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Clinical paper

Awakening after cardiac arrest and post resuscitation hypothermia: Are we pulling the plug too early?☆

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ABSTRACT

Background: Time to awakening after out-of-hospital cardiac arrest (OHCA) and post-resuscitation therapeutic hypothermia (TH) varies widely. We examined the time interval from when comatose OHCA patients were rewarmed to 37 °C to when they showed definitive signs of neurological recovery and tried to identify potential predictors of awakening.
Methods: With IRB approval, a retrospective case study was performed in OHCA patients who were comatose upon presentation to a community hospital during 2006–2010. They were treated with TH (target of 33 °C) for 24 h, rewarmed, and discharged alive. Comatose patients were generally treated medically after TH for at least 48 h before any decision to withdraw supportive care was made. Pre-hospital TH was not used. Data are expressed as medians and interquartile range.
Results: The 89 patients treated with TH in this analysis were divided into three groups based upon the time between rewarming to 37 °C and regaining consciousness. The 69 patients that regained consciousness in ≤48 h after rewarming were termed "early-awakeners". Ten patients regained consciousness 48–72 h after rewarming and were termed "intermediate-awakeners". Ten patients remained comatose and apneic >72 h after rewarming but eventually regained consciousness; they were termed "late-awakeners". The ages for the early, intermediate and late awakeners were 56 [49,65], 62 [48,74], and 58 [55,65] years, respectively. Nearly 67% were male. Following rewarming, the time required to regain consciousness for the early, intermediate and late awakeners was 9 [2,18] (range 0–47), 60.5 [56,64.5] (range 49–71), and 126 [104,151] h (range 73–259), respectively. Within 90 days of hospital admission, favorable neurological function based on a Cerebral Performance Category (CPC) score of 1 or 2 was reported in 67/69 early, 10/10 intermediate, and 8/10 late awakeners.
Conclusion: Following OHCA and TH, arbitrary withdrawal of life support <48 h after rewarming may prematurely terminate life in many patients with the potential for full neurological recovery. Additional clinical markers that correlate with late awakening are needed to better determine when withdrawal of support is appropriate in OHCA patients who remain comatose >48 h after rewarming.

1. Introduction

Over the past decade there have been major advances in post-resuscitation care following successful resuscitation from out-of-hospital cardiac arrest (OHCA). Use of therapeutic hypothermia (TH) in patients who present in a comatose state to the hospital has positively impacted the number of patients who survive with a favorable neurologic outcome.[1,2] However, little is known about the effect of TH on predicting who will ultimately regain consciousness and the time course to awakening. Further, the practice parameters for outcome prediction promulgated by the American Academy of Neurology (AAN) in 2006 pre-date the broad adoption of TH.[3,4]

Recent retrospective and prospective studies indicate that TH and sedation influence neurologic examination and biochemical

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Table 1
The Cerebral Performance Category Scale.

Good outcome
1. Conscious and alert with normal function or only slight disability
2. Conscious and alert with moderate disability
Bad outcome
3. Conscious with severe disability
4. Comatose or persistent vegetative state
5. Brain dead or death from other causes

markers of recovery.[5,6] In the absence of reliable serum and clinical indicators we retrospectively analyzed time to awakening in all of our cardiac arrest survivors between 2006 and 2010. We sought to identify some distinguishing features of those who awoke >72 h following cardiac arrest ("late awakeners").

2. Methods

St. Cloud Hospital (St. Cloud, MN, USA) is a community-based hospital that serves a population of ~500,000 people in central Minnesota, USA. Since January 2006, it has been the clinical policy to treat all resuscitated OHCA patients with TH for 24 h if they were comatose upon intensive care unit admission or were unable to respond intelligibly.[7] TH was administered as part of a protocol by Intensive Care Unit physicians and nurses that included ventilator support, sedation, paralysis to prevent shivering, and treatment with a transdermal temperature management system with the target temperature of 33 °C for 24 h followed by rewarming at 0.2 °C h^{-1}. Fluids and vasopressors were used, as needed to maintain a mean arterial pressure of approximately 70 mmHg during the period of TH. Sedation was reversed once the patient was rewarmed to 37 °C. Once rewarmed to 37 °C, if patients did not regain consciousness within 24–48 h, the decision to continue or withdraw support (mechanical ventilation, use of vasopressor or inotropic agents to hemodynamically stabilize the patient) was made on clinical grounds and in collaboration with family members on a patient by patient basis. The decision not to withdraw support was often made based upon the request of the family. With permission from the St. Cloud Hospital Institutional Review Board, the medical records for all patients between 2006 and 2010 who were treated after OHCA and then discharged alive from the hospital were reviewed. Data were analyzed based on clinical characteristics and the time from restoration of body temperature to 37 °C to the time when the patient regained consciousness, defined as alert and oriented to person, place, or time (A&Ox1). Data were stratified based upon whether patients were A&Ox1 before 48 h after rewarming to 37 °C ("early awakeners"), between 48 and 72 h after rewarming ("intermediate awakeners") and more than 72 h after rewarming ("late awakeners").

Neurological outcomes were evaluated using the Cerebral Performance Category (CPC) scoring system. See Table 1 for a description of the CPC scoring system.

3. Statistical analysis

Due to the non-Gaussian distribution, data are reported as medians, interquartile range [IQR] and absolute range (range). Comparisons between groups were performed by the χ^2 test or Fisher's exact test for categorical variables and by the Mann–Whitney *U* test or Kruskal–Wallis test to compare continuous variables within groups. To investigate correlation between continuous variables, Spearman's rho correlation test was performed. All analyses were 2 sided, and *p* values <0.05 were considered significant. Statistical analysis was performed using SPSS 17 (IBM software).

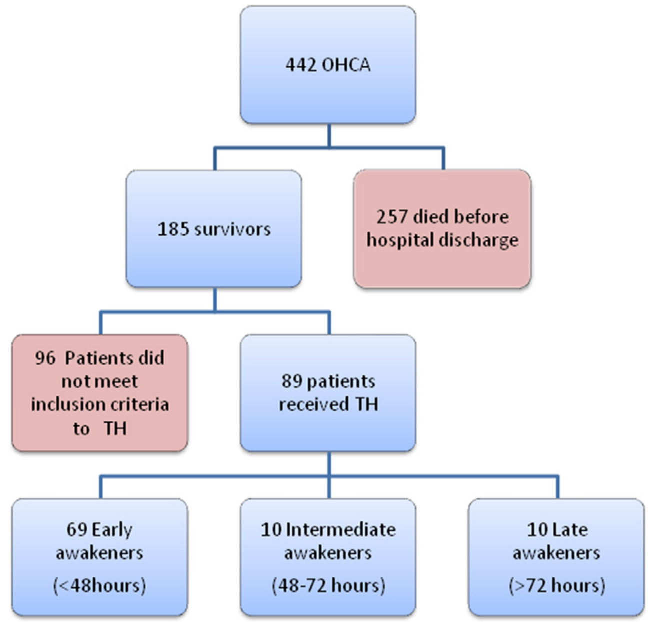


Fig. 1. Outcomes of admitted survivors of OHCA in St. Cloud Hospital between January 2006 and December 2010.

4. Results

Between January 1, 2006 and December 21, 2010, 442 patients were moved to St. Cloud hospital after sustaining cardiac arrest (Fig. 1). A total of 257 patients were excluded as they died prior to hospital discharge whereas 185 patients were discharged alive. Of the 185 survivors, 96 patients were sufficiently awake upon arrival to the intensive care unit so they did not meet the TH protocol inclusion criteria. A total of 89 patients were treated with TH as they were comatose or could only respond to verbal stimuli with an inappropriate and unintelligible sound. Of these 89 patients, 69 patients regained consciousness within 48 h after rewarming, 10 patients between 48 and 72 h, and 10 patients >72 h after rewarming.

Demographic characteristics including age, gender, comorbidities and initial cardiac arrest rhythm are shown in Table 2. A total of 17/20 intermediate and late awakeners had a first recorded rhythm of ventricular fibrillation and there were no intermediate and late awakeners who presented with asystole. There were no late awakeners with a history of obesity or heart failure.

Table 2
Demographic characteristics of the patient population. Age is presented as medians and interquartiles. All data are presented as *n* (%) taking into account missing data. Q5

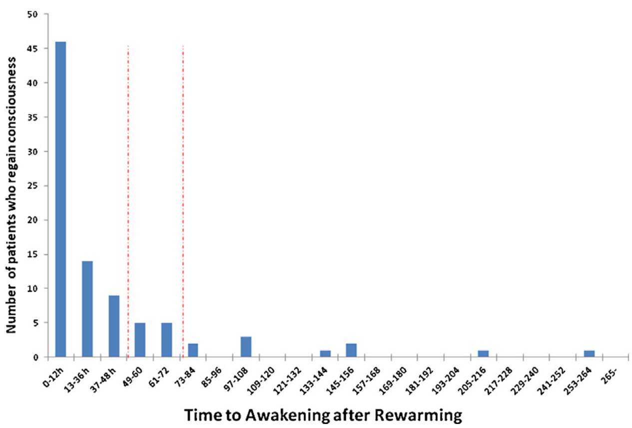
	Early awakeners (*n* = 69)	Intermediate awakeners (*n* = 10)	Late awakeners (*n* = 10)
Age[a]	56 [49,65]	62 [48,74]	58 [55,65]
Male	50 (72%)	9 (90%)	7 (70%)
Female	19 (28%)	1 (10%)	3 (30%)
CAD	22 (33.3%)	3 (30%)	4 (40%)
CHF	3 (4.8%)	1 (10%)	0 (0%)
Obesity	3 (4.3%)	1 (10%)	0 (0%)
DM	7 (10.1%)	1 (10%)	2 (20%)
CRF	0 (0%)	0 (0%)	1 (10%)
HTN	0 (0%)	3 (30%)	4 (40%)
V-Fib/V-Tach	60 (87%)	9 (90%)	8 (80%)
Asystole	4 (6%)	0 (0%)	0 (0%)
PEA	2 (3%)	1 (10%)	2 (20%)
UnKnown	3 (4%)	0 (0%)	0 (0%)

CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; CRF, chronic renal failure; HTN, hypertension.

Table 3
Additional differences between the patient population and their time to awakening.

	Early awakeners (*n* = 69)	Intermediate awakeners (*n* = 10)	Late awakeners (*n* = 10)
911-ALS time min[a]	5 [2.25,9.75] (42)	5.5 [3.25,9] (4)	11 [8.7,17.7] (6)
Time unknown[b]	27 (39%)	6 (60%)	4 (40%)
Witnessed[b]	65 (94%)	9 (90%)	8 (80%)
Unwitnessed[b]	4 (6%)	1 (10%)	2 (20%)
Hours to awakening[a]	9 [2,18]	60.5 [56,64.5]	126 [104.3,151]
Total hospital days[a]	8 [7,13]	14 [13,16]	24 [18,31]
CPC $\leq$ 2 by day 30[b]	65 (94%)	9 (90%)	7 (70%)
CPC $\geq$ 3 on day 30[b]	4 (6%)	1 (8%)	3 (30%)
CPC $\leq$ 2 by day 90[b]	67 (97%)	10 (100%)	8 (80%)
CPC $\geq$ on day 90[b]	2 (3%)	0 (0%)	2 (20%)

ALS, advanced life support; OHCA, out of hospital cardiac arrest; CPC, Cerebral Performance Categories Scale.
[a] Data expressed as medians, interquartiles [IQR] and number of patients (*n*).
[b] Data expressed as number of patients and percentage (%).



Q4 **Fig. 2.** Time to awakening after rewarming. Red lines indicate the 48 and 72 h time-points. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

As shown in Table 3, the time to regain consciousness for the early awakeners was 9 [2,18] h (range 0–47), 60 [56,64] h (range 49–71) for the intermediate awakeners, and 126 [104,151] h (range 73–259) for the late awakeners. The hospital length of stay for the early awakeners was 8 [7,13] days (range 4–38), 14 [13,16] days (range 8–19) for the intermediate awakeners, and 24 [18,31] days (range 6–38) for the late awakeners. Fig. 2 shows the time course for awakening, as defined as alert and oriented to person, place, or time, following treatment with therapeutic hypothermia and the completion of rewarming to 37 °C. The longest time to awakening observed in the TH treated group was 259 h after rewarming.

With univariant analysis there was a trend between the time to awaking and 911-ALS time (p = 0.13). Cerebral Performance Category (CPC) scores were analyzed at 30 days and 90 days after OHCA. Of the 8 patients with a CPC score of $\geq$3 at 30 days after the OHCA, 4/8 improved to a CPC score of $\leq$2 by 90 days (Table 3). There was a significant correlation between time to awakening and CPC score 30 days after OHCA (p = 0.02) but not 90 days after arrest (p = 0.06). There was no correlation between 911-ALS time and CPC score 30 days (p = 0.46) or 90 days (p = 0.64) after arrest.

5. Discussion

Little is known about how long to pursue aggressive medical management in OHCA patients treated with TH once rewarming is completed. Neurological physical examinations are challenging when these patients remain persistently unresponsive, especially after a prolonged period of sedation. Neurological examinations have not been reported to be predictive of who will ultimately regain consciousness.[3,8–11] There are many proposed markers of poor prognosis; the absence of the pupillary light response, corneal reflexes or motor response to pain, an elevated body temperature (>37 °C), the presence of myoclonus, status epilepticus, serum neuron-specific enolase levels >33 μg L^{-1} at day 1–3 post-CPR, or the bilateral absence of the N20 component of the somatosensory evoked potential.[3] However, numerous reports have surfaced of patients with a poor prognosis who ultimately had a good outcome.[8,12]

This case series was motivated by an OHCA survivor at St. Cloud Hospital who had not regained consciousness one week after an OHCA. He was sent to a nursing home only to awaken nearly two weeks after his OHCA and ask, “Why am I in a nursing home?” He proceeded to take a taxi to the hospital where his chief complaint to the emergency medicine physician was shortness of breath. He was fully functional. Based upon this unusual case we examined the clinical outcomes from all patients after TH treatment and rewarming in an effort to better refine our decision-making processes for this patient population. Our intent was to try to determine the average time to awakening after rewarming following TH, to identify any clinical markers that might be associated with late awakening, and to use these observations to guide our decision making related to when to consider withdrawing support in patients who remain comatose after rewarming. At present, the decision to withdraw life support is generally made with the patient’s family but is often based on little clinical outcome data.[3]

Awakening generally takes place within 3 days after CPR, and neurologic impairment is often anticipated when awakening is further delayed.[3] However, in the current case series approximately 20% of the long-term survivors remained comatose and intubated 48 h after rewarming. Upon review of all cases treated with TH who eventually regained consciousness, 81/89 patients had favorable neurological function (CPC $\leq$ 2) 30 days after OHCA. By 90 days 4/8 with poor CPC scores had made a substantial recovery and their CPC scores were $\leq$2. Thus, 95.5% of all patients and 90% of the intermediate or late awakeners had favorable neurological function 90 days after OHCA. These observations suggest that better diagnostic and prognostic tools are critically needed before withdrawing medical support.[13]

Based upon these new observations, we further examined some of the clinical characteristics of the patients and the circumstances surrounding their OHCA in an effort to gain some insight into what clinical criteria might predict a positive outcome. Similar to clinical characteristics and circumstances that are known to result in an increased likelihood for favorable prognosis after OHCA in general, in this case series 8/10 patients who were late awakeners had an initial heart rhythm of ventricular fibrillation, nearly all had a

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witnessed arrest, and many received bystander CPR. The time from 911 call-for-help to advanced life support care may be related to the likelihood of being a late awakener. Age did not appear to be predictive of whether a patient would be a late awakener. While the sample size is too small to draw any definitive conclusions, patients with a witnessed VF arrest and bystander CPR appear to have a greater likelihood of awakening after cardiac arrest, even belatedly.

The medical co-morbidities of heart failure, obesity, and chronic renal failure are known to be associated with increased morbidity and mortality in general.[3,4] While the sample size is too small to draw any definitive conclusions, patients with co-morbidities of coronary artery disease, obesity, congestive heart failure or diabetes mellitus appeared to fare poorly.

The study is limited as it was retrospective and uncontrolled. The results likely underestimate the potential for late awakeners: the decision to withdraw supportive care was made on a case by case basis, with recommendations varying from physician to physician, and without the benefit of the findings from this study. The total effect size related to 'pulling the plug too early' may be further underestimated by efforts to obtain 'do not resuscitate' orders for many comatose patients by those unaware of the potential for late awakening. In addition, some assessment tools that may be predictive of outcomes after cardiac arrest, such as EEG, somatosensory evoked potentials, serial head CT scans,[14] and serum-specific enolase,[10,15,16] were not routinely measured in St. Cloud Hospital during the study period. As well, it was impossible to systematically collect the motor responses of our patients during the time while they were unconscious.[4,12] Further, it was not possible to summarize all of the many reasons why medical support was withdrawn from those patients who died in the hospital after treatment with TH. Most of the decisions were made after the family and the primary provider discussed the likelihood of the patient awakening; over the course of the five years spanning this series multiple different physicians were involved with advising many family members.

While this study was retrospective, it challenges some of the current practices in this field. We found that late awakening, sometimes greater than 72 h after rewarming, was not uncommon and it was often associated with an excellent long-term prognosis. Given the considerable effort and resources expended during the resuscitation and routine post-resuscitation care after OHCA, these findings suggest that serious consideration should be given to continuing life supportive measures in patients who fit the profile of late-awakeners described herein. By allowing such patients more time to regain consciousness, which in some cases can take over a week or more after rewarming, overall survival rates could be increased by >10% for patients admitted alive to the hospital. The findings highlight the knowledge gap in understanding how long we should treat this patient population and the importance of future studies to prospectively determine which neurological tests and patient profiles are predictive of late awakening after OHCA, TH, and rewarming.[16]

Conflict of interest statement

No conflicts of interest to declare.

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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].

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.

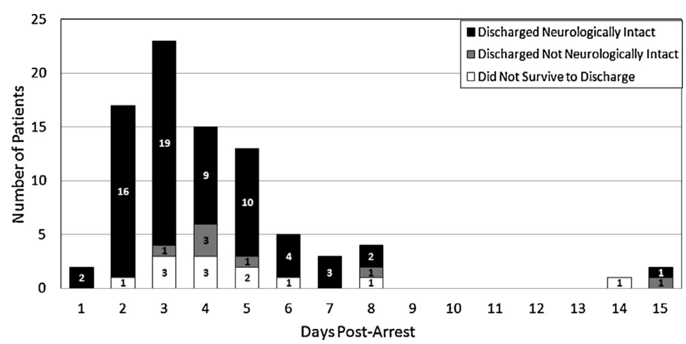

Fig. 1. Time to awakening by day post-arrest.

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.

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.

Table 2
Time to awakening post-arrest.

	Median [IQR] (days)	*p*-value
Time to awakening (*n* = 85)	3.2 [2.2, 4.5]	
Discharged neurologically intact (*n* = 66) Not discharged neurologically intact (*n* = 19)	2.8 [2.0, 4.5] 4.0 [3.5, 7.6]	**0.035**[a]
Survived to discharge (*n* = 73) Did not survive to discharge (*n* = 12)	3.0 [2.1, 4.5] 3.5 [2.4, 4.7]	0.505
ESRD (*n* = 15) No ESRD (*n* = 70)	3.6 [2.4, 6.8] 3.0 [2.1, 4.4]	0.366
VF/VT (*n* = 43) Asystole/PEA (*n* = 39)	2.8 [2.0, 4.4] 3.5 [2.4, 5.1]	0.269
ED/out-of-hospital (*n* = 60) In-hospital (*n* = 25)	3.0 [2.2, 4.6] 3.3 [2.1, 4.2]	0.758
Out-of-hospital VT/VF (*n* = 37) Not out-of-hospital VT/VF (*n* = 46)	2.8 [2.0, 4.4] 3.4 [2.3, 5.0]	0.573
Paralytic used (*n* = 78) No paralytic used (*n* = 7)	3.4 [2.2, 4.5] 2.5 [1.2, 13.7]	0.250
Seizure (*n* = 6) No seizure (*n* = 78)	3.8 [3.2, 6.2] 2.9 [2.1, 4.5]	0.090

[a] Values in bold font are statistically significant.

Table 3
Out-of-hospital VF/VT arrests.

	N (%)
Total out-of-hospital VF/VT arrests	66/191 (35)
Regained awakening	37/66 (56)
Survived to discharge	35/37 (95)
Discharged neurologically intact	35/35 (100)
	Median [IQR]
Time to awakening (days)	2.8 [2.0 –4.4]

Awakening was determined by documentation of a GCS Motor Score of 6 in 76/85 patients (89%); chart notations were used for the remaining 9 patients (11%). Twelve patients (14%) who awakened did not survive to discharge. Of these patients, 10 (83%) had care withdrawn by their families during admission. Twelve patients (6%) were discharged alive but did not awaken prior to discharge.

Median time to awakening for patients discharged in good neurological condition (CPC 1–2) was 2.8 days (IQR 2.0, 4.5) vs. 4.0 days (IQR 3.5, 7.6) for those who survived with poor neurologic outcome (CPC 3–4; $p = 0.035$). Two patients (1%) awakened >7 days post-arrest and were discharged with a good neurologic outcome. Both patients were on extended sedating drips (lorazepam, fentanyl) due to post-arrest myoclonus or agitation. Patients who awakened but did not survive to hospital discharge awakened a median of 3.5 days (IQR 2.4, 4.7) post-arrest vs. 3.0 days (IQR 2.1, 4.5) for those who survived ($p = 0.505$). There was no significant association between time to awakening and age, sex, race, paralytic use, ESRD, initial rhythm, seizure, or location of arrest (in-hospital vs. out-of-hospital). However, only 15 patients had ESRD and awakened, limiting the ability to determine differences related to renal insufficiency.

Fentanyl was the most commonly used analgesic or sedative; 165/193 (85%) patients received fentanyl at some time during the first five days post-arrest. Lorazepam was the next most commonly used, administered to 140/194 (72%) patients; 32% (62/194) received midazolam and 30% (59/194) were given propofol. We found a relationship between the length of time a patient received either fentanyl or lorazepam (but not propofol or midazolam) in the first five days post arrest and awakening (Table 4). In patients with neurologic awakening versus those without, the mean number of days on fentanyl was 3.6 ± 1.3 days vs. 2.6 ± 1.3 days ($p < 0.001$); mean number of days on lorazepam was 2.8 ± 1.4 days vs. 2.1 ± 1.1 days ($p = 0.003$). The duration of time on fentanyl varied between the patients who awakened in ≤ 3 days and those who awakened >3 days post-arrest (3.3 ± 1.4 days vs. 3.9 ± 1.1 days; $p = 0.033$).

Of the patients who awakened, 19/85 (22%) received a paralytic and 40/85 (46%) received at least one dose of fentanyl, lorazepam, propofol, and/or midazolam the same day they awakened. Forty-two patients (49%) awakened ≥ 1 day(s) after all sedatives were discontinued with a mean time to awakening after sedative discontinuation of 2.9 ± 2.0 days. Of the patients who were on a paralytic the same day they awakened, 18/19 (95%) had good neurologic outcome; of the patients not on a paralytic the day they awakened, 48/66 (73%) had good neurologic outcome ($p = 0.042$). In patients who awakened after paralytics were stopped, the mean time to awakening was 3.4 ± 2.9 days. The patients discharged with CPC 1–2 awakened 2.1 ± 2.4 days after paralytic discontinuation; those discharged with CPC 3–5 awakened 4.1 ± 4.0 days after paralytic discontinuation ($p = 0.009$).

With regard to seizure incidence, 35/191 (18%) patients had a seizure post-arrest (3 patients had an ambiguous EEG or lacked seizure documentation); 78/154 (51%) patients who did not have a seizure awakened versus only 6/35 (17%) who had a seizure ($p < 0.001$) with a median time to awakening of 2.9 days (IQR 2.1, 4.5) days vs. 3.8 days (IQR 3.2, 6.2; $p = 0.090$), respectively. In terms of survival, 11/35 (31%) of the patients who had a seizure versus 73/156 (47%) without a seizure ($p = 0.098$) survived to discharge. Only 3/35 (9%) with a seizure versus 62/156 (40%) without had good neurologic outcome ($p < 0.001$).

In order to assess the patient's neurologic status post-arrest, we abstracted a GCS score post-ROSC but prior to receiving TH or a sedative or paralytic. Only 27 patients (14%) did not have a GCS recorded during this time. There was no difference in mortality or neurologic outcome at discharge between those with a recorded GCS and those without. Most (146/167, 87%) had a GCS score of 3. The 21 patients (13%) who had a pre-TH GCS >3 (range: 4–9), however, were more likely to survive to discharge ($p = 0.027$) and have CPC 1–2 at discharge ($p = 0.002$) than patients with a post-ROSC GCS of 3.

A subgroup analysis was performed on the 66/191 (35%) of patients with a shockable out-of-hospital arrest (Table 3). Within this subgroup, 37/66 (56%) awakened; 35/66 (53%) survived to

Table 4
Effects of sedative use on time to awakening.

	All patients	Patients who did not regain awakening		Patients who regained awakening	Patients who regained awakening ≤72 h post-arrest		Patients who regained awakening >72 h post-arrest
Fentanyl							
n	165	85		78	39		39
Days	3.1 ± 1.4	2.6 ± 1.3		3.6 ± 1.3	3.3 ± 1.4		3.9 ± 1.1
p-value			**0.000**[a]			**0.033**[a]	
Lorazepam							
n	140	67		72	34		38
Days	2.5 ± 1.3	2.1 ± 1.1		2.8 ± 1.4	2.6 ± 1.4		3.0 ± 1.5
p-value			**0.003**[a]			0.249	
Propofol							
n	59	23		35	21		14
Days	2.2 ± 0.9	2.3 ± 1.4		2.0 ± 0.7	2.4 ± 1.0		2.1 ± 1.1
p-value			0.324			0.316	
Midazolam							
n	62	35		27	12		15
Days	1.7 ± 1.1	1.7 ± 1.2		1.7 ± 1.1	1.3 ± 0.7		2.1 ± 1.3
p-value			0.994			0.084	

[a] Values in bold font are statistically significant.

discharge with 35/35 (100%) discharged with a good neurologic outcome. The median time to awakening was 2.8 days (IQR 2.0, 4.4). For the 125 patients (65%) who had a nonshockable arrest and/or an in-hospital arrest, the median time to awakening for the 46 (37%) who awakened was 3.4 days (IQR 2.3, 5.0). This between-group difference was not statistically significant ($p = 0.573$).

Care was withdrawn due to family decision in 81/194 (42%) patients; 4/194 (2%) were found to be brain dead and declared dead using brain death protocol. Of these, 33/81 (41%) patients had care withdrawn <72-h post-arrest. The median time from arrest to discontinuation of care was 3.8 days (IQR 2.2, 7.6). In patients made DNR-C, 6/81 (7%) had care withdrawn in the first 24 h post-arrest; 11/81 (14%) during the second 24 h post-arrest; and 16/81 (20%) between 48 and 72 h post-arrest.

Of the 43 patients who awakened ≥72 h (median time: 4.5 days post-arrest), 35/43 (81%) survived to discharge and 29/35 (83%) were discharged with CPC 1–2. Therefore, 15% of our cohort did not awaken by 72 h but had meaningful neurologic recovery by hospital discharge.

Ten patients took >6 days to awaken (median: 7.5 days; range: 6.2–14.5 days). Of these patients, their delayed neurologic recovery was potentially influenced by anti-epileptic medications for prior seizure history ($n = 2$), severe sepsis ($n = 2$), recurrent cardiac arrest ($n = 1$), stroke as the initial admission complaint ($n = 1$), prolonged sedative medications for agitation/post-operative pain ($n = 3$), and ESRD with prolonged sedation via continuous benzodiazepine infusion ($n = 1$).

4. Discussion

In a cohort of 194 comatose TH-treated PCAS patients, shorter time to awakening was significantly associated with better neurologic outcome. Time to awakening was not associated with age, sex, race, initial rhythm, ESRD, paralytic use, seizure, or location of arrest.

Our results are consistent with a prior small single-center investigation of post-arrest patients treated with TH. In a cohort of 47 out-of-hospital arrests, Eid et al. found that meaningful awakening, defined as CPC 1–2, could occur >7 days post-arrest [20]. In contrast, Fugate et al. found that, in their group of 227 out-of-hospital arrest patients, TH did not delay time to awakening past 72 h post-arrest. They defined awakening as both opening eyes spontaneously or to voice and following commands or visually tracking objects [21]. Variability in the reported definitions of meaningful awakening may explain the divergent findings. It may take patients longer to be classified as CPC 1–2 than to respond to motor and visual commands, since the CPC score includes measures of functionality and independence. One of the challenges in determining time to awakening is that there is no strict definition for "awakening". We defined awakening as a purposeful motor response while both Fugate et al. [21] and Eid et al. [20] utilized different surrogate endpoints. Given these varied approaches, standardizing and validating a definition is integral to future investigations.

Additionally, there is no acceptable single instrument of neuroprognostication, causing significant variability in clinician practice and no cohesive protocolized method for determining the potential for neurologic recovery. Neurologic testing tools utilized in determining prognosis include but are not limited to SSEPs [22], cranial imaging modalities [23], serum markers including S100 calcium binding protein B and neuron-specific enolase [24], bedside neurologic examination [25], BIS monitor readings [26], and cEEG [17,27]. In the future, neuroprognostication may rely on a multimodal protocolized approach to diminish variability in timing and method of prognostication [14].

With the 2005 AHA guidelines endorsing TH as standard treatment for comatose post-arrest patients but much of the standard literature on neurologic prognosis not including patients who have undergone hypothermia, neuroprognostication in post-TH patients is complicated and incompletely understood [25]. Therapeutic hypothermia, either directly (through temperature reduction) or indirectly (through accompanying sedative usage), alters the time course of neurologic injury and the speed of neurologic recovery in patients with anoxic encephalopathy [28]. In a structured review of post-arrest neuroprognostication published in 2009, Young found that, once TH was used in post-arrest care, the utility of many neuroprognostication tools employed in patients who did not receive TH was weakened or delayed past 72 h [14].

Although in our study patients who had favorable neurologic outcomes awakened earlier than those who did not, these results must be interpreted cautiously. There was substantial variability in outcome with 29/194 patients (15%) awakening after 72 h and discharged with a good neurologic outcome. At present, no clinical tools exist that independently allow clinicians to make error-free judgments about meaningful neurologic recovery at 72 h post-ROSC. It appears many patients would benefit from multi-modal neuroprognostication models. As shown by Perman et al., PCAS patients treated with TH are sometimes prematurely assigned poor neurologic prognoses, which can lead to self-fulfilling prophesies and premature withdrawal of care [29].

This study has several limitations. Due to its retrospective nature, documented physician assessment used to determine neurologic outcome did not have standardized details regarding the depth of coma. Another limitation is the local variability in sedative and paralytic use in post-arrest patients and their impact on time to awakening. Despite shared post-arrest protocols at the institutions, physician discretion ultimately plays a role in sedative choice. For example, propofol is often reserved for hemodynamically stable patients who do not require vasopressors. Further, some patients may have been maintained on higher doses of fentanyl as a sedative sparing approach and the fact that we did not record doses of medications precludes an analysis of this possibility. Variation in use of bolus versus continuous infusion of medications may have contributed to different times to awakening.

Analysis of certain factors that may influence time to awakening was limited by small numbers of patients in different subgroups. For example, the number of patients who had ESRD and awakened was only 15, which limits the ability to determine the effect of ESRD on awakening. Additionally, six patients in this study had a seizure and awakened, a number which is too small to generalize from about awakening in patients who seize. Finally, patients who had care withdrawn could have potentially recovered from their post-arrest anoxic encephalopathy. This is especially true for the 33 patients who had care withdrawn in the first 72 h post-arrest. Exclusion of these patients likely shortened the time to awakening noted in our study.

In conclusion, optimal neuroprognostication in post-arrest patients treated with TH remains poorly understood. This study demonstrates that early awakening is associated with better neurological status at discharge, but time to awakening post-arrest is highly variable and often longer than three days. Although the overall median time to awakening was 3.2 days, 43/194 (22%) patients in this study awakened >72 h, 67% of whom were discharged with a good neurologic outcome, suggesting the need to reappraise the three days standard set by the AAN in 2006. Further research is required to determine optimal timing of and modalities employed for neuroprognostication in the post-arrest setting, as physician choice is ultimately involved in which neurologic tests are ordered to assist with neuroprognostication. Basic issues requiring study include the relationship between degrees of neurologic injury at the time of TH initiation and time to awakening, optimal duration of aggressive treatment in post-arrest patients, quantification of different neurologic studies together and separately to accurately assess the chance of good outcome, and consideration of chances of recovery with cost of ongoing care to provide the best, most cost-effective care to patients. Prospective studies incorporating formalized neurologic assessments documented in a structured format are needed to further investigate time to awakening in comatose post-arrest patients.

Conflict of interest statement

Ms. Leary has served as a consultant for Stryker Corporation. Dr. Abella receives research support from NHLBI, Phillips Healthcare, Medtronic Inc., and the Doris Duke Foundation, has received honoraria from Medivance Corporation, and serves as a consultant to Velomedix Inc. and serves on the medical advisory board for HeartSine Technologies Inc. Dr. Gaieski has received research support, receives honoraria, and has served as a consultant for Stryker Corporation.

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