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Extracorporeal Cardiopulmonary Resuscitation: One-Year Survival and Neurobehavioral Outcome among Infants and Children with In-Hospital Cardiac Arrest

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Abstract

Objective: To describe neurobehavioral outcomes and investigate factors associated with survival and survival with good neurobehavioral outcome one year after in-hospital cardiac arrest for children who received extracorporeal cardiopulmonary resuscitation (ECPR).

Design: Secondary analysis of the Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital (THAPCA-IH) trial.

Setting: 37 PICUs in the United States, Canada and the United Kingdom.

Patients: Children (n=147) resuscitated with ECPR following in-hospital cardiac arrest.

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Interventions: Neurobehavioral status was assessed using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) at pre-arrest baseline and 12-months post-arrest. Norms for VABS-II are 100 (mean) ±15 (SD). Higher scores indicate better functioning. Outcomes included 12-month survival, 12-month survival with VABS-II decreased by ≤15 points from baseline, and 12-month survival with VABS-II ≥70.

Measurements and Main Results: Of 147 children receiving ECPR, 125 (85.0%) had a pre-existing cardiac condition, 75 (51.0%) were post-cardiac surgery, and 84 (57.1%) were <1 year of age. Duration of chest compressions was >30 minutes for 114 (77.5%). Sixty-one (41.5%) survived to 12 months, 32 (22.1%) survived to 12 months with VABS-II decreased by ≤15 points from baseline, and 39 (30.5%) survived to 12 months with VABS-II ≥70. On multivariable analyses, open-chest cardiac massage was independently associated with greater 12-month survival with VABS-II decreased by ≤15 points and greater 12-month survival with VABS-II ≥70. Higher minimum post-arrest lactate and pre-existing gastrointestinal conditions were independently associated with lower 12-month survival with VABS-II decreased by ≤15 points and lower 12-month survival with VABS-II ≥70.

Conclusions: About a third of children survived with good neurobehavioral outcome one year after receiving ECPR for in-hospital arrest. Open-chest cardiac massage and minimum post-arrest lactate were associated with survival with good neurobehavioral outcome at one year.

Keywords

Infants; children; cardiac arrest; extracorporeal cardiopulmonary resuscitation; adaptive behavior

INTRODUCTION

Extracorporeal cardiopulmonary resuscitation (ECPR) for children with in-hospital cardiac arrest has been increasing in use since first described in 1992 (1–6). ECPR is the rapid deployment of venoarterial extracorporeal membrane oxygenation (ECMO) for circulatory support when conventional cardiopulmonary resuscitation (CPR) fails to achieve sustained return of spontaneous circulation (7, 8). Sustained return of spontaneous circulation occurs when chest compressions are not required for 20 minutes and signs of circulation persist (8). Despite increasing use, long-term survival and neurobehavioral outcomes after ECPR are not well elucidated. Most reports of ECPR are retrospective single center audits (9–13) or based on registry data (2–5, 14–16), and primarily focus on short-term outcomes. For example, ECPR has been associated with greater survival to hospital discharge for children with cardiac disease (15), and greater survival with good neurological outcome at hospital discharge for children receiving conventional CPR for at least 10 minutes (16). Based on available evidence, the American Heart Association (AHA) in collaboration with the International Liaison Committee on Resuscitation (ILCOR) recommends ECPR be considered for children with cardiac diagnoses who have in-hospital cardiac arrest in settings with available expertise, resources and systems to optimize ECPR, but are unable to advise for or against ECPR for other conditions (17–19). Prospective multicenter data evaluating long-term survival and neurobehavioral function after ECPR are needed to further understand outcomes of children resuscitated with this technique.

The Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital (THAPCA-IH) trial was a randomized trial comparing the efficacy of therapeutic hypothermia with that of therapeutic normothermia on survival with good neurobehavioral outcome in children one year after in-hospital cardiac arrest (20). All children recruited to the THAPCA-IH trial were comatose, required mechanical ventilation after return of circulation, and were at high risk for neurologic disability. Neurobehavioral function was assessed longitudinally using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (21). Although neither temperature management strategy demonstrated a significant benefit on survival with good neurobehavioral outcome in the THAPCA-IH trial (20), the use of ECMO at the time of initiation of the temperature management intervention was associated with worse outcomes (22). Not all children treated with ECMO in the THAPCA-IH trial received ECPR. In this secondary analysis of the THAPCA-IH trial, we evaluate only those children for whom ECMO was initiated during active chest compressions or before sustained return of spontaneous circulation >20 minutes was achieved (7, 8). Our objective was to describe neurobehavioral outcomes and investigate factors associated with survival and survival with good neurobehavioral outcome one year post-arrest for children who received ECPR and were recruited to the THAPCA-IH trial.

MATERIALS AND METHODS

Design and setting

This study is a secondary analysis of the THAPCA-IH trial (20). Children were recruited from 37 children's hospitals in the United States, Canada, and the United Kingdom between September 1, 2009 and February 27, 2015. Details of the trial were previously published (20, 23). Institutional review boards at all study sites and the University of Utah Data Coordinating Center approved the study. Caregiver permission was obtained for all participants.

Participants

Children eligible for the THAPCA-IH trial were >48 hours and <18 years of age, had an in-hospital cardiac arrest with chest compressions for ≥2 minutes, and required mechanical ventilation after return of circulation (20). Major exclusion criteria included inability to be randomized within 6 hours of return of circulation, a Glasgow Coma Scale motor score of 5 or 6 (24), and a decision to withhold aggressive treatment. Additional inclusion criteria for this secondary analysis included the receipt of ECPR defined as ECMO initiation during active chest compressions or before sustained return of spontaneous circulation >20 minutes was achieved (7, 8). Of 329 children included in the THAPCA-IH trial, 192 received ECMO after the cardiac arrest. Of these, 147 received ECPR.

Independent Variables

Child characteristics included demographics, body habitus, technology dependence, post-operative from cardiovascular surgery at the time of arrest, previous intensive care unit (ICU) admissions during the hospitalization, and pre-existing conditions. Body habitus was assessed using body mass index-for-age (BMI-for-age) percentiles for children ≥2 years old, and weight-for-length percentiles for children <2 years old (25). Children were considered

obese if their BMI-for-age or weight-for-length was ≥95th percentile, and underweight if <5th percentile (25). Technology dependence was defined as presence of a tracheostomy or percutaneous feeding tube prior to the cardiac arrest. Pre-existing conditions included cardiac, respiratory, neurologic, gastrointestinal, prenatal, pulmonary hypertension, immune compromised status, renal, and other conditions. Pre-existing cardiac conditions included congenital heart disease, single ventricle, acquired heart disease, arrhythmia, and pre-existing cardiac transplant.

Cardiac arrest and ECMO characteristics included primary etiology of arrest, initial cardiac rhythm at the time chest compressions were started, duration of chest compressions, number of epinephrine doses during the arrest, epinephrine dosing interval, number of defibrillation attempts, use of open-chest cardiac massage, location of arrest within the hospital, presence of an intravenous catheter or endotracheal tube at the time of arrest, THAPCA-IH trial intervention (i.e., therapeutic hypothermia/normothermia), and presence of clinical or electrographic seizures, use of renal replacement therapy, red blood cell transfusion and culture-positive bloodstream infection between the time of randomization in the THAPCA-IH trial (day 0) through day 2 of the THAPCA-IH trial. Primary etiology of arrest was categorized as cardiovascular, respiratory, or other. Initial cardiac rhythm was categorized as asystole, bradycardia, pulseless electrical activity, ventricular tachycardia/fibrillation, or unknown. Epinephrine dosing interval was defined as the duration of chest compressions divided by the total number of epinephrine doses administered during chest compressions. Location of arrest was categorized as emergency department, non-ICU inpatient ward, ICU (including intermediate care), operating room, or other clinical area.

Laboratory data included the minimum and maximum values for PaO_2, $PaCO_2$, blood lactate, international normalized ratio (INR), total bilirubin and alanine aminotransferase (ALT) in the time interval from 2 hours before to 48 hours after the start of the temperature management intervention. Hyperoxia was defined as maximum PaO_2 greater than 200 mm Hg [27 kPa] and hypocapnia as minimum $PaCO_2$ less than 30 mm Hg [3.9 kPa] (26).

Outcomes

Outcomes included 12-month survival, 12-month survival with VABS-II decreased by ≤15 points from pre-arrest baseline, and 12-month survival with VABS-II ≥70. The VABS-II is a caregiver report measure of adaptive behavior applicable from birth to adulthood (21). VABS-II domains include communication, daily living, socialization and motor skills. The number of tasks that can be performed in each domain is standardized for age. In normative U.S. populations, the mean VABS-II is 100, and the standard deviation is 15. Higher scores indicate better functioning. Caregivers completed baseline VABS-II assessments (reflecting pre-arrest status) at the local sites within 24 hours of randomization into the THAPCA-IH trial, and 12-month assessments by telephone with interviewers from the Kennedy Krieger Institute. For the outcome of survival with VABS-II ≥70, only children with baseline VABS-II ≥70 (n=130) were considered.

Statistical Analyses

Clinical characteristics were summarized using frequencies and percentages. Univariate associations between these characteristics and outcomes were examined using the chi-square test of no association. Associations between minimum and maximum reported laboratory values and outcomes were assessed using the Wilcoxon rank-sum test. All clinical characteristics and laboratory values with a univariate p-value <0.1 were considered for modeling. For each outcome, the subset of candidate variables that resulted in the multiple logistic regression model with the best penalized fit based on the Bayesian Information Criterion (BIC) were identified (27). Models were considered to have optimal fit if the BIC was within 2 of the lowest BIC model. Final models were selected from among these based on the clinical meaning and usefulness of the variables. All analyses were completed using SAS software v9.4 (Cary, NC).

RESULTS

Of 147 children, 84 (57.1%) were <1 year old, 94 (63.9%) were male, and 84 (57.1%) were white (Table 1). Twenty-nine (19.7%) were underweight and 21 (14.5%) were obese. Fourteen (9.5%) were technology dependent. Seventy-five (51.0%) were post-cardiac surgery at the time of arrest, and 35 (23.8%) had a previous ICU admission during the hospitalization. One hundred and thirty-seven (93.2%) had at least one pre-existing condition; 125 (85.0%) had a pre-existing cardiac condition, 36 (24.5%) gastrointestinal, 35 (23.8%) respiratory, 34 (23.1%) prenatal, 27 (18.4%) neurologic, 26 (17.7%) immune compromised, 20 (13.6%) renal, 11 (7.5%) pulmonary hypertension, and 39 (26.5%) other condition (Supplemental Digital Content 1). Among 36 with gastrointestinal conditions, 31 (86.1%) also had a cardiac condition, 14 (38.9%) also had a neurologic condition, and 10 (27.8%) were technology dependent.

Primary etiology of arrest was cardiovascular for 116 (78.9%) children (Table 2). Initial cardiac rhythm at the time compressions were started was bradycardia for 86 (58.5%). The duration of chest compressions was >30 minutes for 114 (77.5%). The number of epinephrine doses was >8 for 60 (40.8%), and the epinephrine dosing interval was ≥5 minutes/dose for 105 (71.9%). Forty-three (29.3%) received at least one defibrillation attempt, and 43 (29.3%) received open-chest cardiac massage. The median duration from the start of chest compressions until ECMO initiation was 37 minutes (IQR 22, 51) for the open-chest group and 53 minutes (IQR 36.5, 68.5) for the closed chest group, p<0.001). Seventy-two (49.0%) received therapeutic hypothermia (Supplemental Digital Content 2). Arrest occurred in an ICU for 104 (70.7%).

Clinical or electrographic seizures were reported in 22 (15.0%) children. Renal replacement therapy was used in 35 (23.8%). One hundred and thirty-two (89.8%) received at least one red blood cell transfusion. Seven (4.8%) had a culture-positive bloodstream infection. Hyperoxia occurred in 96 (65.3%) and hypocapnia in 26 (17.7%). Blood lactate declined to <2 mmol/L in 89 (60.5%) within 48 hours of the start of the temperature management intervention. Sixty-one (41.5%) children survived to 12 months, 32 (22.1%) survived to 12 months with VABS-II decreased by ≤15 points from baseline, and 39 (30.5%) survived to 12 months with VABS-II ≥70.

Univariate Associations

Associations between child characteristics and outcomes are shown in Table 1 and Supplemental Digital Content 1. Post-cardiac surgery status was associated with greater 12-month survival. Technology dependence and presence of a pre-existing neurologic condition were associated with lower 12-month survival and lower 12-month survival with VABS-II ≥70. Presence of a gastrointestinal condition was associated with lower 12-month survival with VABS-II decreased by ≤15 points and lower 12-month survival with VABS-II ≥70.

Associations between cardiac arrest/ECMO characteristics and outcomes are shown in Table 2 and Supplemental Digital Content 2. Location of arrest in a non-ICU inpatient ward was associated with lower 12-month survival. Fewer defibrillation attempts, treatment with therapeutic hypothermia, and red blood cell transfusion were associated with lower 12-month survival with VABS-II decreased by ≤15 points. Initial cardiac rhythm (asystole), and duration of chest compressions (46–60 minutes) were associated with lower 12-month survival with VABS-II ≥70. Open-chest cardiac massage and decline in lactate to <2 mmol/L were associated with greater 12-month survival, 12-month survival with VABS-II decreased by ≤15 points, and 12-month survival with VABS-II ≥70.

Associations between laboratory values and outcomes are shown in Supplemental Digital Content 3. Minimum lactate was associated with 12-month survival, 12-month survival with VABS-II decreased by ≤15 points, and 12-month survival with VABS-II ≥70.

Logistic Regression Models

Logistic regression models including variables available up to the time of randomization in the THAPCA-IH trial (THAPCA day 0) are shown in Table 3. Post-cardiac surgery status was independently associated with greater 12-month survival; technology dependence was associated with lower 12-month survival. Open-chest cardiac massage was independently associated with greater 12-month survival with VABS-II decreased by ≤15 points and greater 12-month survival with VABS-II ≥70. Gastrointestinal conditions was associated with lower 12-month survival with VABS-II decreased ≤15 points and lower 12-month survival with VABS-II ≥70.

Logistic regression models including variables available through THAPCA day 2 are shown in Table 4. Acquired heart disease, gastrointestinal conditions, and higher minimum lactate values were independently associated with lower 12-month survival. Open-chest cardiac massage was independently associated with greater 12-month survival with VABS-II decreased by ≤15 points. Gastrointestinal conditions and higher minimum lactate were independently associated with lower 12-month survival with VABS-II decreased by ≤15 points and lower 12-month survival with VABS-II ≥70.

DISCUSSION

Our findings demonstrate 41.5% one-year survival rate for children who were resuscitated with ECPR and recruited to the THAPCA-IH trial. Children receiving ECPR after cardiac surgery had better survival (52.0%) than others. Although few studies describe long-term survival after ECPR, a small single center study recently reported a rate of 62.1% at a

median of 3 years post-arrest with the best survival observed among children with cardiac conditions (28). About a third of children in our study survived with good neurobehavioral outcome after ECPR based on assessments of adaptive behavior using the VABS-II. Higher rates of favorable neurological outcome have been reported following ECPR in retrospective studies using Pediatric Cerebral Performance Category (PCPC) scores (3, 9, 29, 30); however, PCPC lacks detailed assessment. In addition, all children in our study were comatose post-arrest with high risk of neurologic disability. In a single center study, formal neurocognitive testing in ECPR survivors found intelligence quotients to be significantly lower than the population mean with 24% having intellectual disability (31). Good health-related quality of life has been reported among ECPR survivors (28).

Open-chest cardiac massage was frequently reported in our cohort (29.3%) and independently associated with greater survival with good neurobehavioral outcome. Most children resuscitated with ECPR had a pre-existing cardiac condition and about half were post-cardiac surgery at the time of arrest accounting for the high frequency of open-chest massage. Experimental models suggest that open-chest compressions are hemodynamically superior to closed-chest compressions by generating greater arterial pressure, cardiac output, coronary perfusion pressure, and cerebral blood flow (32). An open sternotomy after cardiac surgery may also allow ECMO cannulation to occur more efficiently via of the aorta and right atrium (33). Indeed, median duration from the start of compressions to the initiation of ECMO was shorter in our open-chest group. Aortic cannulation has been associated with lower risk of neurologic injury compared to carotid cannulation during VA ECMO (34).

Our findings demonstrate that higher minimum lactate after ECPR is independently associated with lower survival with good neurobehavioral outcome. Other studies have shown lactate clearance after initiation of ECMO to be an important predictor of outcome (28, 35–38). Lactate is the product of anaerobic metabolism and increases during periods of inadequate oxygen delivery. The association of higher lactate with worse outcomes suggests that adequate oxygen delivery in the context of ECPR may be a key prognostic factor. Duration of chest compressions was >30 minutes in most of our cohort and not independently associated with outcomes; thus, during prolonged CPR, duration of chest compressions may be less important than high quality compressions that maintain oxygen delivery until ECMO is established.

Gastrointestinal conditions were independently associated with lower survival with good neurobehavioral outcome in our cohort. Most children with gastrointestinal conditions had complex multisystem disorders including pre-existing cardiovascular and/or neurologic disorders potentially explaining the association between gastrointestinal conditions and worse outcomes. Therapeutic hypothermia (compared to normothermia) also tended to be associated with lower survival with good neurobehavioral outcome. According to the Extracorporeal Life Support Organization Registry (6), therapeutic hypothermia has been used in over half the reported cases of pediatric ECPR, despite lack of documented benefit in this situation. In observational studies of adults resuscitated with ECPR, therapeutic hypothermia was not associated with neurological outcome at hospital discharge in one report (39) and with improved neurological outcome in another (40). Unintentional sustained hypothermia after ECPR has been associated with poor neurological outcome and in-

hospital mortality (41). However, unintentional sustained hypothermia may be due to dysfunction of central nervous system thermoregulation as a result of severe brain injury from cardiac arrest. An early report from an ongoing trial of therapeutic hypothermia versus normothermia for adults resuscitated with ECPR suggests that therapeutic hypothermia can be administered safely in this situation although findings about the effects on neurologic outcome from the trial have not yet been reported (42).

Unlike other reports, the use of renal replacement therapy during ECMO was not associated with worse outcomes in our study (9, 14, 30, 43). Epinephrine dosing interval was also not associated with outcomes. In our analysis, epinephrine was often administered with a longer dosing interval than the 3–5 minutes recommended by the AHA (44). Decreased use of epinephrine during ECPR has been reported by some clinicians in attempt to avoid excessive afterload that may affect ECMO flow rates (45).

Strengths of our study include the multicenter design, prospective data collection and use of the VABS-II to measure one-year neurobehavioral outcomes. Limitations include the potential selection bias inherent in including children recruited to the THAPCA-IH trial. Children receiving ECPR who were recruited to the THAPCA-IH trial may differ from children receiving ECPR who did not meet the trial's inclusion criteria thereby limiting the generalizability of the findings. Limitations also include the large number of variables evaluated; thus, some associations may be due to chance. Data for some variables were not collected in the THAPCA-IH trial and are lacking. Importantly, these include details of ECMO cannulation and management that could also influence outcomes. Also important, the associations observed do not infer causation.

CONCLUSIONS

Of 147 children with in-hospital cardiac arrest who were comatose after ECPR, about a third survived with good neurobehavioral outcome at one year. Post-cardiac surgery status was associated with one-year survival. Open-chest cardiac massage and minimum post-arrest lactate were associated with one-year survival with good neurobehavioral outcome. Our findings support AHA and ILCOR recommendations to consider ECPR in children with cardiac disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Child Characteristics and Associations with Outcomes

Characteristic	Overall	Survived to 12 months	P-value[a]	VABS-II decreased by ≤ 15 points[b]	P-value[a]	Survived to 12 months with VABS-II ≥ 70[b,c]	P-value[a]
Total	147	61/147 (41.5%)		32/145 (22.1%)		39/128 (30.5%)	
Age			0.253		0.683		0.336
≤ 30 days	28 (19.0%)	12/28 (42.9%)		9/28 (32.1%)		10/22 (45.5%)	
> 30 days-<1 year	56 (38.1%)	29/56 (51.8%)		10/54 (18.5%)		13/51 (25.5%)	
1–4 years	29 (19.7%)	9/29 (31.0%)		6/29 (20.7%)		5/24 (20.8%)	
5–12 years	22 (15.0%)	8/22 (36.4%)		5/22 (22.7%)		8/21 (38.1%)	
≥ 13 years	12 (8.2%)	3/12 (25.0%)		2/12 (16.7%)		3/10 (30.0%)	
Sex			0.998		0.538		0.684
Male	94 (63.9%)	39/94 (41.5%)		22/93 (23.7%)		26/82 (31.7%)	
Female	53 (36.1%)	22/53 (41.5%)		10/52 (19.2%)		13/46 (28.3%)	
Race			0.176		0.057		0.053
Asian	5 (3.4%)	3/5 (60.0%)		2/5 (40.0%)		3/5 (60.0%)	
Black or African American	43 (29.3%)	20/43 (46.5%)		9/42 (21.4%)		13/39 (33.3%)	
White	84 (57.1%)	29/84 (34.5%)		14/83 (16.9%)		16/71 (22.5%)	
Other/Unknown	15 (10.2%)	9/15 (60.0%)		7/15 (46.7%)		7/13 (53.8%)	
Ethnicity			0.354		0.609		0.064
Hispanic or Latino	25 (17.0%)	9/25 (36.0%)		4/25 (16.0%)		4/25 (16.0%)	
Not Hispanic or Latino	110 (74.8%)	49/110 (44.5%)		26/108 (24.1%)		34/94 (36.2%)	
Unknown	12 (8.2%)	3/12 (25.0%)		2/12 (16.7%)		1/9 (11.1%)	
Body habitus			0.435		0.385		0.903
Underweight (<5th percentile)	29 (19.7%)	13/29 (44.8%)		9/28 (32.1%)		7/24 (29.2%)	
Normal/Overweight	95 (64.6%)	36/95 (37.9%)		19/95 (20.0%)		26/86 (30.2%)	
Obese (≥95th percentile)	21 (14.5%)	11/21 (52.4%)		4/20 (20.0%)		6/17 (35.3%)	
Unknown	2 (1.4%)	1/2 (50.0%)		0/2 (0.0%)		0/1 (0.0%)	
Pre-arrest technology dependence	14 (9.5%)	2/14 (14.3%)	0.030	1/14 (7.1%)	0.157	0/10 (0.0%)	0.029
Post-operative cardiac surgery	75 (51.0%)	39/75 (52.0%)	0.008	20/74 (27.0%)	0.142	23/65 (35.4%)	0.220
Previous PICU admission during current hospitalization	35 (23.8%)	12/35 (34.3%)	0.321	4/34 (11.8%)	0.098	7/32 (21.9%)	0.223

[a] All p-values from chi-squared test of no association. Categories of "unknown" were excluded from the analysis of body habitus.

[b] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.

[c] Only subjects with baseline VABS-II ≥70 were included for this outcome.

Table 2.

Cardiac Arrest Characteristics and Associations with Outcomes

Characteristic	Overall	Survived to 12 months	P-value[a]	VABS-II decreased by ≤ 15 points[b]	P-value[a]	Survived to 12 months with VABS-II ≥ 70[b,c]	P-value[a]
Total	147	61/147 (41.5%)		32/145 (22.1%)		39/128 (30.5%)	
Primary etiology of cardiac arrest			0.140		0.286		0.306
Cardiovascular event	116 (78.9%)	51/116 (44.0%)		28/114 (24.6%)		32/99 (32.3%)	
Respiratory event	26 (17.7%)	10/26 (38.5%)		4/26 (15.4%)		7/24 (29.2%)	
Other	5 (3.4%)	0/5 (0.0%)		0/5 (0.0%)		0/5 (0.0%)	
Cardiac rhythm at start of chest compressions			0.109		0.265		0.027
Asystole	7 (4.8%)	1/7 (14.3%)		0/7 (0.0%)		0/5 (0.0%)	
Bradycardia	86 (58.5%)	32/86 (37.2%)		16/84 (19.0%)		16/70 (22.9%)	
Pulseless electrical activity	30 (20.4%)	16/30 (53.3%)		8/30 (26.7%)		12/30 (40.0%)	
Ventricular fibrillation or tachycardia	19 (12.9%)	11/19 (57.9%)		7/19 (36.8%)		10/18 (55.6%)	
Unknown	5 (3.4%)	1/5 (20.0%)		1/5 (20.0%)		1/5 (20.0%)	
Duration of chest compressions (minutes)			0.230		0.478		0.015
≤ 15	11 (7.5%)	5/11 (45.5%)		2/10 (20.0%)		4/10 (40.0%)	
16–30	22 (15.0%)	8/22 (36.4%)		5/22 (22.7%)		4/17 (23.5%)	
31–45	37 (25.2%)	21/37 (56.8%)		12/37 (32.4%)		17/32 (53.1%)	
46–60	33 (22.4%)	13/33 (39.4%)		5/32 (15.6%)		5/30 (16.7%)	
> 60	44 (29.9%)	14/44 (31.8%)		8/44 (18.2%)		9/39 (23.1%)	
Total number of doses of epinephrine administered			0.576		0.508		0.913
0–2	27 (18.4%)	10/27 (37.0%)		3/26 (11.5%)		7/23 (30.4%)	
3–5	38 (25.9%)	19/38 (50.0%)		9/37 (24.3%)		12/35 (34.3%)	
6–8	21 (14.3%)	7/21 (33.3%)		6/21 (28.6%)		5/19 (26.3%)	
> 8	60 (40.8%)	24/60 (40.0%)		13/60 (21.7%)		14/50 (28.0%)	
Unknown	1 (0.7%)	1/1 (100.0%)		1/1 (100.0%)		1/1 (100.0%)	
Epinephrine dosing interval (min/dose)			0.783		0.927		0.201
No epinephrine recorded	3 (2.0%)	2/3 (66.7%)		1/3 (33.3%)		2/2 (100.0%)	
< 3 min/dose	8 (5.4%)	3/8 (37.5%)		2/8 (25.0%)		3/8 (37.5%)	
3 - < 5 min/dose	30 (20.4%)	14/30 (46.7%)		7/30 (23.3%)		8/25 (32.0%)	

Characteristic	Overall	Survived to 12 months	P-value[a]	VABS-II decreased by ≤ 15 points[b]	P-value[a]	Survived to 12 months with VABS-II ≥ 70[b,c]	P-value[a]
5 - < 8 min/dose	42 (28.6%)	15/42 (35.7%)		7/41 (17.1%)		8/36 (22.2%)	
≥ 8 min/dose	63 (42.9%)	26/63 (41.3%)		14/62 (22.6%)		17/56 (30.4%)	
Unknown	1 (0.7%)	1/1 (100.0%)		1/1 (100.0%)		1/1 (100.0%)	
Number of defibrillation attempts			0.432		0.031		0.077
None	104 (70.7%)	44/104 (42.3%)		17/102 (16.7%)		23/90 (25.6%)	
1	13 (8.8%)	4/13 (30.8%)		3/13 (23.1%)		4/12 (33.3%)	
2	16 (10.9%)	5/16 (31.3%)		5/16 (31.3%)		5/15 (33.3%)	
> 2	14 (9.5%)	8/14 (57.1%)		7/14 (50.0%)		7/11 (63.6%)	
Open-chest cardiac massage			0.023		0.003		0.010
No	104 (70.7%)	37/104 (35.6%)		16/103 (15.5%)		22/92 (23.9%)	
Yes	43 (29.3%)	24/43 (55.8%)		16/42 (38.1%)		17/36 (47.2%)	
Treatment Assigned			0.194		0.050		0.084
Hypothermia	72 (49.0%)	26/72 (36.1%)		11/72 (15.3%)		15/64 (23.4%)	
Normothermia	75 (51.0%)	35/75 (46.7%)		21/73 (28.8%)		24/64 (37.5%)	

[a] All p-values from chi-squared test of no association. Categories of “unknown” were excluded from the analysis of total number of epinephrine doses administered, epinephrine dosing interval, and number of defibrillation attempts.

[b] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.

[c] Only subjects with baseline VABS-II ≥70 were included for this outcome.

Table 3.

Logistic Regression Models with Early Variables[a]

Characteristic	Odds Ratio (95% CI)	P-value
Survival to 12 months[b]		
Post-operative cardiac surgery		0.006
No	Reference	
Yes	2.63 (1.32, 5.24)	
Pre-arrest technology dependence		0.033
No	Reference	
Yes	0.18 (0.04, 0.87)	
Survival to 12 months with VABS-II decreased ≤15 points from baseline[c,d]		
Open-chest cardiac massage		0.009
No	Reference	
Yes	3.09 (1.33, 7.18)	
Gastrointestinal condition		0.047
No	Reference	
Yes	0.27 (0.07, 0.99)	
Treatment Assigned		0.065
Hypothermia	0.45 (0.19, 1.05)	
Normothermia	Reference	
Survival to 12 months with VABS-II ≥ 70[c,e]		
Gastrointestinal condition		0.012
No	Reference	
Yes	0.19 (0.05, 0.69)	
Open-chest cardiac massage		0.023
No	Reference	
Yes	2.67 (1.15, 6.23)	
Treatment Assigned		
Hypothermia	0.49 (0.22, 1.10)	0.084
Normothermia	Reference	

[a] Models include variables available up to the time of randomization in the THAPCA-IH trial (THAPCA day 0).

[b] Modeling is based on the 147 complete records in which all potential predictors and the outcome are non-missing.

[c] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.

[d] Modeling is based on 145 complete records in which all potential predictors and the outcome are non-missing

[e] Modeling is based on 128 complete records in which all potential predictors and the outcome are non-missing.

Table 4.

Logistic Regression Models with Early and Late Variables[a]

Characteristic	Odds ratio (95% CI)	P-value
Survival to 12 months[b]		
Acquired heart disease		0.014
No	Reference	
Yes	0.30 (0.11, 0.78)	
Gastrointestinal condition		0.031
No	Reference	
Yes	0.38 (0.15, 0.92)	
Minimum Lactate (mmol/L)[c]	0.64 (0.49, 0.84)	0.001
Survival to 12 months with VABS-II decreased ≤ 15 points from baseline[d,e]		
Gastrointestinal condition		0.022
No	Reference	
Yes	0.21 (0.06, 0.80)	
Minimum Lactate (mmol/L)[c]	0.68 (0.48, 0.97)	0.035
Open-chest cardiac massage		0.036
No	Reference	
Yes	2.57 (1.06, 6.22)	
Treatment Assigned		0.053
Hypothermia	0.41 (0.17, 1.01)	
Normothermia	Reference	
Survival to 12 months with VABS-II ≥ 70[d,f]		
Gastrointestinal condition		0.006
No	Reference	
Yes	0.17 (0.05, 0.60)	
Minimum Lactate (mmol/L)[c]	0.78 (0.61, 0.99)	0.038

[a] Models include variables available through THAPCA day 2. Day of randomization is day 0.

[b] Modeling is based on the 139 complete records in which all potential predictors and the outcome are non-missing.

[c] Time interval is from 2 hours before to 48 hours after the start of the temperature management intervention.

[d] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.

[e] Modeling is based on the 142 complete records in which all potential predictors and the outcome are non-missing.

[f] Modeling is based on the 122 complete records in which all potential predictors and the outcome are non-missing.