Published in final edited form as:

Crit Care Med. 2016 December ; 44(12): e1165–e1174. doi:10.1097/CCM.0000000000002003.

Functional Outcome Trajectories after Out-of Hospital Pediatric Cardiac Arrest

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Abstract

Objective—To analyze functional performance measures collected prospectively during the conduct of a clinical trial that enrolled children (up to age 18 years), resuscitated after out-of-hospital cardiac arrest, who were at high risk for poor outcomes.

Design—Children with Glasgow Motor Scales <5, within 6 hours of resuscitation, were enrolled in a clinical trial that compared two targeted temperature management interventions (THAPCA-OH, NCT00878644). The primary outcome, 12-month survival with Vineland Adaptive Behavior Scales, second edition (VABS-II) score ≥70, did not differ between groups.

Setting—38 North American pediatric ICU's.

Participants—295 children were enrolled; 270/295 had baseline VABS-II scores ≥70; 87/270 survived one year.

Interventions—Targeted temperatures were 33.0°C and 36.8°C for hypothermia and normothermia groups.

Measurements and Main Results—Baseline measures included VABS-II, Pediatric Cerebral Performance Category(PCPC), and Pediatric Overall Performance Category (POPC). PCPC and POPC were rescored at hospital discharges; all three were scored at 3 and 12 months. In survivors with baseline VABS-II scores ≥70, we evaluated relationships of hospital discharge PCPC with 3 and 12 month scores, and between 3 and 12 month VABS-II scores. Hospital discharge PCPC scores strongly predicted 3 and 12 month PCPC ($r=0.82, 0.79$; $p<0.0001$) and VABS-II scores ($r=-0.81, -0.77$; $p<0.0001$) Three month VABS-II scores strongly predicted 12 month performance ($r=0.95$, $p<0.0001$). Hypothermia treatment did not alter these relationships.

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Conclusions—In comatose children, with Glasgow Motor Scales <5 in the initial hours after out-of-hospital cardiac arrest resuscitation, function scores at hospital discharge and at 3 months predicted 12-month performance well in the majority of survivors.

Keywords

coma prognosis; hypothermia; cardiac arrest outcome

Children who remain comatose in the initial hours after resuscitation from a cardiac arrest are at great risk for poor neurodevelopmental outcomes. We completed a randomized controlled trial to determine if therapeutic hypothermia (target temperature, 33.0°C, 48h) improved survival and neurobehavioral outcome in children (2 days-18 years old) resuscitated after out-of-hospital(OH) cardiac arrest(CA)(THAPCA-OH, NCT00878644)(1). In contrast with the design of initial studies of hypothermia in comatose adult CA survivors(2,3), in our comparator group, temperatures were actively managed to maintain normothermia (36.8°C) for the 120 hour intervention period. The primary THAPCA-OH outcome was a combined measure of survival and Vineland Adaptive Behavior Scales, Second Edition (VABS-II) age-corrected standard score 70 twelve months later(1,4–7). There were no outcome differences between the treatment groups(1).

The primary neurological inclusion criterion was a Glasgow Coma Scale motor response below five within six hours after return of circulation; a score of five represents localizing pain or (for <2 years old) withdrawing to touch. This report focuses on functional outcome measures that were prospectively collected in during the THAPCA-OH trial. We obtained baseline measures [Pediatric Cerebral Performance Category (PCPC), Pediatric Overall Performance Category (POPC)(8)and VABS-II (9,10)] within 24 hours of enrollment. PCPC and POPC were re-scored at ICU and hospital discharge. PCPC, POPC, and VABS-II were scored at 3 and 12 months. We examined the relationships between concurrent PCPC and VABS-II scores, evaluated the predictive strength of hospital discharge and 3 month function measures for 12 month performance, characterized the trajectories of functional outcomes in survivors, and determined the influence of selected factors (related to baseline characteristics, CA severity, and medical complications) on 12 month VABS-II scores.

Methods

Study population

270 of 295 randomized cases were eligible for the primary outcome; 25 were ineligible because baseline VABS-II scores were <70 (or for two, POPC and/or PCPC 3). One year outcomes were available for 260/270 eligible cases; 87/260 survived for one year, and 12-month VABS-II scores were obtained in 85/87. Analyses that described the range of VABS-II scores in each PCPC and POPC category included all data. Analyses of predictive relationships between hospital discharge and three month measures and subsequent scores were restricted to data from survivors who were eligible for the primary outcome. The Institutional Review Boards of all participating sites approved the protocol and informed consent documents.

Functional Assessment Measures

PCPC and POPC—These 6 point scales (1=normal; 2=mild disability; 3=moderate disability; 4=severe disability; 5=coma or vegetative; 6=brain death) are widely used to describe pediatric ICU patient outcomes (8,9); scoring criteria are described in Supplemental Data. PCPC rates neurological functioning whereas POPC rates overall health including neurological functioning.

VABS-II—The VABS-II (10) is a semi-structured caregiver interview-based measure of function, examining communication, daily living, socialization, and motor skills. It assesses adaptive behaviors, defined as “the individual’s performance on daily-life activities necessary for personal and social independence”. The VABS-II Adaptive Behavioral Composite score was selected because it is standardized for the full age range and expected functional outcome range of the study population. Parent-caregiver rating forms and survey interview forms yield equivalent responses. The survey interview is suitable for centralized administration; telephone administration was validated versus in-person administration(11). In normative populations, the mean VABS-II score is 100 (standard deviation=15).

Baseline scoring—Within 24 hours of study enrollment, site research coordinators scored baseline pre-arrest function. PCPC/POPC were scored from medical records and family interviews. A primary caregiver completed the baseline VABS-II rating form. Twenty-four subjects without a baseline VABS-II were included in the primary outcome if POPC and PCPC scores were 1–2.

ICU and hospital discharge—PCPC/POPC were scored at ICU and hospital discharge by site research coordinators from review of medical records.

3 and 12 month scoring—A trained research assistant (at Kennedy Krieger Institute, Baltimore, MD) conducted semi-structured telephone interviews to obtain PCPC, POPC, and VABS-II scores at 3 and 12 months (for the primary outcome groups, n=90 at 3 months, n=85 at 12 months). Neuropsychological and neurological evaluations were obtained after the 12 month VABS-II in about 2/3 of survivors. Results of neuropsychological testing and their relationships with VABS-II composite, domain, and subdomain scores at 12 months have been reported (12); neurological examinations will be reported separately.

Data analysis

Distributions of binary and categorical factors were compared using the Fisher’s exact test. Continuous factors were compared using the Wilcoxon rank-sum test. Magnitudes of Pearson correlation were compared using Fisher’s *z*-transformation(13). Magnitudes of correlations between two measures were compared using Dunn and Clark’s *z* statistic(14). Comparisons of magnitudes of correlation of selected measures with two other measures (specifically, assessing whether correlations of hospital discharge PCPC with VABS-II at 3 months and at 12 months differ) was performed using Hotelling’s *t* statistic(15). To quantify association of baseline and other factors with 12-month VABS-II scores, standard linear regression models were fit with VABS-II as the outcome variable and the factors (continuous or categorized) as predictors. Factors showing a trend of association ($p<0.10$) in univariate

models were considered as candidate predictors for inclusion in multivariable models, which were fit by a backward stepwise selection routine, retaining factors with $p < 0.10$. Separate multivariable models were fit using baseline predictors only (Table 1, Model 1), and using baseline predictors and post-randomization factors (Table 1, Model 2). Analyses were fit using SAS software version 9.4, excepting correlation comparisons, performed in R version 3.1.1(16) using the package cocor (17).

Results

Supplementary Table 1 details baseline characteristics in the eighty-seven 12 month survivors included in the primary outcome; there were no group differences. CPR duration could not be accurately ascertained in many survivors and was not compared. CA etiology was a respiratory event in about two-thirds; the initial EKG rhythm was asystole, bradycardia, or pulseless electrical activity in a similar fraction. At ICU discharge, 30/87 had POPC scores of 1–2; at hospital discharge, 32/87 had PCPC scores in this range.

We evaluated the relationships of concurrently obtained PCPC and VABS-II scores in all cases with available data (Figure 1. A-C) at baseline ($n=269$)(A), at 3 months ($n=99$)(B), and at 12 months ($n=94$)(C). Data are presented as box and whisker plots to illustrate the full range of VABS-II scores associated with each category. Mean VABS-II scores were close to 100 in cases assigned a PCPC score of 1, and declined with higher PCPC scores. Pearson correlations between PCPC and VABS-II were -0.61 at baseline, -0.90 at 3 months, and -0.90 at 12 months ($p < 0.001$, for all); the magnitude of correlation was higher for 3-month and 12-month assessments than for baseline, and not different between 3 and 12 month time-points. There were no differences in the correlations between the treatment arms. Supplementary Table 2 summarizes VABS-II scores that corresponded with PCPC and POPC categories in these data sets; since relationships of VABS-II scores with PCPC and POPC categories were very similar, for subsequent predictive analyses only PCPC scores were used.

Since predictive analyses were restricted to the survivors who were eligible for the primary outcome of THAPCA-OH, we replicated the 3 and 12 month comparisons of VABS-II and PCPC scores in these survivors at 3 months ($n=84$) and 12 months ($n=85$); trends were the same (Supplementary Figure 1).

Figure 2 illustrates the relationship between hospital discharge PCPC score and subsequent PCPC measures in the primary outcome group survivors at 3 months(A) and 12 months(B). Each horizontal bar illustrates the proportion of survivors in each PCPC category in relationship with their hospital discharge PCPC scores. Hospital discharge PCPC scores strongly influenced subsequent performance and trends were similar at both time intervals ($r=0.82$, 0.79 ; both $p < 0.0001$, Pearson correlations) with no treatment group differences (not shown). Overall, from hospital discharge until 12 months, 42/85(49%) remained in the same PCPC category, and only 10/85(12%) changed by at least 2 categories. Eighty-four percent of cases with scores of 1–2 (normal or mild disability) at hospital discharge remained in this range. No case scored at PCPC=5 (coma or vegetative) at hospital discharge improved beyond a severe disability category; however, about half were scored in the severe disability

group (PCPC=4) at 12 months. Only 35% with severe disability scores (PCPC=4) at discharge attained higher scores subsequently.

Supplementary Figure 2 compares 3 and 12 month PCPC scores. Three month measures strongly influenced 12 month function (Pearson correlation, $r=0.95$, $p<0.0001$); however there were modest improvements in a significant minority (including about 1/3 of cases described as comatose or vegetative at month 3). No case changed by more than one PCPC category between 3 and 12 months.

Hospital discharge PCPC scores also strongly predicted 3 month and 12 month VABS-II scores (Figure 3. A–B) (Pearson correlations, $r=-0.81$, -0.77 ; both $p<0.0001$); there was no difference between treatment groups. Similarly, there was a strong relationship between 3 month PCPC category and 12 month VABS-II score (Pearson correlation, $r=-0.85$, $p<0.0001$, not shown). Fifteen survivors attained VABS-II scores 100 at 12 months; of note, their hospital discharge PCPC scores ranged from 1–4 (ten with PCPC=1, one with PCPC=2, two with PCPC=3, two with PCPC=4). The range of 12-month VABS-II scores corresponding with each PCPC category was widest for those who were in the severe disability category (PCPC=4) at hospital discharge.

Figure 3. C illustrates the remarkably close relationship between 3 and 12 month VABS-II scores in both treatment groups (Pearson correlations: overall $r=0.95$; hypothermia group $r=0.94$; normothermia group $r=0.96$; $p<0.0001$, for all). Nine cases had changes in their VABS-II scores of 15 points (1 SD) between 3 and 12 months (increases in 6, declines in 3); in only one case did the score change influence the THAPCA-OH outcome category (i.e. from <70 to 70).

Although the data demonstrated a robust relationship between PCPC score categories at hospital discharge and subsequent VABS-II scores, individual cases at the extremes or outside the ranges of the majority of scores were identified. Of 23 cases with PCPC scores in the severe disability category (PCPC=4) at hospital discharge, 10 were ultimately classified in the favorable outcome range (12-month VABS-II scores 70). Of interest, 8 of 10 with substantial improvements were from the hypothermia group (Supplementary Table 3). In contrast, four children with PCPC scores of 1–2 at hospital discharge had 12 month VABS-II scores in the 61–69 range (three in the normothermia group).

We analyzed the relationships of pre-arrest, CA and resuscitation, and early post-intervention period events to 12 month VABS-II composite scores in survivors eligible for the primary outcome (Table 1). In univariate analyses, older age had a modest negative association, cardiac and other non- respiratory CA etiologies had substantial positive associations, clinically or electrographically diagnosed seizures had an adverse association, and duration of ICU and hospital stays had modest but highly significant negative associations with 12-month scores. Factors showing a trend of association ($p<0.10$) were considered as candidate predictors in two multivariable models: “Model 1” only considered pre-randomization predictors and “Model 2” also evaluated post-randomization variables. In both, increasing age predicted worse outcome ($p<0.001$), and cardiac and other non-respiratory CA etiologies strongly predicted better scores ($p=0.01$); in Model 1, number of

epinephrine doses had a significant adverse association, as did duration of ICU stay in Model 2.

Discussion

THAPCA-OH compared survival and neurobehavioral outcomes in children (2 days-18 years old), who remained comatose after OH-CA resuscitation and were treated with hypothermia or normothermia; outcomes did not differ between these targeted temperature management interventions(1). The rationale for selection of the VABS-II composite score and the defined “favorable outcome” cut-point, two standard deviations below the reference population mean, have been reported(4). Less than half of eligible survivors (42/85) attained the pre-determined favorable outcome, VABS-II score ≥ 70 , and only fifteen (of 260 eligible cases) attained the mean population norm score (≥ 100).

The 12 month outcome evaluation was a pragmatic compromise between the typical 18 month follow-up in neonatal encephalopathy trials and the 3–6 month time intervals applied in adult brain injury outcome studies. Three month VABS-II scoring was incorporated to optimize retention and follow-up, to assess whether hypothermia influenced the recovery trajectory, and to evaluate the predictive accuracy of 3 month scores for 12 month outcomes. Retention rates were $>90\%$ and hypothermia did not significantly influence the strong relationships between early (hospital discharge or 3 month) and subsequent functional measures.

We collected PCPC scores to facilitate comparisons with other outcome studies in pediatric and adult CA survivors(18–22). In contrast with studies that emphasized relatively good outcomes in pediatric CA survivors, only thirty-two cases in the THAPCA-OH primary outcome group (about 35% of survivors) had PCPC scores of 1–2 at hospital discharge. A retrospective review of pediatric CPR survivors reported that 77% had the same PCPC score one year later as prior to the event, and concluded that long-term survivors have little or no change in neurological status; however, most of their cases had in-hospital CA(21). Another publication cited 87% good outcomes (PCPC=1–2) at one year(22); this study included children with rapid post-resuscitation recovery whereas all children enrolled in the THAPCA-OH trial remained comatose upon admission to the ICU.

Our data provided a unique opportunity to determine the ranges of VABS-II scores corresponding with each PCPC category. There was a consistent inverse relationship between PCPC category and VABS-II score. Mean and median VABS-II scores corresponding with each PCPC category were similar in all analyses; the range of VABS-II scores was widest in the severe disability category(PCPC=4). These results were not precisely comparable with published findings in a more diverse pediatric ICU patient population(9). In that study outcomes were evaluated one or six months after hospital discharge, stratified by age, and PCPC categories were compared with scores obtained on an earlier version of VABS; trends were similar.

Hospital discharge PCPC scores had substantial predictive power for 3 and 12 month PCPC scores ($r=0.82, 0.79$) and VABS-II scores ($r=-0.81, -0.77$), respectively, and did not differ

between treatment groups. Moreover, 3 month VABS-II scores were strongly correlated with 12 month performance on the same measures in both treatment groups. In future clinical trials of a similar pediatric population a study design that incorporated primary outcome evaluation at three months after resuscitation could be considered; however, particularly in young infants, such an approach would not be advisable. Three month assessments could provide robust measures for interim analyses.

Congruent with results of the THAPCA-OH trial, in analyses limited to 12 month survivors, hypothermia had no impact on VABS-II scores. In both univariate and multivariate analyses, older age had a modest deleterious effect; the factors contributing to this differential vulnerability are uncertain. The most potent variable identified was cardiac etiology, which was associated with higher scores than respiratory etiology. This trend likely reflects the deleterious effects of hypoxia prior to CA with respiratory etiology. Early seizures were associated with worse outcomes only in the univariate model; however, seizure burden and treatment efficacy were not assessed in the THAPCA-OH protocol, thus limiting interpretation of this association. In contrast with findings from other pediatric studies in high-risk populations (23,24), socio-economic status and family function measures had no impact on outcomes.

An important question is whether these results can influence clinical practice. In children who remain comatose after CA, families and physicians seek rapid and accurate prognostic assessments. On-going treatments, including sedation and paralytics, constrain the utility of neurological examination. Early neuroimaging was not included in the THAPCA-OH protocol.

Our data highlight the prognostic limitations of early clinical assessments. The study population included children who were unresponsive to deep pain after resuscitation and then recovered to normal or close to normal function; no specific characteristics identified these cases, although younger age and a cardiac etiology exerted positive influences. Moreover, although severe disability scores at hospital discharge strongly predicted poor 12-month function, ten of 85 survivors improved substantially. Some cases could reflect scoring inaccuracies; inter-rater reliability among site coordinators was not evaluated. Information regarding post-hospital discharge rehabilitation interventions was not systematically collected. Although we found no treatment group differences in the predictive strength of early assessments for subsequent performance, eight of ten who improved from severe disability to favorable outcome underwent hypothermia, and we question whether this treatment may sometimes delay clinical recovery.

These results provide new information about the trajectories of functional outcomes in children and adolescents who are resuscitated but remain comatose in the initial hours after out-of-hospital CA. The function scores obtained at hospital discharge and at 3 months predicted 12 month VABS-II composite scores well in the majority of survivors. These data will inform the designs of future clinical trials and help clinicians interpret the prognostic significance of functional assessments obtained at hospital discharge in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support for the conduct of the THAPCA-OH Trial was funding from NIH U01HL094345 (FWM) and U01HL094339 (JMD).

We appreciate the contributions of the families who participated in the THAPCA-OH trial.

Additional Supportive Funding. Support in part from the following federal planning grants contributed to the planning of the THAPCA Trials: HD044955 (to Dr. Moler) and HD050531 (to Dr. Moler). Additional in part support from the following research networks: Pediatric Emergency Care Applied Research Network (PECARN) from cooperative agreements U03MC00001, U03MC00003, U03MC00006, U03MC00007, and U03MC00008; and the Collaborative Pediatric Critical Care Research Network (CPCCRN) from cooperative agreements U10HD500009, U10HD050096, U10HD049981, U10HD049945, U10HD049983, U10HD050012 and U10HD049934. Site support from P30HD040677, UL1TR000003UL1, RR 024986, and UL1 TR 000433.

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Figure 1. Relationship of VABS-II and PCPC scores

A–C illustrate the VABS-II scores that corresponded with each PCPC score category in all THAPCA-OH enrolled subjects with available data at baseline (n= 269) (A), at 3 months (n=99) (B), and at 12 months (n=94) (C). PCPC category definitions are: 1= Normal; 2 = Mild disability; 3 = Moderate Disability; 4 = Severe disability; 5 = Coma or vegetative. Data for all cases (left bar), and separately for hypothermia (middle bar) and normothermia (right bar) groups, are presented as box and whisker plots. Each shaded box represents the interquartile range (IQR)(middle one-half of the data), the horizontal line within the box is the median, and symbols ($\diamond$) are means; upper and lower whiskers represent the maximum and minimum values excluding outliers (defined as data points more than 1.5 IQRs from the box). The relationships between VABS-II scores and PCPC categories are all significant ($p<0.001$): (Pearson correlations: A. $r = -0.61$; B–C. $r = -0.9$). There were no differences in

the relationships between VABS-II scores and PCPC categories between normothermia and hypothermia groups.

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Figure 2. Hospital discharge PCPC score and 3 and 12 month PCPC scores

These graphs illustrate the distributions of 3 month (A) and 12 month (B) PCPC scores that corresponded with each category of hospital discharge PCPC score in THAPCA-OH primary outcome group survivors. The y axis labels are hospital discharge PCPC scores; numbers of survivors per PCPC category with available data at 3 (A) and 12 months (B) respectively were: PCPC 1, n= 22 and 22; PCPC 2, n=10 and 9; PCPC 3, n=8 and 8; PCPC 4, n=21 and 23; PCPC 5, n=23 and 23. Each horizontal bar illustrates the percentage of cases in each PCPC category at follow-up (numbers within each section of the bars are the assigned follow-up scores). Hospital discharge PCPC scores strongly influenced subsequent scores (Pearson correlations: $r=0.82, 0.79$; both $p<0.0001$). Treatment group had no effects (not shown).

Figure 3. Hospital discharge PCPC score and 3 and 12 month VABS-II scores

Panels A–B illustrate 3 month (A) and 12 month (B) VABS-II scores that correspond with each category of hospital discharge PCPC score in THAPCA-OH survivors eligible for the primary outcome. Data are presented for all cases (left bar) and for hypothermia (middle bar) and normothermia (right bar) groups, as box and whisker plots. Each shaded box represents the interquartile range (IQR) (middle one-half of the data), the horizontal line within the box is the median, and symbols ($\diamond$) are means, upper and lower whiskers represent the maximum and minimum values, excluding outliers (defined as data points more than 1.5 IQRs from the box). Hospital discharge PCPC scores strongly influenced 3

month (A) and 12 month (B) VABS-II scores (Pearson correlations: $r = -0.81, -0.77$, respectively, $p < 0.0001$; no effect of treatment group). C. Illustrates corresponding 3 month and 12 month VABS-II scores; scores were tightly linked in both treatment groups ($r = 0.95$, $p < 0.0001$).

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Table 1

Relationships of selected variables to 12 month VABS-II composite scores

Factor	Univariate Coef ^a ±SE	Univariate p-value	Model 1 Baseline Only Coef ^a ±SE	Model 1 p-value	Model 2 All Factors Coef ^a ±SE	Model 2 p-value
Baseline characteristics						
Treatment (hypothermia vs. normothermia)	2.68±6.33	0.67				
Age in years at CA (continuous, per year increase)	-1.09±0.51	0.04	-1.76±0.50	<0.001	-2.15±0.47	<0.001
Gender (male)	1.04±6.99	0.88				
Race		0.13				
Ethnicity		0.74				
Baseline VABS-II score	0.15±0.20	0.47				
SES (education level)		0.22				
Some high school or less	[reference]					
High school graduate/GEID	-3.13±9.04					
Vocational school or some college	12.67±9.38					
College degree	15.11±9.84					
Graduate or doctoral degree	10.06±10.25					
Family function measure	2.02±7.46	0.79				
CA Etiology		0.01				
Respiratory	[reference]		[reference]		[reference]	
Cardiac	24.43±8.13		31.08±7.73	0.001	30.46±7.15	<0.001
Other/unknown ^b	4.58±8.66		26.2±9.18	0.006	22.00±8.04	0.008
Arrest severity measures						
No. of epinephrine doses (per one dose increase)	-2.23±1.28	0.09	-3.49±1.24	0.006	Not in final model	
Pre-randomization lactate (per one unit increase)	-1.87±0.91	0.04	Not in final model		Not in final model	
Complications over 120 h intervention period						
Clinical or EEG diagnosed seizures	-12.07±6.17	0.05			Not in final model	
Repeat CA	-13.09±12.0	0.28				
Post 120 h intervention						
Duration of ICU stay	-0.50±0.16	0.003				
Duration of hospital stay	-0.41±0.09	<0.001			-0.65±0.15	<0.001

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Coef: Coefficients from linear regression models with 12 month VABS-II scores as outcome in subjects eligible for THAPCA-OH primary outcome. Factors marked “Not in final model”, were considered as predictors in the multivariable model, and then excluded using stepwise selection criteria.

Other CA etiologies include: neurological event, multiple organ system failure, drug overdose, electrolyte imbalance, and unknown.