patients to regain neurologic responsiveness post-arrest. We sought to determine the duration to post-arrest awakening and factors associated with times to such responsiveness.
Methods: We performed a retrospective chart review of consecutive TH-treated PCAS patients at three hospitals participating in a US cardiac arrest registry from 2005 to 2011. We measured the time from arrest until first documentation of "awakening", defined as following commands purposefully.
Results: We included 194 consecutive TH-treated PCAS patients; mean age was 57 ± 16 years; 59% were male; 40% had an initial shockable rhythm. Mean cooling duration was 24 ± 8 h and mean rewarming time was 14 ± 13 h. Survival to discharge was 44%, with 78% of these discharged with a good neurologic outcome. Of the 85 patients who awakened, median time to awakening was 3.2 days (IQR 2.2, 4.5) post-cardiac arrest. Median time to awakening for a patient discharged in good neurological condition was 2.8 days (IQR 2.0, 4.5) vs. 4.0 days (IQR 3.5, 7.6) for those who survived to discharge without a good neurological outcome ($p = 0.035$). There was no significant association between initial rhythm, renal insufficiency, paralytic use, post-arrest seizure, or location of arrest and time to awakening.
Conclusion: In TH-treated PCAS patients, time to awakening after resuscitation was highly variable and often longer than three days. Earlier awakening was associated with better neurologic status at hospital discharge.

1. Introduction

Sudden cardiac arrest (SCA) affects approximately 300,000 people annually in the U.S. with a survival rate of <10% at hospital discharge [1] and significant long-term neurologic deficits in up to 50% of survivors [2,3]. Both SCA patients who suffer such deficits and those who regain meaningful neurologic function generally remain comatose for days post-arrest, often secondary to anoxic encephalopathy and complicated by pharmacologic interventions. Consequently, a consensus statement put forth by the American Academy of Neurology (AAN) in 2006 addressing the value of prognostic indicators in SCA patients, recommends delaying neuroprognostication for at least 72 h post-arrest [2]. Recent innovations have altered the approach to post-arrest care, particularly the use of therapeutic hypothermia (TH) [4–9], requiring reassessment of the applicability of the AAN recommendation [10–14].

In this investigation, our primary outcome was time to awakening in comatose post-cardiac arrest syndrome (PCAS) patients treated with TH. The secondary outcome examined neurologic function at discharge, described by Cerebral Performance Category (CPC) score. Several clinical factors were identified that might influence time to awakening, including medications administered, comorbid conditions, and seizure. We hypothesized that patients who survive with good neurologic function will have a shorter time to awakening than those who survive with poor neurologic function. Further, we sought to investigate whether patient-level factors (age, sex, race, renal sufficiency) or arrest-level factors (initial rhythm, location of arrest) were associated with time to awakening.

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2. Methods

We utilized SCA data from the Penn Alliance for Therapeutic Hypothermia (PATH) database, an internet-based registry hosted at the University of Pennsylvania. The PATH database includes SCA data in the pre-hospital, emergency department, and in-hospital settings, focusing on post-arrest care, particularly TH. Open to any U.S. institution, it tracks all patients who experience SCA and receive cardiopulmonary resuscitation. This investigation received approval from the University of Pennsylvania Institutional Review Board.

Data from three hospitals within the University of Pennsylvania Health System were analyzed: the Hospital of the University of Pennsylvania (a 700 bed tertiary-care academic medical center), Penn Presbyterian Medical Center (a 300 bed tertiary-care and community hospital) and Pennsylvania Hospital (a 400 bed community hospital), all located in Philadelphia, PA. Data were collected on consecutive PCAS patients treated with TH between 05/2005 and 10/2011. Inclusion criteria included resuscitation from SCA with post-arrest neurologic injury (not following commands as demonstrated by a Glasgow Coma Scale [GCS] Motor Score <6) with no primary neurologic cause of arrest. Temperature management was provided using intravenous chilled saline, ice packs, and/or an external cooling device. Patients, cooled to a target temperature of 32–34 °C as soon as possible after return of spontaneous circulation (ROSC), were maintained at target temperature for 24 h, followed by gradual active rewarming (0.25–0.33 °C/h) until reaching 36 °C.

The PCAS protocol does not explicitly stipulate when and if neurologists should become involved; it does recommend continuous electroencephalogram (cEEG) and Bispectral Index (BIS) monitoring while patients are paralyzed with continuation as clinically indicated. There is no formal protocol for neuroprognostication; patients are evaluated with combinations of cEEG, BIS, bedside neurologic exam, computerized tomography, magnetic resonance imaging (MRI), and somatosensory evoked potentials (SSEPs). Specific combinations are used at the discretion of the attending intensivist and as recommended by neurologic consultation.

The primary outcome, neurologic awakening, was defined as first post-arrest documented GCS Motor Score of 6. Patient GCS was determined by chart review of examinations by the primary attending intensivist, bedside nurse, and/or neurology consultant. If GCS was not specifically documented, chart notations of the degree of neurologic function and motor activity were used. A secondary neurologic outcome, CPC score at discharge, was abstracted from the medical record and dichotomized into "good" (CPC 1–2) or "poor" (CPC 3–5).

The protocols make sedation and paralytic recommendations, but usage is at the discretion of the treating physician. These recommendations include the administration of a bolus of paralytics when hypothermia is initiated; continuous infusion of paralytics through the induction, maintenance, and rewarming phases; and stopping paralytic infusion as soon as clinically possible after normothermia. The protocol also recommends that sedatives and analgesics be administered with paralytics. Administration of paralytics (cisatracurium, vecuronium, pancuronium, and rocuronium) and sedatives or analgesics (fentanyl, propofol, lorazepam, and midazolam) were recorded since these drugs may affect awakening in patients who are comatose after SCA [15,16]. Documentation of daily drug administration through the first five days post-arrest and the last dosage were noted. Whether a patient had end stage renal disease (ESRD) requiring dialysis was documented, as these patients may have delayed clearance of the aforementioned medications. Seizure activity (identified by chart notation or documented EEG interpretation of seizure) and concomitant antiepileptic use was documented since it may delay awakening. Seizures and epileptiform activity definitions conformed to our neurology department criteria, as presented in a prior manuscript [17].

We also collected do-not-resuscitate (DNR) status because of its potential to alter the cohort of patients eligible to awaken. At the study hospitals, DNR status is split into three categories: DNR-A (all therapy but no further resuscitation); DNR-B (no new therapies or resuscitation); and DNR-C (comfort care only) [18].

Statistical analysis was conducted using commercially available statistical software (STATA 11, Statacorp, College Station, TX) to perform nonparametric *K*-sample tests on the equality of medians when the data was not normally distributed [19] and Student's *t*-tests when it was. Chi-squared tests were used to evaluate demographic variables.

Table 1
Demographics.

	N (%)
Male	114/194 (59)
Race	
Black	89/194 (46)
White	85/194 (44)
Other	20/194 (10)
VF/VT[a]	76/190 (40)
Out-of-hospital/ED arrest	148/194 (76)
Out-of-hospital VF/VT[b]	66/191 (35)
Survived to discharge	85/194 (44)
Discharged neurologically intact	66/194 (34)
Care withdrawn before hospital discharge[c]	81/190 (43)
	Median [IQR]
Age (years)	59 [48,68]
Duration of TH (h)	24 [21,26]
Duration of rewarming (h)	11 [7,16]
Time from arrest to withdrawal of care (days)	3.8 [2.2, 7.6]

[a] 4 patients lack documented initial rhythm.
[b] 3 patients missing information.
[c] 4 patients had care withdrawn according to brain death protocol.

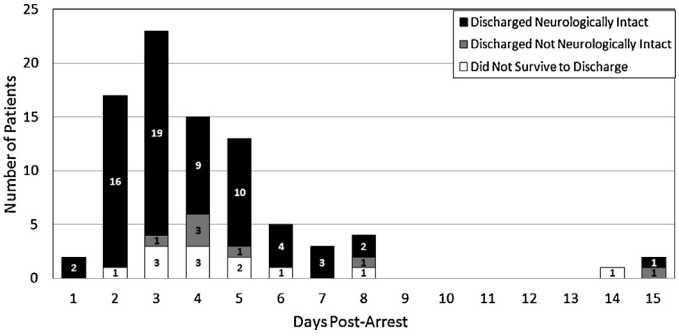

Fig. 1. Time to awakening by day post-arrest.

3. Results

During the study period, 201 consecutive PCAS patients were treated with TH via a standardized post-arrest protocol. Seven patients were excluded because of a primary neurologic arrest etiology, leaving a final cohort of 194. The mean age was 57 ± 16 years; 114/194 (59%) were male; 76/190 (40%) had VF/VT as an initial arrest rhythm. Forty-four percent (85/194) survived to hospital discharge, with 78% (66/85) of these patients discharged with CPC 1–2 (Table 1). Of the 44% (85/194) who awakened, the median time to awakening was 3.2 days (IQR 2.2, 4.5) post-arrest (Table 2 and Fig. 1). Two of the 85 (2%) awakened in the first 24 h post-arrest, 17/85 (20%) between 24 and 48 h post-arrest, 24/85 (28%) between 48 and 72 h post-arrest, and 42/85 (49%) >72 h post-arrest.