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The effect of hypothermia “dose” on vasopressor requirements and outcome after cardiac arrest

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Abstract

Objectives—We evaluated the association between TH use and “dose” and cumulative vasopressor and inotrope requirement, survival, and neurologic outcome.

Background—Therapeutic hypothermia (TH) improves outcome after cardiac arrest, but may increase vasopressor and inotrope requirements.

Methods—Chart review of in- and out-of-hospital cardiac arrests between 1/1/2005 and 3/15/2010. Data included demographic information, category of post-cardiac arrest illness severity ((I) awake, (II) coma (not following commands but intact brainstem responses) + mild cardiopulmonary dysfunction (SOFA [Sequential Organ Failure Assessment] cardiac + respiratory score <4), (III) coma + moderate-severe cardiopulmonary dysfunction (SOFA cardiac + respiratory score ≥4), and (IV) coma without brainstem reflexes), cumulative vasopressor index (CVI), inotrope use, survival, and neurologic outcome. The “dose” of TH (hours*temperature below threshold) was calculated using thresholds of 34°C and 35°C. Data were analyzed using descriptive statistics, Student’s-t test, Wilcoxon test, and chi-squared analysis. Linear and logistic regression evaluated the effect of hypothermia “dose” on total CVI, survival and neurologic outcome.

Results—Among 361 comatose patients, 233 (65%) received TH. Vasopressor administration (measured by CVI) was higher in normothermic subjects (60.2% vs. 46.4%; p=0.016). Using a 34°C threshold, SOFA respiratory subscore and PEA arrest predicted total CVI. Using a 35°C threshold, severity of coma, SOFA respiratory subscore, PEA arrest and use of inotropic agents in addition to vasopressors predicted total CVI. Initial motor examination predicted survival and neurologic outcome, while TH “dose” did not.

Conclusions—TH delivery is not associated with vasopressor requirement. TH “dose” is not associated with total CVI, survival, or good outcome. Vasopressor or inotropic requirement should not contraindicate TH use.

Introduction

Sudden cardiac arrest is the leading cause of death in North America, claiming approximately 300,000 lives each year. [1] Therapeutic hypothermia (TH) and multidisciplinary care plans including TH improve neurological outcomes. [2-7] Consequently, international guidelines recommend TH for out-of-hospital cardiac arrest (OHCA) with a primary rhythm of ventricular fibrillation/ventricular tachycardia and consideration of TH for other rhythms or for in-hospital cardiac arrests (IHCA). [8] Despite these guidelines, concern for hemodynamic instability may reduce the frequency of TH use in comatose post-cardiac arrest patients. [5, 9-12] Given that cardiac disease is a common precipitant of cardiac arrest [13] and myocardial stunning [14, 15] is common after cardiac arrest, hemodynamic instability is common. [16]

The effect of TH on hemodynamics after cardiac arrest is unclear. TH increases systemic vascular resistance and lowers cardiac index. [3] In contrast, TH reduces myocardial infarct size [17, 18] Furthermore, TH increases carotid artery vasodilation, which may improve cerebral perfusion. [19] Therefore, the interaction between TH and hemodynamic instability is complex.

While case series report the safety and feasibility of TH in post-cardiac arrest patients experiencing cardiogenic shock, these studies have not quantified the intensity of vasoactive drug use during TH. [20, 21] This study tested whether patients receiving TH required more vasopressor or inotropic agents than normothermic patients, and whether the depth and duration of TH affected the dose of vasopressors or inotropes. As a secondary analysis, this study tested whether dose of TH was related to survival and neurologic outcome among subjects treated with hypothermia.

Methods

Setting

Data were collected as part of a prospective quality improvement database. Subjects did not provide written informed consent for that data collection. The University of Pittsburgh Institutional Review Board deemed retrospective review and analysis of these quality improvement data to be an exempt activity.

Study Population

Subjects were adults (≥ 18 years) admitted to the emergency department or intensive care unit at a single tertiary care center after cardiac arrest and return of pulses between 1/1/2005 and 3/15/2010. Cardiac arrest was defined as receiving chest compressions or rescue shock by a professional healthcare provider. Subjects with both IHCA and OHCA were included. Cardiac arrests occurring in the emergency department were classified as IHCA. In 2007, our facility implemented a multi-disciplinary post-cardiac arrest care plan, including TH, for

this patient population. [7] Locally, subjects requiring vasopressors or inotropic support after cardiac arrest were not excluded from TH.

Treatment Protocol

Hypothermia was rapidly induced with intravenous infusion of 20-30cc/kg of 4°C saline solution and by surface cooling with cooling blankets and ice packs. Endovascular cooling is rarely used in our facility. If intravenous fluids and surface cooling is insufficient, nasogastric lavage with cold saline is also employed. The goal temperature was 33°C, however temperatures between 32-34°C were considered to be within the target range. Cooling duration was for 24 hours after return of spontaneous circulation (ROSC). Temperature was monitored with the following preference for sites: pulmonary artery catheter, esophagus, bladder, and rectum; however the majority of subjects were monitored with esophageal temperature probes. Subjects were rewarmed at a goal rate of 0.25°C/hr. Sedation with propofol or benzodiazepines was recommended to prevent shivering. Paralysis was frequently employed during induction of TH in our facility, but continuous infusions of paralytics once goal temperature has been achieved were rarely used. Since 2009, our facility has provided continuous electroencephalography to this population given the risk of nonconvulsive status epilepticus. [22]

Fluid infusion and use of vasopressors and inotropes were recommended to achieve a urine output of 0.5mL/kg/hr and mean arterial pressure 80mm Hg to ensure adequate cerebral perfusion. [23] In our institution, vasopressor choices are based on individual clinician preference.

Measures

Demographic information, including age, gender, location of arrest (IHCA vs. OHCA), initial rhythm of arrest, survival, good neurologic outcome, and TH treatment were abstracted from the medical record. Good neurologic outcome can be defined as a discharge disposition to home or acute rehabilitation facility, a Cerebral Performance Category (CPC) of 1 or 2, or a Modified Rankin Score (mRS) of 3. We report each of these as they measure different aspects of the subject's outcome. [24]

Initial neurologic examination without sedation within the first 6 hours of return of spontaneous circulation was recorded using the Full Outline of Unresponsiveness (FOUR) score by one of the study physicians (JCR, FXG, and CWC). [25] This 16-point score is designed to evaluate the comatose patient with greater texture than the Glasgow Coma Scale, which is one subscale in the SOFA. The FOUR score is comprised of a 0-4 score for Motor, Brainstem, Respiratory, and Eye responses. A lower score signifies greater impairment. Organ system dysfunction was determined using the individual organ dysfunction subscales of the Sequential Organ Function Assessment (SOFA) scale. [26] Four categories of post-cardiac arrest illness severity were defined by neurological examination and SOFA score on presentation: I) awake, II) coma (not following commands but intact brainstem responses) + mild cardiopulmonary dysfunction (SOFA cardiac + respiratory score <4), III) coma + moderate-severe cardiopulmonary dysfunction (SOFA cardiac + respiratory score ≥4), and IV) coma without brainstem reflexes. In prior work,

category of post-cardiac arrest illness severity is associated with survival, good outcome and development of multiple organ failure. [27] [Table 1]

Each vasopressor drug (epinephrine, norepinephrine, phenylephrine, dopamine, and vasopressin) and dosage was measured. In order to standardize vasopressor dosing, we calculated the cumulative vasopressor index (CVI). [28] CVI values were log-transformed for analysis as they were not normally distributed. This measure does not account for inotropic support such as dobutamine and milrinone, which were analyzed separately. In addition, core temperature, mean arterial blood pressure, heart rate, and fluid balance were recorded. Values were obtained hourly during the first 36 hours after cardiac arrest.

Analysis

Demographic data were analyzed using descriptive statistics, Student's-t test for mean and Mann-Whitney-Wilcoxon test for medians, and chi-squared analysis or Fisher's exact test, as appropriate. Given that TH is not indicated in awake patients, category I post-cardiac arrest illness severity patients were excluded from the analyses.

When comparing the "dose" of TH on total CVI, two separate thresholds for hypothermia were used, as some physicians use a goal temperature of 34°C. A "dose" of hypothermia was defined as the temperature hours below the threshold during TH. We used two thresholds: below 34°C and below 35°C. Candidate variables for predicting CVI were FOUR Motor score, FOUR Brainstem score, SOFA respiratory subscore, inotrope use, and "dose" of hypothermia. For each patient a temperature versus time curve was fit and then the area under the curve was calculated to determine the dose. To gauge the amount of information lost due to measurement error (temperature not taken on the hour) and missing data (temperature not taken every hour), a Monte Carlo simulation study was conducted, which we describe in the next paragraph.

As temperature data are taken sporadically in a clinical setting, we wanted to gauge the impact of this missing information on our estimation of dose of hypothermia. A Monte Carlo simulation was conducted. For the simulation, we assumed the relationship between temperature and time followed a smooth (cosine) curve so that the dose of TH is well known. Three doses were considered: low (9°C hours), medium (18°C hours), and high (36°C hours). Dose and the outcome variable were assumed to follow a logistic regression model and the probabilities of outcome were specified as 0.56, 0.62, and 0.73 for low, medium, and high dose respectively. To mimic the actual clinical setting, 60% of the time-temperature data points were removed. The regression coefficient for both the actual curve and the curve with data points randomly removed were estimated. The simulation was repeated 1000 times, each time a new set of outcomes and a new set of removed datapoints were generated. The variability was compared showing that the amount of information lost due to missing temperature data is miniscule, resulting in a decrease of only 1.5% efficiency. That is the variability in the estimates was only 1.5% larger in the data with missing information than in the complete data. Knowing this, we felt that our procedure for estimating dose was not substantially influenced by the incomplete temperature curves.

Within TH subjects, we estimated the association between hypothermia “dose” and survival or good outcome. Candidate variables included FOUR Motor score, FOUR Brainstem score, SOFA cardiac subscore, and SOFA respiratory subscore, location of arrest, and primary rhythm of arrest because these have been associated with outcomes in prior work. [27, 29] In the CPC and mRS outcome analysis, inclusion of FOUR Brainstem and primary rhythm of arrest resulted in an overfit model. Thus, these variables were removed from this model.

Results

A total of 510 charts were reviewed and 149 subjects were awake on arrival leaving 361 subjects for analysis. In the 361 comatose subjects, those receiving TH were younger, more likely to experience VF/VT as the primary rhythm of arrest, more likely to experience OHCA, and demonstrate category II baseline illness severity. [Table 2] The use of vasopressors (measured by CVI) was more common in the normothermic cohort. Fluid balance was similar between cohorts at 24 and 36 hours. Mean arterial blood pressure was higher in hypothermic subjects than normothermic subjects at 24 and 36 hours.

Category III subjects receiving TH (those with coma and intact brainstem responses and moderate-severe cardiopulmonary dysfunction) were less likely to require vasopressor support or dobutamine than normothermic subjects. [Table 3] Dobutamine was used in conjunction with vasopressor medications in 64 subjects (30 in the hypothermia group and 34 in the normothermia group). Dobutamine alone was used in 1 normothermic subject and 3 TH subjects. Milrinone use was not associated with any post cardiac-arrest category of initial illness severity and was used in conjunction with a vasopressor medication in 29 subjects (12 in the hypothermia group and 17 in the normothermia group). Milrinone alone was used in 2 normothermic subjects and 3 TH subjects.

Multivariate linear regression was used to determine predictors of total CVI. [Table 4] Using either a 34°C or 35°C threshold, SOFA Respiratory subscore predicted total CVI. Hypothermia “dose” based on either a 34°C or 35°C threshold did not predict survival while FOUR Motor score and FOUR Brainstem score did. [Table 5]

The FOUR motor subscore was associated with a good outcome defined as discharge to home or acute rehabilitation facility. [Table 5] None of the variables were associated with a CPC 2 or mRS 3.

Discussion

In this large retrospective dataset, subjects receiving TH were not more likely to require vasopressors following resuscitation from cardiac arrest. In fact, category III subjects treated with TH received less vasopressors or dobutamine than their normothermic counterparts. These data are important as category III subjects are at highest risk for hemodynamic compromise because of their initial severity of cardiopulmonary dysfunction. These findings suggest that TH is not associated with worsening of hemodynamic status. Therefore, the need for vasopressor or inotropic support should not be a contraindication to receiving TH. Other studies support our findings. One prior study found that there was no significant change in outcome in hemodynamically unstable patients receiving hypothermia, but

stratified patients based on intervention (intra-aortic balloon counterpulsation) instead of by initial illness severity. [20] Another study found that the neurologic benefits and improved outcomes of TH can be achieved in patients with shock, but did not specifically look at the effects of TH on hemodynamic stability. [30] Others noted an increase in vasopressor requirement that corresponded to a decrease in cardiac index during induction of TH. [31]

Importantly, hypothermia “dose” was not independently associated with total CVI dose in subjects receiving TH. Moreover, the “dose” of hypothermia was not associated with either survival or good outcome. On average, our subjects did receive 23 hours of TH when defined as $<35^{\circ}\text{C}$, demonstrating that the intended “dose” was administered. The optimal “dose” of TH is unknown. In this observational study, the range of hypothermia doses may be insufficient to capture the lowest effective dose or the maximum dose above which side-effects predominate. It is possible that an analysis with a wider range of TH durations or randomization to specific TH durations would identify a relationship between dose and outcome.

There are several limitations of this study. First, the temperature data were recorded hourly and some data points were missing. Minute-to-minute variation in temperature may influence outcome, and cannot be completely accounted for in this study. Despite this, the Monte Carlo modeling suggested that the missing data and irregular sampling observed would have minimal effects on the model. Second, these data were obtained before and after implementation of a comprehensive care plan, including TH. Comparison of hypothermia and normothermia groups lacks the rigor of a controlled trial. However, we have previously demonstrated improved outcome in our facility following implementation of a care plan that includes TH. [7] Third, these data explored only one range of TH “dose.” The optimal “dose” of TH after cardiac arrest remains unknown. Fourth, the proportion of subjects receiving inotropic support in each category of post-cardiac arrest illness severity is small, limiting the analysis of inotropic support. The number of patients with a CPC 2 or mRS 3 is low, limiting our ability to determine the effect of TH “dose” on these outcome measures. Finally, it is possible that vasopressor-dependent subjects treated before the standardized post-arrest care plan was adopted in 2007 may not have received TH because of concerns for hemodynamic instability. However, the equal proportions of category IV illness severity in both cohorts argues against a systemic exclusion of these subjects requiring vasopressors or inotropes from the study.

In summary, TH delivery is not associated with increased vasopressor requirement. Vasopressors are less commonly required in category III (coma + moderate-severe cardiopulmonary dysfunction) subjects receiving TH than their normothermic counterparts. The “dose” of hypothermia is not associated with total CVI, survival, or good outcome. Vasopressor or inotrope requirement should not be a contraindication to TH use.

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Table 1

Categories of initial post-arrest illness severity. FOUR- Full Outline of Unresponsiveness, SOFA- Serial Organ Function Assessment.

Category	FOUR Motor+ Brainstem Score	SOFA Cardiovascular+ Respiratory Score	Description
I	8	Any	Awake – Follows commands
II	4-7	<4	Coma with preserved brainstem reflexes
III	4-7	4	Coma with preserved brainstem reflexes, and severe cardiopulmonary failure
IV	<4	Any	Coma with loss of some or all brainstem reflexes

Table 2

Demographic data. VF/VT- ventricular fibrillation/ventricular tachycardia, PEA-pulseless electrical activity, OHCA- out of hospital cardiac arrest, MAP- mean arterial blood pressure, CVI- summative cardiovascular index.

	Hypothermia (N=233)	Normothermia (N=128)	p-value
Age	58.5 (17)	64.4 (16)	0.001
Male	126 (54.1%)	64 (50%)	0.527
Rhythm			
VF/VT	98 (42.1%)	39 (30.5%)	0.041
PEA	58 (24.9%)	49 (38.3%)	
Asystole	48 (20.6%)	23 (18%)	
Unknown	29 (12.4%)	17 (13.3%)	
OHCA	175 (75.1%)	53 (41.4%)	<0.001
Category of Arrest			
II	89 (38.2%)	29 (22.7%)	<0.001
III	35 (15%)	38 (29.7%)	
IV	109 (46.8%)	61 (44.7%)	
Initial 24 hours (median, IQR)			
Fluid balance (mL)	-264 (-1337, 1242)	-72 (-1294, 562)	0.773
Median MAP (mmHg)	83 (75, 93)	79 (70, 86)	>0.001
CVI	2.5 (0, 43)	19.5 (0, 53)	0.072
Initial 36 hours (median, IQR)			
Fluid balance (mL)	-188 (-1451, 1980)	-284 (-1170, 631)	0.717
MAP (mmHg)	82 (75, 89)	77 (70, 87)	0.005
CVI	7.5 (0, 68)	20.5 (0, 83)	0.168
Received CVI medication	108 (46.4%)	77 (60.2%)	0.016
Received dobutamine	30 (12.9%)	24 (18.8%)	0.179
Received milrinone	12 (5.2%)	8 (6.2%)	0.844
Dose of TH in hours (median, IQR)			
34°C cutoff	10.1 (5, 16)	--	
35°C cutoff	23.3 (13, 32)	--	
Survival	75 (32.2%)	45 (35.2%)	0.649
Length of Stay (days)	10.5 (13.7)	12.8 (16.4)	0.176

Table 3

Rate of vasopressor, dobutamine and milrinone use by category of post-cardiac arrest illness. CVI Drugs- any drug in the cumulative vasopressor index.

	Hypothermia	Normothermia	p-value
Category II	(n = 89)	(n = 29)	
CVI Drugs	29 (33%)	10 (35%)	0.85
Dobutamine	10 (11%)	3 (10%)	0.89
Milrinone	5 (6%)	0 (0%)	0.33
Category III	(n = 35)	(n = 38)	
CVI Drugs	18 (51%)	29 (76%)	0.03
Dobutamine	3 (9%)	10 (26%)	0.05
Milrinone	1 (3%)	3 (8%)	0.62
Category IV	(n = 109)	(n = 61)	
CVI Drugs	61 (56%)	38 (62%)	0.42
Dobutamine	17 (16%)	11 (18%)	0.68
Milrinone	6 (6%)	6 (10%)	0.56

Table 4

Predictors of total cardiovascular index shown as coefficients. Other inotrope- use of dobutamine or milrinone.

	Estimate (95% CI)	p
Dose below 34°C	0.06 (−0.13, 0.25)	0.54
FOUR Motor	−0.19 (−0.49, 0.12)	0.22
FOUR Brainstem	−0.06 (−0.24, 0.11)	0.47
SOFA Respiratory	0.25 (0.04, 0.46)	0.02
SOFA Cardiac	0.08 (−0.12, 0.28)	0.42
Other inotrope	0.50 (−0.04, 1.03)	0.07
PEA	−0.61 (−1.29, 0.07)	0.08
Asystole	−0.40 (−1.20, 0.39)	0.31
Unknown	−0.60 (−1.51, 0.30)	0.19
Dose below 35°C	0.08 (−0.11, 0.27)	0.40
FOUR Motor	−0.19 (−0.49, 0.12)	0.22
FOUR Brainstem	−0.07 (−0.25, 0.11)	0.45
SOFA Respiratory	0.24 (0.04, 0.45)	0.02
SOFA Cardiac	0.09 (−0.11, 0.29)	0.37
Other inotrope	0.51 (−0.02, 1.04)	0.06
PEA	−0.65 (−1.32, 0.03)	0.06
Asystole	−0.46 (−1.27, 0.35)	0.26
Unknown	−0.63 (−1.53, 0.28)	0.17

Table 5

Predictors of survival and good outcome based on discharge disposition (defined as discharge home or acute rehabilitation facility), CPC 2, and mRS of 3. OHCA- out of hospital cardiac arrest, CPC- Cerebral Performance Category, mRS- Modified Rankin Score.

	Odds Ratio (95% CI)	p
Survival		
Dose below 34°C	0.95 (0.65, 1.37)	0.78
FOUR Motor	2.50 (1.56, 4.19)	<0.001
FOUR Brainstem	1.81 (1.30, 2.63)	<0.001
SOFA Respiratory	0.71 (0.49, 1.01)	0.06
SOFA Cardiac	0.89 (0.60, 1.30)	0.56
OHCA	2.03 (0.57, 7.89)	0.29
PEA	0.26 (0.06, 1.06)	0.07
Asystole	1.08 (0.28, 4.20)	0.91
Unknown	0.42 (0.10, 1.70)	0.23
Dose below 35°C	0.91 (0.62, 1.31)	0.60
FOUR Motor	2.49 (1.56, 4.18)	<0.001
FOUR Brainstem	1.82 (1.30, 2.65)	<0.001
SOFA Respiratory	0.72 (0.50, 1.01)	0.07
SOFA Cardiac	0.89 (0.60, 1.29)	0.53
OHCA	2.00 (0.56, 7.78)	0.30
PEA	0.27 (0.06, 1.11)	0.08
Asystole	1.14 (0.29, 4.55)	0.85
Unknown	0.44 (0.10, 1.85)	0.27
Discharge Disposition		
Dose below 34°C	0.90 (0.60, 1.32)	0.59
FOUR Motor	2.46 (1.45, 4.48)	<0.001
FOUR Brainstem	1.44 (0.99, 2.16)	0.07
SOFA Respiratory	0.83 (0.57, 1.18)	0.30
SOFA Cardiac	1.06 (0.69, 1.62)	0.78
OHCA	4.10 (0.83, 31.64)	0.11
PEA	0.13 (0.01, 0.81)	0.07
Asystole	0.74 (0.13, 3.41)	0.70
Unknown	0.80 (0.18, 3.27)	0.75
Dose below 35°C	0.87 (0.59, 1.25)	0.45
FOUR Motor	2.47 (1.45, 4.48)	<0.001
FOUR Brainstem	1.45 (0.99, 2.17)	0.06
SOFA Respiratory	0.83 (0.58, 1.19)	0.31
SOFA Cardiac	1.05 (0.68, 1.60)	0.82
OHCA	3.98 (0.81, 30.68)	0.12

	Odds Ratio (95% CI)	p
PEA	0.14 (0.01, 0.87)	0.07
Asystole	0.80 (0.14, 3.80)	0.78
Unknown	0.86 (0.19, 3.61)	0.84
CPC 2 *		
Dose below 34°C	2.02 (0.79, 6.31)	0.17
FOUR Motor	2.85 (0.94, 13.61)	0.11
SOFA Respiratory	0.87 (0.37, 1.97)	0.73
SOFA Cardiac	0.88 (0.19, 2.13)	0.81
OHCA	0.46 (0.04, 10.74)	0.54
Dose below 35°C	1.98 (0.77, 6.76)	0.21
FOUR Motor	2.78 (0.93, 12.62)	0.11
SOFA Respiratory	0.88 (0.38, 1.96)	0.75
SOFA Cardiac	0.87 (0.20, 2.08)	0.79
OHCA	0.55 (0.05, 12.86)	0.64
mRS 3 *		
Dose below 34°C	1.36 (0.61, 3.31)	0.46
FOUR Motor	2.53 (0.95, 9.52)	0.10
SOFA Respiratory	0.81 (0.38, 1.63)	0.56
SOFA Cardiac	0.82 (0.18, 1.87)	0.70
OHCA	0.69 (0.08, 15.40)	0.76
Dose below 35°C	1.22 (0.58, 2.99)	0.63
FOUR Motor	2.46 (0.94, 8.91)	0.10
SOFA Respiratory	0.82 (0.39, 1.63)	0.57
SOFA Cardiac	0.82 (0.19, 1.85)	0.70
OHCA	0.78 (0.09, 17.21)	0.84

* In the CPC and mRS outcome analysis, inclusion of FOUR Brainstem and primary rhythm of arrest resulted in an overfit model. Thus, these variables were removed from this model.