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Clinical paper

Paediatric in-hospital cardiac arrest: Factors associated with survival and neurobehavioural outcome one year later

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ABSTRACT

Objective: To investigate clinical characteristics associated with 12-month survival and neurobehavioural function among children recruited to the Therapeutic Hypothermia after Paediatric Cardiac Arrest In-Hospital trial.
Methods: Children (n = 329) with in-hospital cardiac arrest who received chest compressions for ≥2 min, were comatose, and required mechanical ventilation after return of circulation were included. Neurobehavioural function was assessed using the Vineland Adaptive Behaviour Scales, second edition (VABS-II) at baseline (reflecting pre-arrest status) 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.
Results: Asystole as the initial arrest rhythm, administration of >4 adrenaline doses, and higher post-arrest blood lactate concentration were independently associated with lower 12-month survival; an adrenaline dosing interval of 3–<5 min and open chest compressions were independently associated with greater 12-month survival. Use of extracorporeal membrane oxygenation (ECMO) and higher blood lactate were independently associated with lower 12-month survival with VABS-II decreased by ≤15 points from baseline; open chest compressions was independently associated with greater 12-month survival with VABS-II decreased by ≤15 points. Asystole as the initial rhythm, use of ECMO, and higher blood lactate were independently associated with lower 12-month survival with VABS-II ≥70; open chest compressions was independently associated with greater 12-month survival with VABS-II ≥70.
Conclusions: Cardiac arrest and resuscitation factors are associated with long-term survival and neurobehavioural function among children who are comatose after in-hospital arrest.

INTRODUCTION

Cardiac arrest in children is an uncommon event that often leads to death or poor functional outcome among survivors. Cardiac arrest characteristics, interventions and outcomes differ between arrests occurring in in-hospital and out-of-hospital settings [1–3]. For example, physiologic monitoring, shorter response times, and the presence of skilled personnel are more typical of in-hospital than out-of-hospital arrests. Outcomes of in-hospital cardiac arrest are better than out-of-hospital arrest, yet only about a third of children with in-hospital arrest survive to discharge with good functional outcome [2,4,5].

Most in-hospital paediatric cardiac arrests occur in intensive care units (ICU) [4]. Incidence rates are estimated at 1%–3% for children in paediatric ICU [6–8] and 3% to 6% in cardiac ICU [9–11]. Epidemiologic studies of paediatric in-hospital cardiac arrest are primarily based on registries with voluntary reporting of data, or are retrospective single institution studies [4–5,7–11]. Outcomes

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have generally been limited to mortality at hospital discharge and functional status among survivors using subjective measures such as the Paediatric Cerebral Performance Category (PCPC) scale [12]. A recent meta-analysis of paediatric cardiac arrest studies concluded there is a need for collaborative, prospective and potentially predictive data on paediatric cardiac arrest to more clearly understand predictors of survival and long-term neurological outcome [13].

The Therapeutic Hypothermia after Paediatric Cardiac Arrest (THAPCA) trials were two independent, parallel multicentre randomised controlled trials comparing the efficacy of therapeutic hypothermia versus therapeutic normothermia on survival with good neurobehavioural outcome one year after paediatric cardiac arrest in the in-hospital (THAPCA-IH) and out-of-hospital (THAPCA-OH) settings [14,15]. Children included in the THAPCA trials were comatose, required mechanical ventilation after return of circulation, and were at high risk for neurologic injury. Neurobehavioural function was evaluated longitudinally in the THAPCA trials from baseline (reflecting pre-arrest status) through 12 months post-arrest using the Vineland Adaptive Behaviour Scales, second edition (VABS-II) [16]. Therapeutic hypothermia, as compared to therapeutic normothermia, did not confer a significant benefit in survival with favourable functional outcome at 12 months post-arrest in either the in-hospital or out-of-hospital trial. We previously described clinical characteristics associated with 12-month survival and neurobehavioural function among children with out-of-hospital cardiac arrest recruited to the THAPCA-OH trial [17]. In this study, we investigate clinical characteristics associated with 12-month survival and neurobehavioural function among children with in-hospital cardiac arrest recruited to the THAPCA-IH trial.

METHODS

Design and setting

This study is a secondary analysis of data collected for the THAPCA-IH trial.[14] Thirty-seven children's hospitals in the United States, Canada, and the United Kingdom recruited children between September 1, 2009 and February 27, 2015. Details of the trial were previously published [14,18–20]. The study was approved by the institutional review boards at all study sites and the Data Coordinating Centre at the University of Utah. Parental permission was obtained for all participants.

Participants

Children eligible for the THAPCA-IH trial were >48 h and <18 years of age, had a cardiac arrest that began within the walls of a hospital, received chest compressions for ≥2 min, and required mechanical ventilation after return of circulation. Major exclusion criteria included inability to be randomised within 6 h of return of circulation, a Glasgow Coma Scale motor score of 5 or 6 [21], and a decision to withhold aggressive treatment. A full list of exclusion criteria was previously published [14,18]. Of 2791 children meeting inclusion criteria, 329 were randomised to therapeutic hypothermia or therapeutic normothermia within 6 h of return of circulation.

Independent Variables

Data were collected by trained research coordinators at the time of study entry by medical record review and direct interaction with parents and clinicians. Data included child demographics, pre-existing conditions, body habitus, primary aetiology of arrest, presence of an intravenous catheter or endotracheal tube at the time of arrest, initial arrest rhythm, duration of chest compressions, number of doses of adrenaline (epinephrine) during the arrest, adrenaline dosing interval, number of defibrillation attempts, use of open chest cardiac compressions, use of extracorporeal membrane oxygenation (ECMO) at the time of initiation of the THAPCA-IH study intervention, day and time of arrest, location of arrest within the hospital, previous ICU admissions during the hospitalisation in which the arrest occurred, and laboratory values recorded post-arrest but prior to the THAPCA-IH study intervention.

Child demographics included age, sex, race and ethnicity. Pre-existing conditions included cardiac, respiratory, neurologic, gastrointestinal, prenatal, pulmonary hypertension, and other conditions. Body habitus was evaluated using body mass index-for-age (BMI-for-age) percentiles for children ≥2 years of age, and weight-for-length percentiles for children <2 years of age [22]. If a subject's actual length was not available (n = 15), the median length-for-age adjusted for sex was used to determine the BMI-for-age or weight-for-length percentile. Children were considered obese if their BMI-for-age or weight-for-length was ≥95th percentile, and underweight if <5th percentile as recommended by the U.S. Centres for Disease Control and Prevention [22]. Primary aetiology of arrest was categorised as cardiovascular, respiratory, or other. Initial arrest rhythm was categorised as bradycardia, pulseless electrical activity (PEA), ventricular tachycardia/fibrillation (VF/VT), asystole, or unknown. The adrenaline dosing interval was defined as the duration of chest compressions divided by the total number of adrenaline doses administered during chest compressions. Day of arrest was categorised as weekday or weekend. Weekday was defined as Monday 12:00 AM to Friday 11:59 PM and weekend as Saturday 12:00 AM to Sunday 11:59 PM. Time of arrest was categorised as daytime or night time. Daytime was defined as 7:00 AM to 6:59 PM and night time as 7:00 PM to 6:59 AM. Location of arrest was categorised as emergency department, non-ICU hospital ward, ICU (including intermediate care), operating room, other clinical location (e.g., radiology suite) or non-clinical location (e.g., cafeteria).

Outcomes

Neurobehavioural function was assessed using the VABS-II [16]. The VABS-II is a caregiver report measure of adaptive behaviour from birth to adulthood. Adaptive behaviour is defined as performance on daily life activities necessary for personal and social independence. VABS-II domains include communication, daily living, socialisation and motor skills. The number of tasks that can be performed in each domain is standardised for the child's age. In normative U.S. populations, the mean VABS-II is 100, and the standard deviation is 15. 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. Baseline VABS-II assessments (reflecting pre-arrest status) were completed by parents with the assistance of research coordinators at the sites within 24 h of randomisation into the THAPCA-IH trial. Parents completed 12-month VABS-II assessments by telephone with interviewers from the Kennedy Krieger Institute.

Statistical analyses

Clinical characteristics were summarised using frequencies and percentages. Univariate associations between these characteristics and the outcomes were examined using either the chi-square test of no association or the Cochran-Armitage test for trend. In these associations, categories of "unknown" were excluded from the analysis only for the body habitus, number of adrenaline doses administered, adrenaline dosing interval, and number of defibrillation attempts. Associations between laboratory values and outcomes

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]	P-value[a]
Total	329	155/327 (47.4%)		93/317 (29.3%)		96/257 (37.4%)	
Age in years			0.093		0.244		0.557
<1 year	165 (50.2%)	86/164 (52.4%)		48/158 (30.4%)		52/133 (39.1%)	
1–4 years	77 (23.4%)	33/76 (43.4%)		24/75 (32.0%)		20/59 (33.9%)	
5–12 years	48 (14.6%)	20/48 (41.7%)		15/48 (31.3%)		16/38 (42.1%)	
>13 years	39 (11.9%)	16/39 (41.0%)		6/36 (16.7%)		8/27 (29.6%)	
Sex			0.439		0.716		0.130
Male	196 (59.6%)	89/195 (45.6%)		54/189 (28.6%)		51/152 (33.6%)	
Female	133 (40.4%)	66/132 (50.0%)		39/128 (30.5%)		45/105 (42.9%)	
Race			0.870		0.712		0.266
Asian	9 (2.7%)	5/9 (55.6%)		4/9 (44.4%)		4/7 (57.1%)	
Black or African American	97 (29.5%)	47/97 (48.5%)		26/92 (28.3%)		26/73 (35.6%)	
White	189 (57.4%)	86/188 (45.7%)		52/183 (28.4%)		53/152 (34.9%)	
Other/Unknown	34 (10.3%)	17/33 (51.5%)		11/33 (33.3%)		13/25 (52.0%)	
Ethnicity			0.675		0.661		0.641
Hispanic or Latino	66 (20.1%)	30/66 (45.5%)		18/65 (27.7%)		18/51 (35.3%)	
Not Hispanic or Latino	245 (74.5%)	118/244 (48.4%)		72/236 (30.5%)		75/193 (38.9%)	
Unknown	18 (5.5%)	7/17 (41.2%)		3/16 (18.8%)		3/13 (23.1%)	
Body Habitus			0.981		0.723		0.622
Underweight	67 (20.4%)	33/67 (49.3%)		20/62 (32.3%)		15/47 (31.9%)	
Normal/Overweight	205 (62.3%)	94/203 (46.3%)		58/199 (29.1%)		65/167 (38.9%)	
Obese	52 (15.8%)	26/52 (50.0%)		15/51 (29.4%)		15/41 (36.6%)	
Unknown	5 (1.5%)	2/5 (40.0%)		0/5 (0.0%)		1/2 (50.0%)	
Any pre-existing condition	299 (90.9%)	139/298 (46.6%)	0.380	85/291 (29.2%)	0.867	85/231 (36.8%)	0.582
Cardiac condition	220 (66.9%)	101/219 (46.1%)	0.509	64/216 (29.6%)	0.867	65/176 (36.9%)	0.837
Respiratory condition	109 (33.1%)	50/108 (46.3%)	0.779	30/105 (28.6%)	0.833	27/79 (34.2%)	0.483
Neurologic condition	105 (31.9%)	45/104 (43.3%)	0.307	32/103 (31.1%)	0.639	19/59 (32.2%)	0.351
Gastrointestinal condition	100 (30.4%)	40/99 (40.4%)	0.095	25/97 (25.8%)	0.355	17/68 (25.0%)	0.014
Prenatal condition	86 (26.1%)	38/86 (44.2%)	0.487	24/86 (27.9%)	0.733	22/58 (37.9%)	0.918
Pulmonary hypertension	20 (6.1%)	4/19 (21.1%)	0.018	4/19 (21.1%)	0.413	3/13 (23.1%)	0.275
Other pre-existing condition	148 (45.0%)	64/147 (43.5%)	0.206	38/140 (27.1%)	0.445	37/109 (33.9%)	0.332
Single Ventricle	73 (22.2%)	30/73 (41.1%)	0.221	18/72 (25.0%)	0.358	18/58 (31.0%)	0.258

[a] P-values for Body Habitus and Age Category from two-sided Cochran-Armitage test for trend. All other p-values from chi-squared test of no association.
[b] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.

were assessed using the Wilcoxon rank-sum test. Logistic regression models were run for each outcome to estimate odds ratios and 95% confidence intervals. For these models, the clinical characteristics that had a univariate p-value <0.1 were entered into the model using a backward selection approach and only those with a $p < 0.05$ were retained in the final model. All analyses were completed using SAS software v9.4 (Cary, NC).

Results

Of 329 children, 196 (59.6%) were male, 189 (57.4%) were White, and 165 (50.2%) were <1 year of age (Table 1). Two hundred and ninety-nine (90.9%) had at least one pre-existing condition; 220 (66.9%) had a pre-existing cardiac condition (188 of which were congenital heart disease), 109 (33.1%) respiratory, 105 (31.9%) neurologic, 100 (30.4%) gastrointestinal, 86 (26.1%) prenatal, 20 (6.1%) pulmonary hypertension, and 148 (45.0%) other condition. Sixty-seven (20.4%) were underweight and 52 (15.8%) were obese.

Primary aetiology of arrest was cardiovascular for 214 (65.0%), respiratory for 100 (30.4%) and other for 15 (4.6%) (Table 2). Three hundred and one (91.5%) had intravenous access and 213 (64.7%) were intubated at the time of arrest. Initial arrest rhythm was bradycardia for 189 (57.4%), PEA for 69 (21.0%), VF/VT for 34 (10.3%) and asystole for 24 (7.3%). The duration of chest compressions was ≤15 min for 138 (41.9%), >15–≤30 min for 53 (16.1%) and >30 min for 138 (41.9%). The number of adrenaline doses was >4 for 156 (47.4%) and the adrenaline dosing interval was 3 to <5 min for 85 (25.8%). Sixty-seven (20.3%) received at least one defibrillation attempt. Fifty-six (17.0%) received open-chest compressions; of these 53 (94.6%) had a pre-existing cardiac condition, 51 (91.0%) had congenital heart disease, and 44 (78.5%) went on to receive ECMO. ECMO was utilised in a total of 180 (54.7%) at the time of initiation of the THAPCA-IH study intervention. Arrest occurred on a weekday for 272 (82.7%), and during the daytime for 226 (68.7%). Arrest occurred in an ICU for 202 (61.4%). Fifty-nine (17.9%) had a previous ICU admission during the hospitalisation in which the arrest occurred. Post-arrest laboratory values showed a median pH of 7.3 (Q_1, Q_3 7.3, 7.4), blood glucose concentration of 10.2 mmol/L (Q_1, Q_3 6.4, 15.2 mmol/L) (183 mg/dL (Q_1, Q_3 116, 274 mg/dL)) and blood lactate concentration of 6.6 mmol/L (Q_1, Q_3 2.8, 11.9 mmol/L) (Supplemental Material 1).

Univariate associations

The presence of pre-existing pulmonary hypertension was associated with lower 12-month survival, and pre-existing gastrointestinal condition was associated with lower 12-month survival with VABS-II ≥70 (Table 1). Asystole as the initial cardiac arrest rhythm was associated with lower 12-month survival and lower 12-month survival with VABS-II ≥70 (Table 2). Longer duration of chest compressions, >4 doses of adrenaline, and use of ECMO were associated with lower 12-month survival, 12-month survival with VABS-II decrease by ≤15 points from baseline, and 12-month survival with VABS-II ≥70; adrenaline dosing interval 3–<5 min was associated with greater 12-month survival, 12-month survival with VABS-II decrease by ≤15 points, and 12-month survival with VABS-II ≥70. Open chest compressions was associated with greater 12-month survival with VABS-II decrease by ≤15 points from baseline and 12-month survival with VABS-II ≥70. Associations between post-arrest laboratory values and outcomes are shown in Supplemental Material 1. Lower blood pH and platelet count, and higher blood lactate concentration, aspartate aminotransferase

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]	P-value[a]
Total	329	155/327 (47.4%)		93/317 (29.3%)		96/257 (37.4%)	
Primary aetiology of cardiac arrest			0.675		0.332		0.901
Cardiovascular event[c]	214 (65.0%)	99/213 (46.5%)		59/206 (28.6%)		63/171 (36.8%)	
Respiratory event	100 (30.4%)	50/99 (50.5%)		32/97 (33.0%)		29/74 (39.2%)	
Other	15 (4.6%)	6/15 (40.0%)		2/14 (14.3%)		4/12 (33.3%)	
Initial cardiac arrest rhythm			0.003		0.368		<.001
Asystole	24 (7.3%)	4/24 (16.7%)		3/24 (12.5%)		2/17 (11.8%)	
Bradycardia	189 (57.4%)	85/187 (45.5%)		53/181 (29.3%)		48/143 (33.6%)	
Pulseless electrical activity	69 (21.0%)	39/69 (56.5%)		21/67 (31.3%)		25/58 (43.1%)	
Ventricular fibrillation or tachycardia	34 (10.3%)	22/34 (64.7%)		12/33 (36.4%)		20/30 (66.7%)	
Unknown	13 (4.0%)	5/13 (38.5%)		4/12 (33.3%)		1/9 (11.1%)	
Duration of chest compressions			0.012		0.001		0.004
Less than or equal to 15 min	138 (41.9%)	78/137 (56.9%)		52/129 (40.3%)		51/103 (49.5%)	
More than 15 to less than or equal to 30 min	53 (16.1%)	23/53 (43.4%)		14/53 (26.4%)		11/37 (29.7%)	
More than 30 min	138 (41.9%)	54/137 (39.4%)		27/135 (20.0%)		34/117 (29.1%)	
Total number of doses of adrenaline administered			0.003		0.002		0.011
0	15 (4.6%)	11/15 (73.3%)		9/14 (64.3%)		8/12 (66.7%)	
1	38 (11.6%)	22/38 (57.9%)		14/35 (40.0%)		12/27 (44.4%)	
2	52 (15.8%)	28/51 (54.9%)		18/51 (35.3%)		20/43 (46.5%)	
3	36 (10.9%)	20/36 (55.6%)		11/31 (35.5%)		12/25 (48.0%)	
4	31 (9.4%)	18/31 (58.1%)		10/30 (33.3%)		11/26 (42.3%)	
More than 4	156 (47.4%)	55/155 (35.5%)		30/155 (19.4%)		32/123 (26.0%)	
Unknown	1 (0.3%)	1/1 (100.0%)		1/1 (100.0%)		1/1 (100.0%)	
Adrenaline Dosing Interval[d]			0.004		0.022		0.005
No adrenaline recorded	15 (4.6%)	11/15 (73.3%)		9/14 (64.3%)		8/12 (66.7%)	
<3 min/dose	77 (23.4%)	35/76 (46.1%)		23/74 (31.1%)		23/56 (41.1%)	
3–<5 min/dose	85 (25.8%)	51/85 (60.0%)		26/81 (32.1%)		32/66 (48.5%)	
5–<8 min/dose	72 (21.9%)	25/71 (35.2%)		16/70 (22.9%)		14/56 (25.0%)	
≥8 min/dose	79 (24.0%)	32/79 (40.5%)		18/77 (23.4%)		18/66 (27.3%)	
Unknown	1 (0.3%)	1/1 (100.0%)		1/1 (100.0%)		1/1 (100.0%)	
Time of arrest[e]			0.423		0.355		0.531
Day	226 (68.7%)	110/225 (48.9%)		68/220 (30.9%)		68/176 (38.6%)	
Night	103 (31.3%)	45/102 (44.1%)		25/97 (25.8%)		28/81 (34.6%)	
Day of arrest[f]			0.774		0.890		0.758
Weekday	272 (82.7%)	127/270 (47.0%)		77/261 (29.5%)		79/209 (37.8%)	
Weekend	57 (17.3%)	28/57 (49.1%)		16/56 (28.6%)		17/48 (35.4%)	
Location of arrest within hospital			0.962		0.921		0.514
Emergency department	43 (13.1%)	21/42 (50.0%)		13/42 (31.0%)		10/29 (34.5%)	
Non-intensive care inpatient ward	34 (10.3%)	15/34 (44.1%)		9/32 (28.1%)		7/27 (25.9%)	
Intensive care unit (includes intermediate care)	202 (61.4%)	97/201 (48.3%)		58/194 (29.9%)		63/159 (39.6%)	
Operating room	27 (8.2%)	13/27 (48.1%)		7/26 (26.9%)		9/20 (45.0%)	
Other clinical location	20 (6.1%)	8/20 (40.0%)		6/20 (30.0%)		7/19 (36.8%)	
Non-clinical location	3 (0.9%)	1/3 (33.3%)		0/3 (0.0%)		0/3 (0.0%)	
IV present at the time of arrest			0.601		0.702		0.071
No	25 (7.6%)	10/25 (40.0%)		5/23 (21.7%)		3/20 (15.0%)	
Yes	301 (91.5%)	143/299 (47.8%)		87/291 (29.9%)		93/236 (39.4%)	
Unable to determine	3 (0.9%)	2/3 (66.7%)		1/3 (33.3%)		0/1 (0.0%)	
Intubated at the time of arrest			0.365		0.085		0.422
No	112 (34.0%)	56/111 (50.5%)		34/106 (32.1%)		33/91 (36.3%)	
Yes	213 (64.7%)	96/212 (45.3%)		56/207 (27.1%)		62/165 (37.6%)	
Unable to determine	4 (1.2%)	3/4 (75.0%)		3/4 (75.0%)		1/1 (100.0%)	
Previous ICU admission during current hospitalisation			0.253		0.066		0.284
No	270 (82.1%)	131/268 (48.9%)		82/260 (31.5%)		82/211 (38.9%)	
Yes	59 (17.9%)	24/59 (40.7%)		11/57 (19.3%)		14/46 (30.4%)	
Number of defibrillation attempts			0.935		0.793		0.278
None	260 (79.0%)	124/259 (47.9%)		72/250 (28.8%)		69/199 (34.7%)	
1	22 (6.7%)	9/22 (40.9%)		7/21 (33.3%)		7/18 (38.9%)	
2	23 (7.0%)	10/23 (43.5%)		7/23 (30.4%)		10/22 (45.5%)	
3	8 (2.4%)	4/8 (50.0%)		2/8 (25.0%)		4/8 (50.0%)	
4	6 (1.8%)	3/6 (50.0%)		1/6 (16.7%)		2/2 (100.0%)	
More than 4	8 (2.4%)	5/8 (62.5%)		4/8 (50.0%)		4/7 (57.1%)	
Unknown	2 (0.6%)	0/1 (0.0%)		0/1 (0.0%)		0/1 (0.0%)	
Open chest cardiac compressions			0.058		0.043		0.036
No	273 (83.0%)	122/271 (45.0%)		71/263 (27.0%)		73/212 (34.4%)	
Yes	56 (17.0%)	33/56 (58.9%)		22/54 (40.7%)		23/45 (51.1%)	
ECMO at treatment initiation[g]			0.006		0.001		<.001
No	149 (45.3%)	82/147 (55.8%)		54/140 (38.6%)		51/100 (51.0%)	
Yes	180 (54.7%)	73/180 (40.6%)		39/177 (22.0%)		45/157 (28.7%)	

[a] All p-values from chi-squared test of no association.
[b] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.
[c] Cardiovascular event includes cardiovascular events due congenital heart disease and not due to congenital heart disease.
[d] Associations were also examined after excluding the category "No adrenaline recorded." Dosing interval was found to be associated with Survival to month 12 (p = 0.039), but not with either VABS-II decreased by ≤15 points (p = 0.43) or Survival with VABS-II ≥ 70 (p = 0.14).
[e] Day is defined as 7:00 AM to 6:59 PM; night as 7:00 PM–6:59 AM.
[f] Weekday is defined as Monday 12:00 AM to Friday 11:59 PM; weekend as Saturday 12:00 AM to Sunday 11:59 PM.
[g] ECMO is extracorporeal membrane oxygenation.

Table 3
Logistic Regression Models.

Characteristic	Odds Ratio (95% CI)	P-value
Survived to 12 months		
Blood lactate (mmol/L)	0.94 (0.89, 0.98)	0.008
Initial cardiac arrest rhythm		0.002
Bradycardia	Reference	
Asystole	0.09 (0.02, 0.43)	
Pulseless electrical activity	1.29 (0.68, 2.44)	
Ventricular fibrillation or tachycardia	3.08 (1.25, 7.61)	
Unknown	0.70 (0.18, 2.80)	
Adrenaline doses		0.026
4 or fewer	Reference	
More than 4	0.52 (0.30, 0.92)	
Adrenaline dosing interval		0.048
No adrenaline recorded	1.03 (0.23, 4.63)	
<3 min/dose	0.50 (0.24, 1.06)	
3–< 5 min/dose	Reference	
5–< 8 min/dose	0.42 (0.20, 0.89)	
≥8 min/dose	0.35 (0.16, 0.75)	
Open chest compressions performed		0.022
No	Reference	
Yes	2.21 (1.12, 4.34)	
VABS-II decreased by ≤ 15 points[a]		
Blood lactate (mmol/L)	0.92 (0.88, 0.97)	0.003
Open chest cardiac compressions		0.007
No	Reference	
Yes	2.53 (1.28, 5.00)	
ECMO at treatment initiation[b]		0.030
No	Reference	
Yes	0.52 (0.29, 0.94)	
Survived to 12 months with VABS ≥ 70[a]		
Blood lactate (mmol/L)	0.93 (0.88, 0.99)	0.014
Initial cardiac arrest rhythm		<.001
Bradycardia	Reference	
Asystole	0.13 (0.02, 1.05)	
Pulseless electrical activity	1.75 (0.86, 3.56)	
Ventricular fibrillation or tachycardia	6.60 (2.40, 18.11)	
Unknown	0.33 (0.04, 2.91)	
Open chest cardiac compressions		0.023
No	Reference	
Yes	2.46 (1.13, 5.32)	
ECMO at treatment initiation[b]		0.002
No	Reference	
Yes	0.34 (0.17, 0.67)	

[a] VABS-II is Vineland Adaptive Behavior Scales, Second Edition.
[b] ECMO is extracorporeal membrane oxygenation.

activity, and international normalized ratio were associated with a lower frequency of all three outcomes. Blood glucose concentration was not associated with outcomes.

Logistic regression models

Asystole as the initial arrest rhythm, administration of >4 adrenaline doses, and higher post-arrest blood lactate concentration were independently associated with lower 12-month survival; an adrenaline dosing interval of 3 to <5 min and open chest compressions were independently associated with greater 12-month survival (Table 3). Use of extracorporeal membrane oxygenation (ECMO) and higher blood lactate concentration were independently associated with lower 12-month survival with VABS-II decreased by ≤15 points from baseline; open chest compressions was independently associated with greater 12-month survival with VABS-II decreased by ≤15 points. Asystole as the initial rhythm, use of ECMO, and higher blood lactate concentration were independently associated with lower 12-month survival with VABS-II ≥70; open chest compressions was independently associated with greater 12-month survival with VABS-II ≥70.

Discussion

Our findings demonstrate several clinical characteristics that are independently associated with 12-month survival and neurobehavioural function among children who are comatose and require mechanical ventilation after in-hospital cardiac arrest irrespective of hypothermia treatment. These characteristics include asystole as the initial arrest rhythm, number of adrenaline doses, adrenaline dosing interval, use of open chest cardiac compressions, use of ECMO, and post-arrest blood lactate concentration.

Initial arrest rhythm has previously been associated with outcome after paediatric in-hospital and out-of-hospital cardiac arrest [23–26]. In a recent meta-analysis, initial non-shockable rhythms were found to have an average odds ratio for survival of 0.59 (95% CI 0.35-1.0) compared to shockable rhythms [13]. Our findings concur with prior research by demonstrating that an initial rhythm of asystole is independently associated with lower 12-month survival and 12-month survival with VABS-II ≥70, whereas VF/VT is independently associated with greater 12-month survival and 12-month survival with VABS-II ≥70. Although not evaluated in our study, prior research suggests that secondary shockable rhythms occurring during resuscitation may have worse outcomes than initial shockable rhythms [27].

Number of adrenaline doses and adrenaline dosing interval were independently associated with 12-month survival in our study. The inverse relationship observed between number of adrenaline doses and survival can be expected since more adrenaline doses are administered the longer cardiac arrest and resuscitation attempts persist. Longer duration of arrest results in a longer period of low cardiac output with increased potential for organ injury. Longer duration of arrest has been associated with decreased survival after both paediatric in-hospital and out-of-hospital arrest [3,6,9,17,24,28]. Our findings also show an adrenaline dosing interval of 3–<5 min results in greater 12-month survival than more or less frequent dosing. These findings support current American Heart Association (AHA) guidelines that recommend adrenaline administration at intervals of 3–5 min during resuscitation [29]. These findings are in contrast to those of a recent study based on data from the AHA Get with the Guidelines-Resuscitation registry suggesting longer adrenaline dosing intervals (>5–<8 min and 8–<10 min) improve survival to hospital discharge following paediatric in-hospital cardiac arrest [30]. It is possible that these conflicting findings are due to differences in the populations studied, with those in our study being more severely ill as suggested by post-arrest coma and the need for mechanical ventilation. Also, in the prior study, the dosing interval was calculated as the time between the first adrenaline dose and the resuscitation endpoint, divided by the number of adrenaline doses administered after the first dose [30]. In our study, the time of first adrenaline dose was not recorded; thus the dosing interval was calculated as the duration of chest compressions divided by the total number of adrenaline doses administered during compressions.

The use of open chest cardiac compressions was independently associated with greater 12-month survival and 12-month survival with good neurobehavioural function in our study. Open chest cardiac compressions are infrequent among children who have not had a recent median sternotomy. Although we did not record whether children who received open chest compressions had a sternotomy prior to cardiac arrest, we believe this is likely because most had a known pre-existing cardiac condition, primarily congenital heart disease. For children who have undergone cardiac surgery, reopening the chest may allow correction of mechanical or other reversible factors that led to the cardiac arrest [31]. Open chest compressions may also be a surrogate for having invasive hemodynamic monitoring in place to guide resuscitation since such monitoring would generally be performed in post-operative cardiac patients.

Open chest compressions may increase arterial pressures, cardiac output, coronary perfusion pressure, return of spontaneous circulation and cerebral blood flow [31]. Our data show 78.5% of patients who had open chest compressions went on to ECMO. This suggests that open chest compressions did not adequately restore their circulation for the long-term, although it may have stabilized them enough to be placed on ECMO. Unfortunately, we are unable to determine the extent to which the association between open chest compressions and better outcome is due to patient characteristics (post-operative state, reversible causes, invasive monitoring) or hemodynamic benefits of directly compressing the heart; however, patient characteristics may be most likely. Current AHA guidelines suggest that open chest compressions may be helpful if employed during surgery when the chest or abdomen is already open, or in the early post-operative period after cardiothoracic surgery [32].

ECMO was used at the time of initiation of study intervention in over half of the children recruited to the THAPCA-IH trial, and in this secondary analysis was found to be independently associated with lower 12-month survival with good neurobehavioural function. ECMO was either initiated during cardiopulmonary resuscitation (E-CPR) or after return of spontaneous circulation but before study intervention. In either case, children receiving ECMO likely represent the more severely ill within this cohort, and therefore have worse outcomes than those not receiving ECMO. Prior research in children with cardiac arrest after cardiac surgery has similarly shown that the use of ECMO is independently associated with increased mortality at ICU discharge [33]. However, in a study that included only children with refractory in-hospital cardiac arrest ($\geq$10 min), children receiving E-CPR had increased survival to hospital discharge and survival with favourable neurologic outcome based on PCPC scores compared to those receiving conventional CPR [34].

Lactic acidosis after cardiac arrest results from inadequate oxygen delivery and anaerobic metabolism occurring both before and during the cardiac arrest. Hyperglycaemia and the administration of adrenaline during cardiac arrest are also believed to contribute to lactic acidosis. Elevated blood lactate levels in the 6 h prior to arrest and in the first 24 h post-arrest have been shown to be associated with hospital mortality after paediatric cardiac arrest [35–37]. Studies have also shown elevated blood lactate levels in the first 24 h post-arrest to be associated with poor neurologic outcome based on PCPC scores [5,36]. Findings from our study demonstrate that elevated blood lactate concentration after in-hospital cardiac arrest is associated with lower 12-month survival and worse neurobehavioural function among survivors based on VABS-II scores. We previously reported a similar association between post-arrest blood lactate concentration and 12-month survival and 12-month survival with VABS-II $\geq$70 after out-of-hospital cardiac arrest using data from the THAPCA-OH trial [17].

Strengths of our study include the multicentre design and the use of the VABS-II to measure neurobehavioural function at baseline and 12 months after in-hospital cardiac arrest. Limitations include the select sample of children recruited to the THAPCA-IH trial which limits the generalizability of our findings. Children recruited to the THAPCA-IH trial were comatose and required mechanical ventilation after cardiac arrest and therefore represent those at high risk of death or neurologic injury. However, these children are also the population for which better understanding of potential prognostic factors may be most useful to clinicians counselling families. Only 155 (47.4%) children survived to 12-months; thus, the number of children who had 12-month neurodevelopmental assessment with VABS-II is small. Other limitations include the large number of variables evaluated, as well as lack of data on some potentially important variables (e.g., time to first adrenaline dose) [30,38]. Variation in post-arrest management might also affect associations between cardiac arrest characteristics and outcomes. Missing data for some variables, such as laboratory values, limited our ability to include them in logistic regression models.

Conclusions

For children who are comatose and require mechanical ventilation after in-hospital cardiac arrest, several factors including initial arrest rhythm, number of adrenaline doses and dosing interval, use of open chest cardiac compressions, use of ECMO, and post-arrest blood lactate concentration are associated with survival and neurobehavioural function at 1 year. Knowledge of these factors may be useful for improving resuscitation practices, identifying children at risk for poor long-term outcomes, and counselling families.

Conflict of interest

There are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.01.013.

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