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Clinical paper

The association of early post-resuscitation hypotension with discharge survival following targeted temperature management for pediatric in-hospital cardiac arrest



Alexis A. Topjian^{a,*}, Russell Telford^c, Richard Holubkov^c, Vinay M. Nadkarni^a, Robert A. Berg^a, J. Michael Dean^c, Frank W. Moler^b, for the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) Trial Investigators¹

^a The Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States

^b The CS Mott Children's Hospital, University of Michigan, Ann Arbor, MI, United States

^c The University of Utah, Department of Pediatrics, Salt Lake City, UT, United States

Abstract

Aim: Approximately 40% of children who have an in-hospital cardiac arrest (IHCA) in the US survive to discharge. We aimed to evaluate the impact of post-cardiac arrest hypotension during targeted temperature management following IHCA on survival to discharge.

Methods: This is a secondary analysis of the therapeutic hypothermia after pediatric cardiac arrest in-hospital (THAPCA-IH) trial. "Early hypotension" was defined as a systolic blood pressure less than the fifth percentile for age and sex for patients not treated with extracorporeal membrane oxygenation (ECMO) or a mean arterial pressure less than fifth percentile for age and sex for patients treated with ECMO during the first 6 h of temperature intervention. The primary outcome was survival to hospital discharge.

Results: Of 299 children, 142 (47%) patients did not receive ECMO and 157 (53%) received ECMO. Forty-two of 142 (29.6%) non-ECMO patients had systolic hypotension. Twenty-three of 157 (14.7%) ECMO patients had mean arterial hypotension. After controlling for confounders of interest, non-ECMO patients who had early systolic hypotension were less likely to survive to hospital discharge (40.5% vs. 72%; adjusted OR [aOR] 0.34; 95%CI, 0.12–0.93). There was no difference in survival to discharge by blood pressure groups for children treated with ECMO (30.4% vs. 49.3%; aOR = 0.60; 95%CI, 0.22–1.63).

Conclusions: In this secondary analysis of the THAPCA-IH trial, in patients not treated with ECMO, systolic hypotension within 6 h of temperature intervention was associated with lower odds of discharge survival. Blood pressure groups in patients treated with ECMO were not associated with survival to discharge.

Keywords: Targeted temperature management, Hypotension, Cardiac arrest, Child

* Corresponding author at: Division of Pediatric Critical Care, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, United States.

¹ See Appendix A.

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Introduction

In-hospital cardiac arrest (IHCA) occurs in >6000 children each year in the United States.^{1,2} In recent years, more than 95% of resuscitations occur in ICUs, with approximately 3% receiving extracorporeal cardiopulmonary resuscitation (E-CPR).³ Outcomes from IHCA are improving, however, many survivors of pediatric IHCA sustain short and long-term neurologic morbidity.^{4,5}

The Post-Cardiac Arrest Syndrome is characterized by myocardial dysfunction, a systemic ischemia-reperfusion response, brain injury, and multi-organ dysfunction.^{6–8} Early post-resuscitation systolic hypotension (within 6 h of return of circulation [ROC]) following pediatric cardiac arrest is common and associated with increased rates of in-hospital mortality and unfavorable functional outcomes.⁹ In a secondary analysis of the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trial out-of-hospital cardiac arrest (THAPCA-OH), both the presence and burden of systolic hypotension in the first 6 h after randomization to either therapeutic hypothermia or normothermia was associated with decreased survival to discharge.¹⁰

The THAPCA trial for IHCA (THAPCA-IH) was a randomized controlled trial comparing therapeutic hypothermia (33 °C) to therapeutic normothermia (36.8 °C) for 48 h after pediatric IHCA.¹¹ Approximately 55% of these patients were treated with extracorporeal membrane oxygenation (ECMO). In this secondary analysis of the THAPCA-IH trial, we aim to evaluate the impact of hypotension within 6 h of study intervention on survival to hospital discharge in patients treated with and without ECMO.

Methods

The trial design, protocol and results of the THAPCA-IH trial have been previously published.^{11–14}

THAPCA-IH trial

The THAPCA-IH trial was conducted from September 1, 2009 through February 27, 2015 in 37 pediatric intensive care units in the United States, Canada and United Kingdom.¹¹

Children >48 h and <18 years of age who had an IHCA, received >2 min of chest compressions, and remained mechanically ventilated after ROC were eligible. Major exclusion criteria were inability to randomize within 6 h of ROC and a Glasgow Coma Scale motor response of 5 or 6. The complete list of exclusion criteria is included in the appendix of the original publication.¹¹ Subjects were randomized 1:1 to either therapeutic hypothermia or therapeutic normothermia within 6 h of ROC.

The temperature intervention was initiated as soon as possible after randomization (median 21 min [11, 47]) and maintained for 120 h in both groups: therapeutic hypothermia: 33 °C (range 32–34 °C) or therapeutic normothermia: 36.8 °C (range 36–37.5 °C).¹¹ Subjects were sedated and pharmacologically paralyzed to achieve target temperature using external cooling blankets (Cincinnati Sub-Zero). Subjects who received therapeutic hypothermia were cooled to 32–34 °C, maintained in this range for 48 h, and rewarmed over approximately 16–24 h to 36.8 °C which was actively maintained through hour 120. Subjects randomized to therapeutic normothermia had their core temperature actively maintained in the 36–37.5 °C range through 120 h.

Per the THAPCA protocol, blood pressure was monitored by an arterial catheter. Blood pressures were documented hourly during induction, maintenance and rewarming. There was no explicit hemodynamic management protocol, however, protocol training recommended the clinical team maintain blood pressure in a normal range for age and diagnosis accounting for preload, contractility and afterload. The primary outcome of THAPCA-IH was survival with a favorable neurologic outcome at 12 months.

Hypotension study

All subjects included in the THAPCA-IH trial were eligible for this study. Subjects were excluded if they did not have the temperature intervention initiated or blood pressure measurements available. This secondary study was exempt by The Children's Hospital of Philadelphia Institutional Review Board.

For patients not treated with ECMO (non-ECMO), hypotension was defined as a systolic blood pressure (SBP), diastolic blood pressure (DBP) or mean arterial blood pressure (MAP) less than the fifth percentile derived from normative data for age, sex and height.¹⁵ Mean arterial blood pressure (MAP) normative values were derived using the equation $1/3 \text{ SBP} + 2/3 \text{ DBP}$.¹⁵ Because patients treated with veno-arterial ECMO do not have a pulse, SBP may overestimate hypotension and DBP may underestimate hypotension¹⁶ and therefore, for patients treated with ECMO, hypotension was defined as a MAP less than the fifth percentile for age. Hourly invasive arterial blood pressure measurements (SBP, DBP and MAP) were recorded during the first 6 h of temperature intervention. Blood pressures between ROC and TTM intervention initiation were not available. If a measured height was not available, the 50th percentile for height was used for normalization. This was done for 14 subjects. If the measured height was above the 97th percentile or below the 3rd percentile, the 97th or 3rd percentiles were used, respectively. This was done for 121 subjects. Our primary exposure variable was at least one episode of hypotension during the first 6 h following temperature intervention (early hypotension). Hypotension burden was defined as the percentage of hypotensive measurements during this time period.

Time 0 was defined as the time of initiation of the temperature intervention. Therefore, the 0–6 h blood pressure time period occurred for patients treated with therapeutic hypothermia during induction or induction and maintenance and the corresponding time period for patients treated with therapeutic normothermia.

Data collected in the THAPCA-IH trial included subject demographics, arrest characteristics and post-cardiac arrest care data after intervention initiation. Nights and weekends were defined as previously published.¹⁷ The number of vasoactive agents were counted from the subject's concomitant medication log and included: epinephrine, phenylephrine, norepinephrine, dobutamine, and dopamine. Vasopressin, milrinone and steroids (hydrocortisone, methylprednisolone) were analyzed as yes or no. Indications for medication administration and the timing of medication initiation, dosing, titration or discontinuation within a 24-h period were not documented. Additional variables collected in the THAPCA-IH trial were the hospital location of arrest, previous PICU hospitalization during the current hospitalization, the presence of septic shock with hypotension, whether open chest CPR was performed, the epinephrine dosing interval and the use of ECMO at the time of treatment initiation.

Medications administered were documented by day from randomization (day 0) which concluded at midnight of each day. Day of medication administration was aligned with blood pressure time

period (0–6 h) for each subject. If subjects' time period crossed two days, the higher number of vasoactive agents was used for analysis. Description of vasoactive medications by phase (induction or maintenance) could not be performed because of the variable time to achieve maintenance phase.

Frequencies and percentages or median and quartiles were used to summarize subject, arrest, and post-arrest care characteristics. Univariate associations between characteristics and the presence of hypotension were assessed using the Wilcoxon rank-sum test or the Chi-squared test of no association. A stratified analysis was performed evaluating ECMO and non-ECMO patients as separate cohorts. A forward stepwise multivariate logistic regression model estimated the association between early hypotension and survival to hospital discharge. A two-sided p-value of 0.1 was used as criterion for entering or leaving the model. Other variables entered as potential predictors into the model included: age, gender, pre-existing condition, night or weekend arrest, initial cardiac rhythm, primary cardiac arrest etiology, septic shock with hypotension, presence of IV at time of arrest, intubated at time of arrest, previous PICU admission during current hospitalization, open chest CPR, duration of CPR, epinephrine dosing interval, temperature treatment group, time from ROSC/ROC to treatment initiation, maximum or minimum measured lactate, and medications. The primary outcome was survival to hospital discharge. Analyses were completed using SAS software v9.4 (Cary, NC).

Results

Three hundred twenty-nine subjects were eligible. After applying exclusion criteria, 299 subjects were analyzed; 8 patients did not receive TTM and 22 did not have blood pressure measurements available within the first 6 h of treatment. One hundred forty-two (47%) patients did not receive ECMO at temperature treatment initiation (non-ECMO) and 157 (53%) patients received ECMO at temperature treatment initiation. The median time from ROC to TTM initiation was 4.9 h [4.0, 5.8].

Patients were analyzed in two subgroups, those who did not receive ECMO (non-ECMO) and those who received ECMO.

Non-ECMO patients

During the first 6 h of temperature intervention, 42 of 142 subjects (29.6%) had at least one episode of systolic hypotension, 15 (10.6%) had at least one episode of diastolic hypotension and 20 (14.1%) had at least one episode of mean arterial hypotension. Subjects who had early systolic hypotension were more likely to have a pre-existing renal condition, an initial rhythm of asystole or PEA, a higher minimum lactate level, or to have received therapeutic normothermia (Table 1). They were less likely to be black or white; have a preexisting neurologic condition or acyanotic congenital heart disease, an initial cardiac arrest

Table 1 – Patient and cardiac arrest characteristics by systolic hypotension group (0–6 h) non-ECMO patients.

	Any hypotensive systolic pressure (0–6 h)			p-Value
	Overall (N = 142)	No (N = 100)	Yes (N = 42)	
Age at randomization (months)	17.0 [4.0, 102.0]	16.5 [4.0, 45.5]	29.5 [4.0, 153.0]	0.323 ^a
Male	78 (54.9%)	55 (55.0%)	23 (54.8%)	0.979 ^b
Race				0.046 ^b
Black or African American	40 (28.2%)	30 (30.0%)	10 (23.8%)	
White	81 (57.0%)	60 (60.0%)	21 (50.0%)	
Other/unknown	21 (14.8%)	10 (10.0%)	11 (26.2%)	
Ethnicity				0.976 ^b
Hispanic or Latino	32 (22.5%)	23 (23.0%)	9 (21.4%)	
Not Hispanic or Latino	103 (72.5%)	72 (72.0%)	31 (73.8%)	
Unknown	7 (4.9%)	5 (5.0%)	2 (4.8%)	
Any pre-existing condition	127 (89.4%)	93 (93.0%)	34 (81.0%)	0.033 ^b
Pre-existing conditions				
Cardiac condition	75 (52.8%)	59 (59.0%)	16 (38.1%)	0.023 ^b
Congenital heart disease	68 (47.9%)	56 (56.0%)	12 (28.6%)	0.003 ^b
Congenital acyanotic heart disease	59 (41.5%)	49 (49.0%)	10 (23.8%)	0.005 ^b
Congenital cyanotic heart disease	9 (6.3%)	7 (7.0%)	2 (4.8%)	0.617 ^b
Acquired heart disease	17 (12.0%)	11 (11.0%)	6 (14.3%)	0.582 ^b
Arrhythmia	18 (12.7%)	15 (15.0%)	3 (7.1%)	0.199 ^b
Heart transplant	2 (1.4%)	2 (2.0%)	0 (0.0%)	0.356 ^b
Cyanotic heart disease (baseline sat <85%)	9 (6.3%)	7 (7.0%)	2 (4.8%)	0.617 ^b
Pulmonary hypertension	5 (3.5%)	4 (4.0%)	1 (2.4%)	0.633 ^b
Pulmonary hypertension – associated with CHD	4 (2.8%)	4 (4.0%)	0 (0.0%)	0.189 ^b
Pulmonary hypertension – not associated with CHD	1 (0.7%)	0 (0.0%)	1 (2.4%)	0.122 ^b
Prenatal condition	46 (32.4%)	33 (33.0%)	13 (31.0%)	0.812 ^b
Respiratory condition	58 (40.8%)	40 (40.0%)	18 (42.9%)	0.752 ^b
Immunocompromised	17 (12.0%)	12 (12.0%)	5 (11.9%)	0.987 ^b
Transplant	5 (3.5%)	4 (4.0%)	1 (2.4%)	0.633 ^b
Gastrointestinal condition	52 (36.6%)	38 (38.0%)	14 (33.3%)	0.598 ^b
Endocrine condition	14 (9.9%)	10 (10.0%)	4 (9.5%)	0.931 ^b
Renal condition	18 (12.7%)	9 (9.0%)	9 (21.4%)	0.042 ^b
Neurologic condition	66 (46.5%)	51 (51.0%)	15 (35.7%)	0.096 ^b

Table 1 (continued)

	Any hypotensive systolic pressure (0–6 h)			p-Value
	Overall (N = 142)	No (N = 100)	Yes (N = 42)	
Failure to thrive	22 (15.5%)	16 (16.0%)	6 (14.3%)	0.797 ^b
Other pre-existing condition	55 (38.7%)	41 (41.0%)	14 (33.3%)	0.392 ^b
Night or weekend arrest	54 (38.0%)	35 (35.0%)	19 (45.2%)	0.251 ^b
Initial cardiac arrest rhythm				0.011 ^b
Asystole	13 (9.2%)	4 (4.0%)	9 (21.4%)	
Bradycardia	86 (60.6%)	67 (67.0%)	19 (45.2%)	
Pulseless electrical activity (PEA)	24 (16.9%)	15 (15.0%)	9 (21.4%)	
Ventricular fibrillation or tachycardia	13 (9.2%)	10 (10.0%)	3 (7.1%)	
Unknown	6 (4.2%)	4 (4.0%)	2 (4.8%)	
Primary etiology of cardiac arrest				0.009 ^b
Cardiac	67 (47.2%)	51 (51.0%)	16 (38.1%)	
Respiratory	61 (43.0%)	44 (44.0%)	17 (40.5%)	
Other	11 (7.7%)	5 (5.0%)	6 (14.3%)	
Unknown	3 (2.1%)	0 (0.0%)	3 (7.1%)	
Septic shock with hypotension	11 (7.7%)	10 (10.0%)	1 (2.4%)	0.121 ^b
Location within hospital at time of arrest				0.121 ^b
Emergency department	34 (23.9%)	18 (18.0%)	16 (38.1%)	
Non-intensive care inpatient ward	18 (12.7%)	14 (14.0%)	4 (9.5%)	
Intensive care unit (includes intermediate care)	70 (49.3%)	55 (55.0%)	15 (35.7%)	
Operating room	11 (7.7%)	8 (8.0%)	3 (7.1%)	
Other clinical location (radiology, laboratory, etc.)	7 (4.9%)	4 (4.0%)	3 (7.1%)	
Non-clinical location (cafeteria, waiting room, etc.)	2 (1.4%)	1 (1.0%)	1 (2.4%)	
IV present at the time of arrest	123 (86.6%)	90 (90.0%)	33 (78.6%)	0.028 ^b
Intubated at the time of arrest	76 (53.5%)	53 (53.0%)	23 (54.8%)	0.967 ^b
Previous PICU admission during current hospitalization	17 (12.0%)	13 (13.0%)	4 (9.5%)	0.560 ^b
Number of defibrillation attempts at hospital				0.598 ^b
None	120 (84.5%)	85 (85.0%)	35 (83.3%)	
1 or more	20 (14.1%)	13 (13.0%)	7 (16.7%)	
Unknown	2 (1.4%)	2 (2.0%)	0 (0.0%)	
Open chest compressions performed	11 (7.7%)	8 (8.0%)	3 (7.1%)	0.862 ^b
Duration of chest compressions	8.5 [5.0, 20.0]	8.0 [5.0, 20.5]	10.0 [4.0, 18.0]	0.268 ^b
Duration of chest compressions				0.542 ^b
Less than or equal to 15 min	97 (68.3%)	70 (70.0%)	27 (64.3%)	
More than 15 to less than or equal to 30 min	26 (18.3%)	16 (16.0%)	10 (23.8%)	
More than 30 min	19 (13.4%)	14 (14.0%)	5 (11.9%)	
Total number of doses of epinephrine administered	3.0 [2.0, 5.0]	3.0 [2.0, 5.0]	3.0 [1.0, 5.0]	0.607 ^a
Epinephrine dosing interval (min/dose)				0.940 ^b
No epinephrine recorded	9 (6.3%)	6 (6.0%)	3 (7.1%)	
<3 min/dose	45 (31.7%)	32 (32.0%)	13 (31.0%)	
3 to <5 min/dose	49 (34.5%)	36 (36.0%)	13 (31.0%)	
5 to <8 min/dose	25 (17.6%)	16 (16.0%)	9 (21.4%)	
≥8 min/dose	13 (9.2%)	9 (9.2%)	4 (9.5%)	
Unknown	1 (0.7%)	1 (1.0%)	0 (0.0%)	
Treatment received				0.002 ^b
Hypothermia	76 (53.5%)	62 (62.0%)	14 (33.3%)	
Normothermia	66 (46.5%)	38 (38.0%)	28 (66.7%)	
Time between ROSC/ROC and treatment initiation (hours)	5.2 [4.5, 6.0]	5.1 [4.5, 6.0]	5.3 [4.2, 6.3]	0.569 ^a
Dose of systolic hypotension (0–6 h)	0.0 [0.0, 14.3]	0.0 [0.0, 0.0]	21.1 [14.3, 42.9]	
Maximum measured lactate (0–6 h)	2.7 [1.5, 6.5]	2.6 [1.4, 5.8]	4.8 [1.9, 10.0]	0.122 ^a
Minimum measured lactate (0–6 h)	2.3 [1.4, 5.3]	2.2 [1.3, 4.3]	4.3 [1.7, 7.2]	0.042 ^a
No medications (0–6 h)	42 (29.6%)	31 (31.0%)	11 (26.2%)	0.567 ^b
Vasoactive Agents (0–6 h)				0.631 ^b
0	53 (37.3%)	39 (39.0%)	14 (33.3%)	
1	46 (32.4%)	34 (34.0%)	12 (28.6%)	
2	35 (24.6%)	22 (22.0%)	13 (31.0%)	
3	8 (5.6%)	5 (5.0%)	3 (7.1%)	
Milrinone (0–6 h)	35 (24.6%)	26 (26.0%)	9 (21.4%)	0.564 ^b
Steroids (0–6 h)	28 (19.7%)	17 (17.0%)	11 (26.2%)	0.209 ^b
Vasopressin (0–6 h)	19 (13.4%)	12 (12.0%)	7 (16.7%)	0.456 ^b
Survival to hospital discharge	89 (62.7%)	72 (72.0%)	17 (40.5%)	<0.001 ^b

^a p-Value is based on the Wilcoxon rank-sum test.^b Chi-squared test of no association.

Table 2 – Associations with survival to hospital discharge (non-ECMO subjects).

			p-Value	Survival to hospital discharge		
	Yes (N = 89)	No (N = 53)		Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) ^a	Adjusted p-value
Any systolic hypotension (0–6 h)	17 (19.1%)	25 (47.2%)	<0.001 ^b	0.26 (0.12, 0.56)	0.34 (0.12, 0.93)	0.035
Age at randomization (years)	1.1 [0.3, 5.1]	2.1 [0.6, 11.2]	0.152 ^c	0.96 (0.91, 1.02)		
Sex			0.510 ^b			
Male	47 (52.8%)	31 (58.5%)		Reference		
Female	42 (47.2%)	22 (41.5%)		1.26 (0.63, 2.50)		
Any pre-existing condition	78 (87.6%)	49 (92.5%)	0.367 ^b	0.58 (0.17, 1.92)		
Night or weekend arrest	31 (34.8%)	23 (43.4%)	0.309 ^b	0.70 (0.35, 1.40)		
Initial cardiac arrest rhythm			0.031 ^b			
Asystole	3 (3.4%)	10 (18.9%)		Reference		
Bradycardia	55 (61.8%)	31 (58.5%)		5.91 (1.51, 23.12)		
Pulseless electrical activity (PEA)	17 (19.1%)	7 (13.2%)		8.10 (1.70, 38.60)		
Ventricular fibrillation or tachycardia	10 (11.2%)	3 (5.7%)		11.11 (1.79, 68.89)		
Unknown	4 (4.5%)	2 (3.8%)		6.67 (0.79, 56.22)		
Primary etiology of cardiac arrest			0.874 ^b			
Cardiac	44 (49.4%)	23 (43.4%)		Reference		
Respiratory	37 (41.6%)	24 (45.3%)		0.81 (0.39, 1.66)		
Other	6 (6.7%)	5 (9.4%)		0.63 (0.17, 2.28)		
Unknown	2 (2.2%)	1 (1.9%)		1.05 (0.09, 12.15)		
Septic shock with hypotension	5 (5.6%)	6 (11.3%)	0.219 ^b	0.47 (0.14, 1.61)		
IV present at the time of arrest	79 (88.8%)	44 (83.0%)	0.536 ^b	1.80 (0.63, 5.12)		
Intubated at the time of arrest	47 (52.8%)	29 (54.7%)	0.970 ^b	0.93 (0.47, 1.86)		
Previous PICU admission during current hospitalization	10 (11.2%)	7 (13.2%)	0.726 ^b	0.83 (0.30, 2.33)		
Open chest compressions performed	9 (10.1%)	2 (3.8%)	0.172 ^b	2.87 (0.60, 13.81)		
Duration of chest compressions	8.0 [4.0, 17.0]	10.0 [7.0, 23.0]	0.019 ^c	0.97 (0.94, 0.99)		
Epinephrine dosing interval (min/dose) ^d			0.124 ^b			
No epinephrine recorded	8 (9.0%)	1 (1.9%)		Reference		
<3 min/dose	30 (33.7%)	15 (28.3%)		0.25 (0.03, 2.19)		
3 to < 5 min/dose	32 (36.0%)	17 (32.1%)		0.24 (0.03, 2.04)		
5 to < 8 min/dose	11 (12.4%)	14 (26.4%)		0.10 (0.01, 0.91)		
≥8 min/dose	7 (7.9%)	6 (11.3%)		0.15 (0.01, 1.53)		
Unknown	1 (1.1%)	0 (0.0%)		Reference		
Treatment received			0.410 ^b			
Hypothermia	50 (56.2%)	26 (49.1%)		Reference		
Normothermia	39 (43.8%)	27 (50.9%)		0.75 (0.38, 1.49)		
Time between ROSC/ROC and treatment initiation (hours)	5.0 [4.3, 5.9]	5.6 [4.8, 6.3]	0.011 ^c	0.69 (0.51, 0.92)	0.56 (0.35, 0.88)	0.013
Maximum measured lactate (0–6 h) ^e	2.3 [1.3, 5.4]	5.4 [2.1, 11.7]	<0.001 ^c	0.88 (0.81, 0.95)		
Minimum measured lactate (0–6 h) ^e	2.0 [1.1, 3.5]	4.3 [2.0, 6.4]	<0.001 ^c	0.85 (0.77, 0.94)	0.84 (0.75, 0.95)	0.006
No medications (0–6 h)	30 (33.7%)	12 (22.6%)	0.162 ^b	1.74 (0.80, 3.79)		
Vasoactive agents (0–6 h)			<0.001 ^b			0.008
0	38 (42.7%)	15 (28.3%)		Reference	Reference	
1	35 (39.3%)	11 (20.8%)		1.26 (0.51, 3.10)	3.00 (0.83, 10.88)	
2	12 (13.5%)	23 (43.4%)		0.21 (0.08, 0.52)	0.32 (0.10, 1.04)	
3	4 (4.5%)	4 (7.5%)		0.39 (0.09, 1.79)	6.16 (0.09, 437.66)	
Milrinone (0–6 h)	19 (21.3%)	16 (30.2%)	0.237 ^b	0.63 (0.29, 1.36)	0.28 (0.08, 1.02)	0.054
Steroids (0–6 h)	10 (11.2%)	18 (34.0%)	<0.001 ^b	0.25 (0.10, 0.59)	0.18 (0.05, 0.62)	0.006
Vasopressin (0–6 h)	6 (6.7%)	13 (24.5%)	0.003 ^b	0.22 (0.08, 0.63)		

CHD: congenital heart disease.

^a All variables considered for entry into logistic regression model using forward stepwise selection. Model is based on the 119 records with all variables non-missing.

^b Chi-squared test of no association.

^c Wilcoxon rank-sum test.

^d p-Value and model based on the 141 records where epinephrine dosing interval and survival are non-missing.

^e p-Value and model based on the 120 records where lactate and survival are non-missing.

rhythm of VF, VT or bradycardia, a cardiac etiology of arrest, or an IV in place at the time of arrest (Table 1). There was no difference in age, sex, arrest time of week or day, duration of CPR, number of epinephrine doses, post arrest vasopressor agents, milrinone or vasopressin. Of the 42 subjects with early hypotension, the median “burden of hypotension” per subject was 21% of measurements [IQR: 14.3%, 42.9%]. Of the 31 subjects with a “burden of hypotension” of at least 14.3% of measurements (i.e., 75% of subjects with early hypotension), 11/31 (35%) did not receive a vasoactive infusion.

Eighty nine (62.7%) subjects survived to discharge. Subjects who had early systolic hypotension had lower rates of survival to hospital discharge (hypotension: 17/42 [40.5%] vs no hypotension: 72/100 [72%], $p < 0.001$) (Table 1). On univariable analysis, lower rates of survival to discharge were also associated with early diastolic hypotension (hypotension: 5/15 [33%] vs no hypotension: 84/127 [66%], $p = 0.013$) and mean arterial hypotension (hypotension: 8/20 [40%] vs no hypotension: 81/122 [66%], $p = 0.024$). Due to small sample size multivariable analysis for diastolic and mean arterial blood pressure was not performed. After controlling for time between ROC and treatment initiation, minimum lactate measured, the number of vasoactive agents administered, and milrinone and steroid administration, early systolic hypotension was associated with significantly decreased odds of discharge survival (adjusted OR = 0.34; 95%CI, 0.12–0.93). (Table 2) Early hypotension burden

(0–6 h) was not associated with survival to discharge on multivariable analysis (per 10% increase in burden, adjusted OR = 0.94; 95% CI, 0.70–1.26).

ECMO patients

During the first 6 h of temperature intervention, 23/157 (14.7%) had at least one episode of mean arterial hypotension. Subjects who had mean arterial hypotension were older, more likely to have pre-existing condition of acquired cardiac disease, pulmonary hypertension without congenital heart disease, a respiratory or neurologic condition, or a higher maximum or minimum lactate level (Table 3). There was no difference in sex, race, arrest time of week, initial rhythm, duration of CPR, number of doses of epinephrine administered, or post-arrest vasoactive agents administered. There was no difference in the prevalence of hypotension by TTM intervention. Of the 23 subjects with early hypotension, the median “burden of hypotension” per subject was 50% of measurements [IQR: 25.0%, 66.7%].

Seventy-three (46.5%) subjects survived to discharge. There was no difference in survival to discharge in patients treated with ECMO who had early mean arterial hypotension versus those who did not have mean arterial hypotension (7 [30.4%] vs 66 [49.3%], $p = 0.095$). After controlling for minimum lactate level in the first 6 h following TTM

Table 3 – Patient and cardiac arrest characteristics by MAP hypotension group (0–6 h) ECMO patients.

	Overall (N = 157)	Any hypotensive MAP (0–6 h)		p-Value
		No (N = 134)	Yes (N = 23)	
Age at randomization (months)	7.0 [1.0, 50.0]	6.0 [1.0, 34.0]	62.0 [4.0, 174.0]	0.004 ^a
Male	100 (63.7%)	89 (66.4%)	11 (47.8%)	0.087 ^b
Race				0.898 ^b
Black or African American	45 (28.7%)	38 (28.4%)	7 (30.4%)	
White	94 (59.9%)	80 (59.7%)	14 (60.9%)	
Other/unknown	18 (11.5%)	16 (11.9%)	2 (8.7%)	
Ethnicity				0.203 ^b
Hispanic or Latino	28 (17.8%)	23 (17.2%)	5 (21.7%)	
Not Hispanic or Latino	120 (76.4%)	105 (78.4%)	15 (65.2%)	
Unknown	9 (5.7%)	6 (4.5%)	3 (13.0%)	
Any pre-existing condition	143 (91.1%)	120 (89.6%)	23 (100.0%)	0.104 ^b
Pre-existing conditions				
Cardiac condition	123 (78.3%)	106 (79.1%)	17 (73.9%)	0.577 ^b
Congenital heart disease	104 (66.2%)	92 (68.7%)	12 (52.2%)	0.123 ^b
Congenital acyanotic heart disease	75 (47.8%)	67 (50.0%)	8 (34.8%)	0.177 ^b
Congenital cyanotic heart disease	29 (18.5%)	25 (18.7%)	4 (17.4%)	0.885 ^b
Acquired heart disease	30 (19.1%)	20 (14.9%)	10 (43.5%)	0.001 ^b
Arrhythmia	41 (26.1%)	36 (26.9%)	5 (21.7%)	0.605 ^b
Heart transplant	10 (6.4%)	9 (6.7%)	1 (4.3%)	0.667 ^b
Cyanotic heart disease (baseline sat <85%)	29 (18.5%)	25 (18.7%)	4 (17.4%)	0.885 ^b
Pulmonary hypertension	12 (7.6%)	10 (7.5%)	2 (8.7%)	0.837 ^b
Pulmonary hypertension – associated with CHD	9 (5.7%)	9 (6.7%)	0 (0.0%)	0.201 ^b
Pulmonary hypertension – not associated with CHD	3 (1.9%)	1 (0.7%)	2 (8.7%)	0.010 ^b
Prenatal condition	30 (19.1%)	23 (17.2%)	7 (30.4%)	0.135 ^b
Respiratory condition	42 (26.8%)	30 (22.4%)	12 (52.2%)	0.003 ^b
Immunocompromised	21 (13.4%)	18 (13.4%)	3 (13.0%)	0.960 ^b
Transplant	12 (7.6%)	10 (7.5%)	2 (8.7%)	0.837 ^b
Gastrointestinal condition	44 (28.0%)	37 (27.6%)	7 (30.4%)	0.781 ^b
Endocrine condition	6 (3.8%)	5 (3.7%)	1 (4.3%)	0.887 ^b
Renal condition	20 (12.7%)	16 (11.9%)	4 (17.4%)	0.469 ^b
Neurologic condition	33 (21.0%)	23 (17.2%)	10 (43.5%)	0.004 ^b

(continued on next page)

Table 3 (continued)

	Overall (N = 157)	Any hypotensive MAP (0–6 h)		p-Value
		No (N = 134)	Yes (N = 23)	
Failure to thrive	10 (6.4%)	10 (7.5%)	0 (0.0%)	0.176 ^b
Other pre-existing condition	39 (24.8%)	34 (25.4%)	5 (21.7%)	0.709 ^b
Night or weekend arrest	71 (45.2%)	61 (45.5%)	10 (43.5%)	0.856 ^b
Initial cardiac arrest rhythm				0.309 ^b
Asystole	7 (4.5%)	6 (4.5%)	1 (4.3%)	
Bradycardia	89 (56.7%)	73 (54.5%)	16 (69.6%)	
Pulseless electrical activity (PEA)	37 (23.6%)	35 (26.1%)	2 (8.7%)	
Ventricular fibrillation or tachycardia	19 (12.1%)	15 (11.2%)	4 (17.4%)	
Unknown	5 (3.2%)	5 (3.7%)	0 (0.0%)	
Primary etiology of cardiac arrest				0.358 ^b
Cardiac	119 (75.8%)	104 (77.6%)	15 (65.2%)	
Respiratory	34 (21.7%)	26 (19.4%)	8 (34.8%)	
Other	1 (0.6%)	1 (0.7%)	0 (0.0%)	
Unknown	3 (1.9%)	3 (2.2%)	0 (0.0%)	
Septic shock with hypotension	15 (9.6%)	13 (9.7%)	2 (8.7%)	0.880 ^b
Location within hospital at time of arrest				0.777 ^b
Emergency department	7 (4.5%)	6 (4.5%)	1 (4.3%)	
Non-intensive care inpatient ward	13 (8.3%)	11 (8.2%)	2 (8.7%)	
Intensive care unit (includes intermediate care)	110 (70.1%)	92 (68.7%)	18 (78.3%)	
Operating room	14 (8.9%)	12 (9.0%)	2 (8.7%)	
Other clinical location (radiology, laboratory, etc.)	12 (7.6%)	12 (9.0%)	0 (0.0%)	
Non-clinical location (cafeteria, waiting room, etc.)	1 (0.6%)	1 (0.7%)	0 (0.0%)	
IV present at the time of arrest	149 (94.9%)	127 (94.8%)	22 (95.7%)	0.860 ^b
Intubated at the time of arrest	116 (73.9%)	98 (73.1%)	18 (78.3%)	0.605 ^b
Previous PICU admission during current hospitalization	38 (24.2%)	33 (24.6%)	5 (21.7%)	0.765 ^b
Number of defibrillation attempts at hospital				0.819 ^b
None	119 (75.8%)	102 (76.1%)	17 (73.9%)	
1 or more	38 (24.2%)	32 (23.9%)	6 (26.1%)	
Open chest compressions performed	33 (21.0%)	29 (21.6%)	4 (17.4%)	0.644 ^b
Duration of chest compressions	38.0 [18.0, 57.0]	37.0 [19.0, 54.0]	48.0 [6.0, 79.0]	0.153 ^b
Duration of chest compressions				0.678 ^b
Less than or equal to 15 min	37 (23.6%)	31 (23.1%)	6 (26.1%)	
More than 15 to less than or equal to 30 min	23 (14.6%)	21 (15.7%)	2 (8.7%)	
More than 30 min	97 (61.8%)	82 (61.2%)	15 (65.2%)	
Total number of doses of epinephrine administered	5.0 [2.0, 11.0]	5.0 [2.0, 11.0]	5.0 [2.0, 11.0]	0.938 ^a
Epinephrine dosing interval (min/dose)				0.662 ^b
No epinephrine recorded	6 (3.8%)	5 (3.7%)	1 (4.3%)	
<3 min/dose	26 (16.6%)	23 (17.2%)	3 (13.0%)	
3 to <5 min/dose	31 (19.7%)	27 (20.1%)	4 (17.4%)	
5 to <8 min/dose	40 (25.5%)	36 (26.9%)	4 (17.4%)	
≥ 8 min/dose	54 (34.4%)	43 (32.1%)	11 (47.8%)	
Treatment received				0.943 ^b
Hypothermia	74 (47.1%)	63 (47.0%)	11 (47.8%)	
Normothermia	83 (52.9%)	71 (53.0%)	12 (52.2%)	
Time between ROSC/ROC and treatment initiation (hours)	4.5 [3.6, 5.5]	4.4 [3.5, 5.3]	5.3 [3.6, 5.8]	0.097 ^a
Dose of MAP hypotension (0–6 h)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	50.0 [25.0, 66.7]	
Maximum measured lactate (0–6 h)	6.2 [3.7, 10.9]	5.9 [3.5, 8.7]	10.2 [4.7, 16.0]	0.009 ^a
Minimum measured lactate (0–6 h)	4.2 [2.5, 9.6]	4.0 [2.4, 7.9]	6.3 [4.0, 14.4]	0.008 ^a
No medications (0–6 h)	59 (37.6%)	52 (38.8%)	7 (30.4%)	0.444 ^b
Vasoactive agents (0–6 h)				0.137 ^b
0	83 (52.9%)	71 (53.0%)	12 (52.2%)	
1	43 (27.4%)	38 (28.4%)	5 (21.7%)	
2	27 (17.2%)	22 (16.4%)	5 (21.7%)	
3	3 (1.9%)	3 (2.2%)	0 (0.0%)	
4	1 (0.6%)	0 (0.0%)	1 (4.3%)	
Milrinone (0–6 h)	44 (28.0%)	36 (26.9%)	8 (34.8%)	0.435 ^b
Steroids (0–6 h)	27 (17.2%)	25 (18.7%)	2 (8.7%)	0.242 ^b
Vasopressin (0–6 h)	16 (10.2%)	13 (9.7%)	3 (13.0%)	0.625 ^b
Survival to hospital discharge	73 (46.5%)	66 (49.3%)	7 (30.4%)	0.095 ^b

CHD: congenital heart disease.

^a p-Value is based on the Wilcoxon rank-sum test.^b Chi-squared test of no association.

Table 4 – Associations with survival to hospital discharge (ECMO Subjects).

	Survival to hospital discharge		p-Value	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) ^a	Adjusted p-value
	Yes (N = 73)	No (N = 84)				
Any MAP hypotension (0–6 h)	7 (9.6%)	16 (19.0%)	0.115 ^b	0.45 (0.17, 1.17)	0.60 (0.22, 1.63)	0.317
Age at randomization (years)	0.4 [0.1, 2.1]	1.2 [0.1, 6.2]	0.101 ^c	0.96 (0.90, 1.02)		
Sex			0.870 ^b			
Male	46 (63.0%)	54 (64.3%)		Reference		
Female	27 (37.0%)	30 (35.7%)		1.06 (0.55, 2.03)		
Any pre-existing condition	67 (91.8%)	76 (90.5%)	1.000 ^b	1.18 (0.39, 3.56)		
Night or weekend arrest	33 (45.2%)	38 (45.2%)	1.000 ^b	1.00 (0.53, 1.88)		
Initial cardiac arrest rhythm			0.022 ^b			
Asystole	1 (1.4%)	6 (7.1%)		Reference		
Bradycardia	39 (53.4%)	50 (59.5%)		4.68 (0.54, 40.50)		
Pulseless electrical activity (PEA)	21 (28.8%)	16 (19.0%)		7.88 (0.86, 72.12)		
Ventricular fibrillation or tachycardia	12 (16.4%)	7 (8.3%)		10.29 (1.02, 103.95)		
Unknown	0 (0.0%)	5 (6.0%)		<0.01 (<0.01, >999.99)		
Primary etiology of cardiac arrest			1.000 ^b			
Cardiac	56 (76.7%)	63 (75.0%)		Reference		
Respiratory	16 (21.9%)	18 (21.4%)		1.00 (0.47, 2.15)		
Other	0 (0.0%)	1 (1.2%)		<0.01 (<0.01, >999.99)		
Unknown	1 (1.4%)	2 (2.4%)		0.56 (0.05, 6.37)		
Septic shock with hypotension	7 (9.6%)	8 (9.5%)	1.000 ^b	1.01 (0.35, 2.93)		
IV present at the time of arrest	71 (97.3%)	78 (92.9%)	0.286 ^b	2.73 (0.53, 13.97)		
Intubated at the time of arrest	52 (71.2%)	64 (76.2%)	0.585 ^b	0.77 (0.38, 1.58)		
Previous PICU admission during current hospitalization	17 (23.3%)	21 (25.0%)	0.853 ^b	0.91 (0.44, 1.90)		
Open chest compressions performed	21 (28.8%)	12 (14.3%)	0.031 ^b	2.42 (1.10, 5.36)		
Duration of chest compressions	36.0 [15.0, 52.0]	38.5 [19.5, 61.5]	0.217 ^c	0.99 (0.98, 1.00)		
Epinephrine Dosing Interval (min/dose)			0.758 ^b			
No epinephrine recorded	3 (4.1%)	3 (3.6%)		Reference		
<3 min/dose	10 (13.7%)	16 (19.0%)		0.63 (0.10, 3.72)		
3 to <5 min/dose	17 (23.3%)	14 (16.7%)		1.21 (0.21, 6.99)		
5 to <8 min/dose	17 (23.3%)	23 (27.4%)		0.74 (0.13, 4.12)		
≥8 min/dose	26 (35.6%)	28 (33.3%)		0.93 (0.17, 5.02)		
Treatment received			0.749 ^b			
Hypothermia	33 (45.2%)	41 (48.8%)		Reference		
Normothermia	40 (54.8%)	43 (51.2%)		1.16 (0.62, 2.17)		
Time between ROSC/ROC and treatment initiation (hours)	4.4 [3.5, 5.3]	4.6 [3.7, 5.6]	0.433 ^c	0.89 (0.71, 1.12)		
Maximum measured lactate (0–6 h) ^d	5.4 [3.5, 8.3]	7.3 [3.9, 14.8]	0.068 ^c	0.93 (0.88, 0.99)		
Minimum measured lactate (0–6 h) ^d	3.4 [2.4, 5.6]	5.7 [3.0, 12.4]	0.003 ^c	0.90 (0.84, 0.97)	0.91 (0.84, 0.98)	0.009
No medications (0–6 h)	31 (42.5%)	28 (33.3%)	0.252 ^b	1.48 (0.77, 2.82)		
Vasoactive agents (0–6 h)			0.980 ^b			
0	40 (54.8%)	43 (51.2%)		Reference		
1	19 (26.0%)	24 (28.6%)		0.85 (0.41, 1.78)		
2	13 (17.8%)	14 (16.7%)		1.00 (0.42, 2.38)		
3	1 (1.4%)	2 (2.4%)		0.54 (0.05, 6.16)		
4	0 (0.0%)	1 (1.2%)		<0.01 (<0.01, >999.99)		
Milrinone (0–6 h)	18 (24.7%)	26 (31.0%)	0.476 ^b	0.73 (0.36, 1.48)		
Steroids (0–6 h)	11 (15.1%)	16 (19.0%)	0.533 ^b	0.75 (0.33, 1.75)		
Vasopressin (0–6 h)	7 (9.6%)	9 (10.7%)	1.000 ^b	0.88 (0.31, 2.50)		

MAP: mean arterial hypotension.

^a All variables considered for entry into logistic regression model using forward stepwise selection. Model is based on the 138 records with all variables non-missing.

^b Fisher's exact test.

^c Wilcoxon rank-sum test.

^d p-Value and model based on the 138 records where lactate and survival are non-missing.

intervention, early mean arterial hypotension was not associated with survival to discharge (adjusted OR=0.60; 95%CI, 0.22–1.63) (Table 4). Early hypotension burden (0–6 h) was not associated with survival to discharge on multivariable analysis (per 10% increase in burden, adjusted OR=0.97; 95%CI, 0.89–1.06).

Discussion

In this secondary analysis of the THAPCA-IH trial, for patients not treated with ECMO, systolic hypotension within 6 h of TTM

intervention occurred in at least one quarter of patients and was associated with decreased odds of survival to discharge. For patients who were treated with ECMO, mean arterial hypotension occurred in 15% of patients and was not associated with survival to discharge. These data highlight the differential impact of post-cardiac arrest hemodynamics in patients treated with or without ECMO support.

We evaluated systolic hypotension as the primary exposure in non-ECMO patients based on previous pediatric cardiac arrest literature.^{9,10} A previous study of combined IHCA and OHCA demonstrated that systolic hypotension occurred in more than 56% of patients with 6 h of ROSC and was independently associated with lower odds of survival to discharge.⁹ More recently, a secondary analysis of the THAPCA–OH trial demonstrated that systolic hypotension within 6 h of temperature intervention, approximately 6–12 h following ROSC, occurred in more than one-quarter of patients and was associated with lower rates of survival to hospital discharge.¹⁰ The rate of hypotension in this THAPCA–IH cohort is similar to the THAPCA–OH rate, although in this current study, blood pressures were measured at a range of 4–10 h following ROSC.

In this study, 62.7% of non-ECMO patients survived to discharge, compared to 38.7% in the THAPCA–OH cohort.¹⁰ Survival rates from IHCA are higher than OHCA, in part due to ischemic time, differences in cause of arrest and in cardiac arrest interventions, such as pre-existing IV access, early CPR from trained care providers and CPR quality guidance.^{18,19} It is presumed that more severe ischemia and hypoxia may be a cause of post-cardiac arrest hypotension, raising the concern that post-cardiac arrest hypotension may be a non-modifiable marker of injury. However, in this in-hospital cohort, early hypotension was not associated with the duration of CPR or number of epinephrine doses. Higher post-cardiac arrest lactate levels, markers of hypoxic-ischemic injury, were associated with both hypotension and outcomes in this study and the THAPCA–OH study.^{20,21} Despite the elevated lactate levels in both THAPCA–IH and THAPCA–OH, almost twice as many survived to discharge among the patients who suffered an IHCA compared with an OHCA, despite the similar prevalence of hypotension. This provides further evidence that hypotension may be a marker of injury severity, but also may be a modifiable risk factor with appropriate treatment.

For non-ECMO patients with at least one episode of hypotension, the median “burden” of hypotension was 21% of measured blood pressures. Of patients with any hypotension, one-third did not receive a vasoactive infusion. The American Heart Association Pediatric Advance Life Support Guidelines recommend, “that parental fluids and/or inotropes or vasoactive drugs be used to maintain a systolic blood pressure greater than fifth percentile for age.”²² A growing body of adult literature demonstrates a dose effect of post-cardiac arrest blood pressure on outcomes, showing that it is not just presence or absence but how low for how long.²³ A recent assessment of “hypotension exposure index (HEI)” which subtracted the dose of hypotension from a normal adult MAP of 65 mmHg demonstrated that a lower HEI (less hypotension) was associated with higher rates of survival to discharge.²⁴ This suggests that treatment to target these indices over time may impact outcome. We were unable to analyze our data in this manner because pediatric blood pressures differ by age and therefore must be normalized for comparison across age groups making a continuous measure difficult to quantify for appropriate analyses.¹⁵

More than half the patients in this cohort were treated with ECMO. For patients treated with veno-arterial ECMO, we used MAP to evaluate hypotension because many patients lack substantial pulsatile blood flow initially with the SBP similar to the MAP. Mean arterial hypotension occurred in 14.7% of patients, and at least 7% of patients were hypotensive for at least half of the study period. More than 60% of patients treated with ECMO received at least 30 min of CPR and had maximum lactate levels of 10.2 [4.7, 16] as compared to the non-ECMO group of whom 68% received less than 15 min of CPR with maximum lactate levels of 4.3 [1.7, 7.2]. Despite more severe cardiac arrest markers, patients treated with ECMO had lower rates of hypotension (14.1% versus 56% in the non-ECMO group.) This may be due to (1) continuous mechanical support from ECMO providing higher levels of cardiac output than a non-ECMO supported native heart with myocardial dysfunction, (2) patients treated with ECMO having less of a systemic ischemic perfusion response or (3) the blood pressure cutpoints selected for comparison in ECMO and Non ECMO groups in our study were not equivalent to compare the impact of blood pressure on outcome.

In this cohort of pediatric cardiac arrests treated with ECMO, mean arterial hypotension was not associated with survival to discharge. While data demonstrate that the use of ECMO for pediatric cardiac arrest is associated with higher survival to discharge, significant confounding by indication has been difficult to identify.²⁵ The physiology of post-arrest care on ECMO has not been well delineated. ECMO support can provide a near normal or normal cardiac output. Cardiac output is impacted by multiple factors including preload, afterload and contractility. Recent adult cardiac arrest literature demonstrates that higher MAP is associated with improved rates of survival and neurologic outcomes, however, ECMO treated patients were not a subgroup.^{26,27} Further delineation of the post-arrest care of this subset of patient in the future will be important.

This study had several limitations. First, this study was a secondary analysis of a randomized controlled trial of TTM of a pediatric IHCA population of which 50% received ECMO and therefore it may not be generalizable to all IHCA survivors treated in pediatric intensive care units. Furthermore, this analysis was on a subpopulation of severe cardiac arrests who were comatose with a post cardiac arrest GCS motor score of <5. Second, blood pressure data were not collected between ROC and intervention, approximately the first 4 h after ROC, a potentially important time when blood pressure and treatment may impact outcomes. Third, vasoactive medication infusion dosing and timing were not available and our data are limited to ordered medications rather than medications confirmed to be administered. Fourth, echocardiogram and ECMO data were not available to characterize myocardial function and cardiac output. Finally, this is an observational study and thus cannot determine cause and effect.

Conclusions

In this secondary analysis of the THAPCA–IH trial, 29.6% of subjects not treated with ECMO had hypotension within 6 h of study intervention. Early post-arrest hypotension in patients not treated with ECMO was associated with a lower odds of discharge survival, even after adjusting for covariates of interest.

Conflict of interest

The authors have no conflict of interest.

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Appendix A

Frank W. Moler^a, Kathleen L. Meert^b, Jamie S. Hutchinson^c, Christopher J.L. Newth^d, Kimberly S. Bennett^e, John T. Berger^f, Alexis A. Topjian^g, Jose A. Pineda^h, Joshua D. Kochⁱ, Charles L. Schleien^j, Heidi J. Dalton^k, George Ofori-Amanfo^l, Denise M. Goodman^m, Ericka L. Finkⁿ, Patrick McQuillen^o, Jerry J. Zimmerman^p, Neal J. Thomas^q, Elise W. van der Jagt^r, Melissa B. Porter^s, Michael T. Meyer^t, Rick Harrison^u, Nga Pham^v, Adam J. Schwarz^w, Jeffrey E. Nowak^x, Jeffrey Alten^y, Derek S. Wheeler^z, Utpal S. Bhalala^A, Karen Lidsky^B, Eric Lloyd^C, Mudit Mathur^D, Samir Shah^E, Theodore Wu^F, Andreas A. Theodorou^G, Ronald C. Sanders Jr.^H, Faye S. Silverstein^a, James R. Christensen^I, Beth S. Slomine^J, Victoria L. Pemberton^J, Brittan Browning^K, Richard Holubkov^K, J. Michael Dean^K

^a C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, United States

^b Children's Hospital of Michigan, Detroit, United States

^c Hospital for Sick Children, Toronto, Ontario, Canada

^d Children's Hospital Los Angeles, Los Angeles, CA, United States

^e Primary Children's Hospital, Salt Lake City, UT, United States

^f Children's National Medical Center, Washington, DC, United States

^g Children's Hospital of Philadelphia, Philadelphia, PA, United States

^h Washington University, St Louis, MO, United States

ⁱ Children's Medical Center Dallas, University of Texas Southwestern Medical School, United States

^j Morgan Stanley Children's Hospital-Columbia University Medical Center, New York, NY, United States

^k Phoenix Children's Hospital, Phoenix, AZ, United States

^l Duke Children's Hospital, Durham, NC, United States

^m Anne and Robert Lurie Children's Hospital of Chicago, Chicago, IL, United States

ⁿ University of Pittsburgh Medical Center, Pittsburgh, PA, United States

^o University of California, San Francisco Benioff Children's Hospital, United States

^p Seattle Children's Hospital, Seattle, WA, United States

^q Penn State Children's Hospital, Hershey, PA, United States

^r University of Rochester Medical Center/Golisano Children's Hospital, Rochester, NY, United States

^s Kosair Charities Pediatric Clinical Research Unit, Department of Pediatrics, University of Louisville and the Kosair Children's Hospital, Louisville, KY, United States

^t Medical College of Wisconsin, Milwaukee, United States

^u Mattel Children's Hospital UCLA, University of California, Los Angeles, United States

^v Children's Healthcare of Atlanta, Atlanta, GA, United States

^w Children's Hospital of Orange County, Orange, CA, United States

^x Children's Hospitals and Clinics of Minnesota, Minneapolis, United States

^y The Children's Hospital of Alabama, Birmingham, United States

^z Cincinnati Children's Hospital, Cincinnati, OH, United States

^A Johns Hopkins Children's Center, Baltimore, MD, United States

^B Rainbow Babies and Children's Hospital, Cleveland, OH, United States

^C Nationwide Children's Hospital, Columbus, OH, United States

^D Loma Linda University Children's Hospital, Loma Linda, CA, United States

^E University of Tennessee Health Science Center, Memphis, United States

^F University of Texas Health Sciences Center at San Antonio, United States

^G Diamond Children's Medical Center, Tucson, AZ, United States

^H Arkansas Children's Hospital, Little Rock, United States

^I Outcome Center, Kennedy Krieger Institute, and Johns Hopkins University, School of Medicine, Baltimore, MD, United States

^J National Heart, Lung, and Blood Institute, Bethesda, MD, United States

^K Data Coordinating Center, University of Utah, Salt Lake City, United States

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