Circulation

ORIGINAL RESEARCH ARTICLE

Association Between Diastolic Blood Pressure During Pediatric In-Hospital Cardiopulmonary Resuscitation and Survival

BACKGROUND: On the basis of laboratory cardiopulmonary resuscitation (CPR) investigations and limited adult data demonstrating that survival depends on attaining adequate arterial diastolic blood pressure (DBP) during CPR, the American Heart Association recommends using blood pressure to guide pediatric CPR. However, evidence-based blood pressure targets during pediatric CPR remain an important knowledge gap for CPR guidelines.

METHODS: All children ≥37 weeks' gestation and <19 years old in Collaborative Pediatric Critical Care Research Network intensive care units with chest compressions for ≥1 minute and invasive arterial blood pressure monitoring before and during CPR between July 1, 2013, and June 31, 2016, were included. Mean DBP during CPR and Utstein-style standardized cardiac arrest data were collected. The hypothesis was that DBP ≥25 mm Hg during CPR in infants and ≥30 mm Hg in children ≥1 year old would be associated with survival. Primary outcome was survival to hospital discharge. Secondary outcome was survival to hospital discharge with favorable neurological outcome, defined as Pediatric Cerebral Performance Categories 1 to 3 or no worse than prearrest baseline. Multivariable Poisson regression models with robust error estimates were used to estimate the relative risk of outcomes.

RESULTS: Blinded investigators analyzed blood pressure waveforms during CPR from 164 children, including 60% <1 year old, 60% with congenital heart disease, and 54% after cardiac surgery. The immediate cause of arrest was hypotension in 67%, respiratory decompensation in 44%, and arrhythmia in 19%. Median duration of CPR was 8 minutes (quartiles, 3 and 27 minutes). Ninety percent survived the event, 68% with return of spontaneous circulation and 22% by extracorporeal life support. Forty-seven percent survived to hospital discharge, and 43% survived to discharge with favorable neurological outcome. Maintaining mean DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old occurred in 101 of 164 children (62%) and was associated with survival (adjusted relative risk, 1.7; 95% confidence interval, 1.2–2.6; P=0.007) and survival with favorable neurological outcome (adjusted relative risk, 1.6; 95% confidence interval, 1.1–2.5; P=0.02).

CONCLUSIONS: These data demonstrate that mean DBP ≥25 mm Hg during CPR in infants and ≥30 mm Hg in children ≥1 year old was associated with greater likelihood of survival to hospital discharge and survival with favorable neurological outcome.

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Key Words: cardiopulmonary resuscitation ■ heart arrest ■ pediatrics ■ survival ■ treatment outcomes AQ3

Sources of Funding, see page XXX

http://circ.ahajournals.org

<zjs;OriginalResearchArticle> • <zjss;10021,10029,10055,10056,10162> • <zdoi;10.1161/CIRCULATIONAHA.117.032270>

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- In this multicenter population of children with invasive arterial blood pressure monitoring during in-hospital intensive care unit cardiac arrests, mean diastolic blood pressure ≥25 mm Hg during cardiopulmonary resuscitation in infants and ≥30 mm Hg in children ≥1 year old was associated with 70% greater likelihood of survival to hospital discharge and 60% higher likelihood of survival with a favorable neurological outcome.
- Survival rates decreased markedly with mean diastolic blood pressure <20 mm Hg in infants and <25 mm Hg in children ≥1 year old.

What Are the Clinical Implications?

- Clinicians should consider targeting diastolic blood pressure ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old during cardiopulmonary resuscitation when invasive arterial blood pressure is monitored.
- When diastolic blood pressure is <20 mm Hg in infants and <25 mm Hg in children ≥1 year old during cardiopulmonary resuscitation, clinicians should consider improving cardiopulmonary resuscitation performance, adding vasopressor medications, or addressing potentially reversible causes.

Each year, >200 000 patients receive cardiopulmonary resuscitation (CPR) for in-hospital cardiac arrests in the United States.[1,2] Although survival rates are increasing, important impediments to further advances are optimal monitoring of CPR and appropriate therapeutic targets during CPR.[3–5] Therefore, the American Heart Association's 2015 guidelines for cardiopulmonary resuscitation recommend the following: "For patients with invasive hemodynamic monitoring in place at the time of cardiac arrest, it may be reasonable for rescuers to use blood pressure (BP) to guide CPR quality," primarily on the basis of data from animal studies.[4,5] However, "because the precise numeric targets for these parameters AQ4 during resuscitation [for adults or children] have not yet been established, these were not specified."[4,5]

AQ5 Among the 5 to 10 000 American children who require in-hospital CPR annually, >95% of CPR occurs in an intensive care unit (ICU).[6,7] Because 40% of these children have invasive arterial BP monitoring in place during CPR, titration of chest compression depth and vasopressor dosing to a BP target are feasible.[8] Therefore, investigators in the Eunice Shriver Kennedy National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) embarked on a prospective assessment of BP monitoring during pediatric CPR.

The overall goal was determination of BP targets to inform American Heart Association pediatric CPR guidelines. Based on animal data and clinical experience, the hypothesis was that a relaxation-phase (diastolic) BP (DBP) ≥25 mm Hg during CPR in infants and ≥30 mm Hg in children ≥1 year old would be associated with increased likelihood of return of spontaneous circulation (ROSC), survival to hospital discharge, and survival to hospital discharge with a favorable neurological outcome.[9–12] In addition, the overall relationships of DBPs with outcomes were evaluated with cubic splines in infants and children ≥1 year old. Because brain perfusion depends on both compression-phase (systolic) BP (SBP) and DBP and because many deaths after ROSC are the result of neurological injuries, the relationship of systolic BP during CPR with outcomes was also evaluated.

METHODS

Study data sets will be publicly available through CPCCRN.org 3 years after study completion.[13]

The PICqCPR study (Pediatric Intensive Care Quality of CPR) is a prospective multicenter cohort study of ICU CPR conducted by the CPCCRN. All children ≥37 weeks' gestation and <19 years old who received chest compressions for ≥1 minute and invasive arterial BP monitoring before and during CPR in a CPCCRN pediatric ICU or pediatric cardiac ICU were eligible. Patients were enrolled from 11 institutions between July 1, 2013, and June 30, 2016. Cardiac arrests were identified at each site with a 24-hour paging system or an intense daily research coordinator screening procedure. The project was approved with waiver of informed consent by the Institutional Review Board at every clinical site and the University of Utah Data Coordinating Center.

Inclusion criteria were invasive arterial BP monitoring before and during CPR; first compression of CPR captured on transmitted arterial BP waveform data; at least 1 minute of continuous arterial BP waveforms; and central venous pressure, respiratory plethysmography, or electrocardiographic artifact available on transmitted arterial BP waveform data to allow determination of CPR starts and stops. Exclusion criteria were inability to determine DBP (eg, lack of arterial waveform resulting from line interruption for blood draw or truncation of BP waveform obscuring DBP) or inability to determine when CPR started and stopped.

The overall goal was to evaluate the association of BP during the relaxation phase of CPR (DBP) with outcomes of ROSC >20 minutes, survival to hospital discharge, and survival to hospital discharge with a favorable neurological outcome. The primary hypothesis was that a mean DBP ≥25 mm Hg during CPR in infants and ≥30 mm Hg in children ≥1 year old would be associated with a higher rate of survival to hospital discharge. Only the index (first) CPR events were evaluated for patients with >1 CPR event because a patient can survive only once per hospitalization.[14] Secondary hypotheses were that these DBPs during CPR would be associated with higher rates of ROSC and survival to discharge with a favorable neurological outcome and that mean compression-phase SBP ≥60 mm Hg during CPR in infants and ≥80 mm Hg in children ≥1 year old would be associated with a higher rate of survival to hospital discharge.

The CPCCRN research coordinators obtained Utstein-style standardized cardiac arrest and CPR data,[14] including the following: patient factors such as demographics, preexisting conditions, and illness categories; arrest characteristics such as interventions in place at time of arrest, first documented rhythm, immediate cause of arrest, duration of CPR, defibrillation shocks, and pharmacological interventions; and outcome data such as ROSC >20 minutes, survival to hospital discharge, and survival to hospital discharge with a favorable neurological outcome. Prearrest BPs were obtained during the 10 minutes before the initiation of CPR. Pediatric Cerebral Performance Categories (PCPC) before arrest and at hospital discharge were documented, as well as pediatric Functional Status Scale scores at baseline and hospital discharge. Survival to hospital discharge with a favorable neurological outcome was defined as PCPC 1 to 3 or no worse than prearrest PCPC.[14,15] Substantive new functional morbidity was defined as an increase in the Functional Status Scale total score of at least 3.[16] The paucity of available arterial BP data during CPR in children precluded accurate sample size determination, so CPCCRN Investigators chose to gather such data for 3 years.

Waveform Analysis

For CPR events that met inclusion criteria, waveform data were printed from the ICU central monitoring system, deidentified, and then transmitted and stored at the Data Coordinating Center. Deidentified arterial waveforms were manually digitized and analyzed by Children's Hospital of Philadelphia investigators (PlotDigitizer, version 2.0, Department of Physics, University of South Alabama) who were blinded to clinical data and survival outcome. SBP was sampled at the peak of the arterial pressure tracing for each compression; DBP was F1 sampled during mid-diastole for each compression (Figure 1). This process allowed extraction of numeric X (time in seconds) and Y (arterial BP) data.[17] Central venous pressure, left atrial pressure, electrocardiographic artifact, and/or respiratory plethysmography tracings were used to determine start, stop, and interruptions of CPR. Mean DBP and mean SBP were determined for each minute of CPR, and mean DBP and mean SBP for each patient were the average BPs over the first 10 minutes of CPR. For patients with <10 minutes of CPR, the mean BPs were determined for the minutes of CPR provided.

Statistical Analysis

Patient and event characteristics were summarized with the use of frequencies and percentages or medians and quartiles. Differences in these characteristics between patients who did and did not survive to hospital discharge were examined with the Fisher exact test for categorical variables, the Cochran-Armitage trend test for ordinal variables, and the Wilcoxon rank-sum test for continuous variables. *P* values are reported on the basis of a 2-sided alternative and considered statistically significant when <0.05. Multivariable Poisson regression models with robust error estimates were used to estimate the relative risk (RR) of survival outcomes based on DBP or SBP over (up to) the first 10 minutes of CPR.[18] These models were adjusted for age category, initial cardiac rhythm, and location

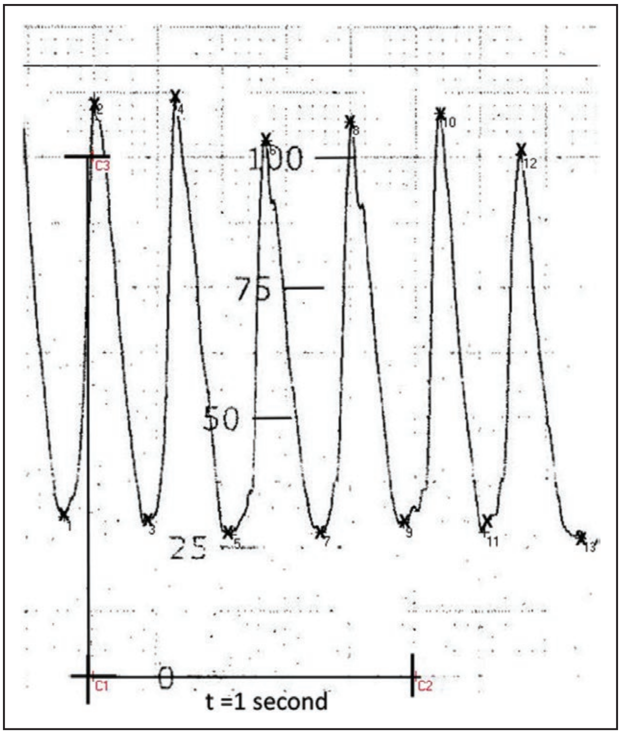

Figure 1. Deidentified arterial blood pressure waveform from a patient in this study with manually digitized systolic and diastolic pressures sampled at the peak and mid-diastole of individual compressions, respectively, as indicated by x. AQ6

of CPR (cardiac versus general pediatric ICU), which were specified a priori on the basis of previously established associations with in-hospital cardiac arrest outcomes,[8,19–23] as well as CPCCRN site, based on differences in overall outcomes at CPCCRN sites.[24] RRs are presented with their 95% confidence intervals (CIs).

The robustness of the main findings was addressed in several ways. First, multivariable models were constructed by use of backward stepwise selection with a criterion of $P>0.1$ for removal of any pre-CPR covariables. The rationale for this approach was to determine whether the association between DBP and outcomes would withstand controlling for additional prearrest characteristics associated with survival. Second, the appropriateness of the a priori thresholds for DBP was assessed. Data-driven thresholds were obtained from receiver-operating characteristics (ROC) curves. However, thresholds based on ROC curves do not account for covariables and may not be optimal in a heterogeneous cohort. Alternatively, cubic splines offer a powerful approach that accommodates adjustment for covariables and allows a careful investigation into the relationship between mean DBP and survival. The cohort was divided by age group with a separate model for children <1 year and for children ≥1 year of age. Each model adjusted for a priori covariables, as in the main model, but included a continuous restricted cubic spline of mean DBP in place of the a priori binary predictor. Internal knots for the spline were placed at the 20th, 40th, 60th, and 80th percentiles. The fitted spline is a smooth curve of the estimated survival rate as a continuous function of DBP, adjusting for covariables

F2 (Figure 2). The predicted survival above and below the a priori threshold for DBP was examined on the fitted spline to assess the appropriateness of the cutoff. Finally, subgroup analyses were performed for patients with >10 minutes of CPR to verify that the mean DBP in the first 10 minutes is still predictive of survival. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC).

On the basis of data from the above analyses, additional post hoc analyses were performed to further address the robustness of the main findings and other considerations. To address the possibility that CPR hemodynamics during the first 5 minutes of CPR may be more relevant for outcome than minutes 6 to 10, the Poisson regression model analyses for relationships of mean DBP ≥25 mm Hg during CPR in infants and ≥30 mm Hg in children ≥1 year of age with hospital discharge outcomes were repeated, with exclusively mean DBP data during the first 5 minutes of CPR used. Because prearrest DBP was higher among infants who survived to hospital discharge compared with infants who did not survive, adjustment for prearrest DBP was forced into an additional Poisson model. To evaluate whether lower mean DBP thresholds in infants and children would also be associated with a higher rate of survival to hospital discharge based on the cubic spline data, the RR of survival with a mean DBP ≥20 mm Hg during CPR in infants and ≥25 mm Hg in children ≥1 year old was evaluated.

RESULTS

Among 244 index CPR events with invasive arterial BP monitoring and ≥1 minute of chest compressions, 164 (67%) met all of the necessary criteria for inclusion in the study. The annual number of CPCCRN ICU admissions in 2014 was 21 926. Data on the number of cardiac arrests or number of children with CPR ≥1 minute were not available. Figure 3 is an Utstein-style diagram F3 of patients included and excluded. Maintaining mean DBP during CPR ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old occurred in 101 of 164 children (62%). Prearrest patient characteristics of this overall cohort are described in Table 1, as are comparisons of AQ10 these characteristics among children who survived to hospital discharge and those who died. Ninety-eight (60%) were <1 year old; 132 (80%) had respiratory insufficiency; 128 (78%) had hypotension; 99 (60%) had congenital heart disease; 88 (54%) were cardiac surgical patients (ie, postoperative when CPR was performed); 77 (47%) had a normal baseline PCPC score (PCPC 1); and 47 (29%) had a mildly abnormal baseline PCPC score (PCPC 2). Among the prearrest characteristics, preexisting hypotension was associated with a significantly lower rate of survival to hospital discharge and congenital heart disease with a higher rate. The characteristics and outcomes of included patients were similar to those of excluded patients (Table I in the online-only Data Supplement).

Event characteristics of the index CPR events in the overall cohort are described in Table 2, as are compari- T2 sons of these characteristics among children who survived to hospital discharge and those who died. Immediate causes of the arrest were hypotension in 67%, respiratory decompensation in 44%, and arrhythmia

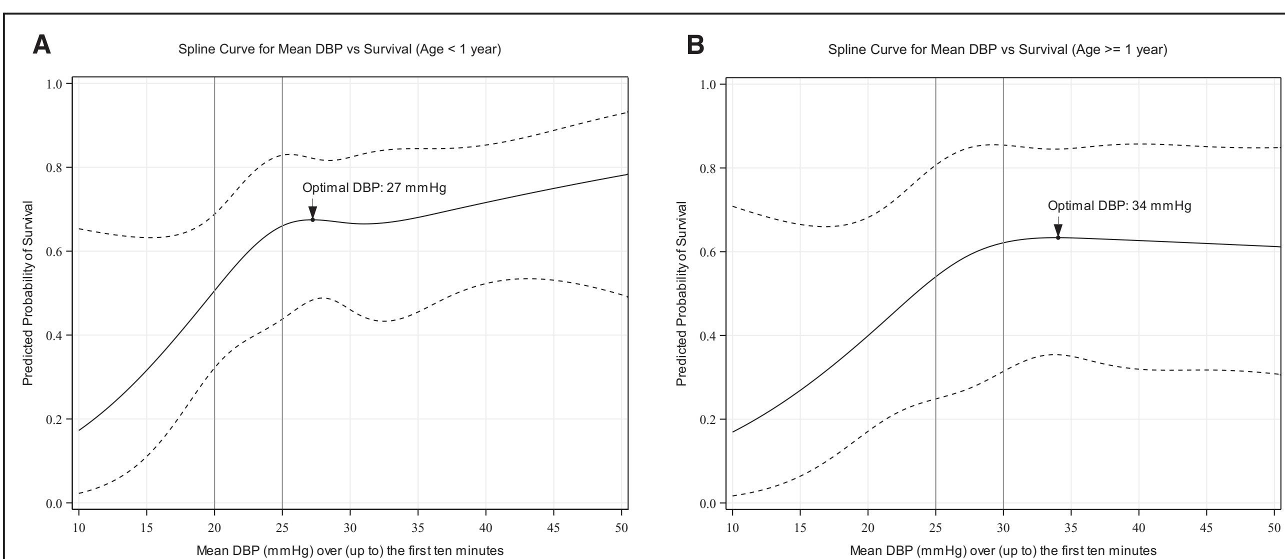

Figure 2. Spline curves showing association of mean diastolic blood pressure (DBP) over (up to) the first 10 minutes of cardiopulmonary resuscitation with survival to hospital discharge in infants (A) and children ≥1 year old (B). AQ7
Top and bottom dashed curves in **A** and **B** represent 95% and 5% confidence interval bands. Arrow shows the point of optimal predicted survival (defined as maximum predicted survival over the interval 15–30 mm Hg for infants and 15–35 mm Hg for children), and vertical lines show mean DBP targets of interest (25 and 20 mm Hg for infants, 30 and 25 mm Hg for children ≥1 year old). Curves were generated with restricted cubic splines for mean DBP with knots at the 20th, 40th, 60th, and 80th percentiles. For infants, DBP with maximum predicted survival was 27 mm Hg; predicted survival was 63% (35%, 84%). AQ8
For children, DBP with maximum predicted survival was 34 mm Hg; predicted survival was 67% (48%, 82%). AQ9

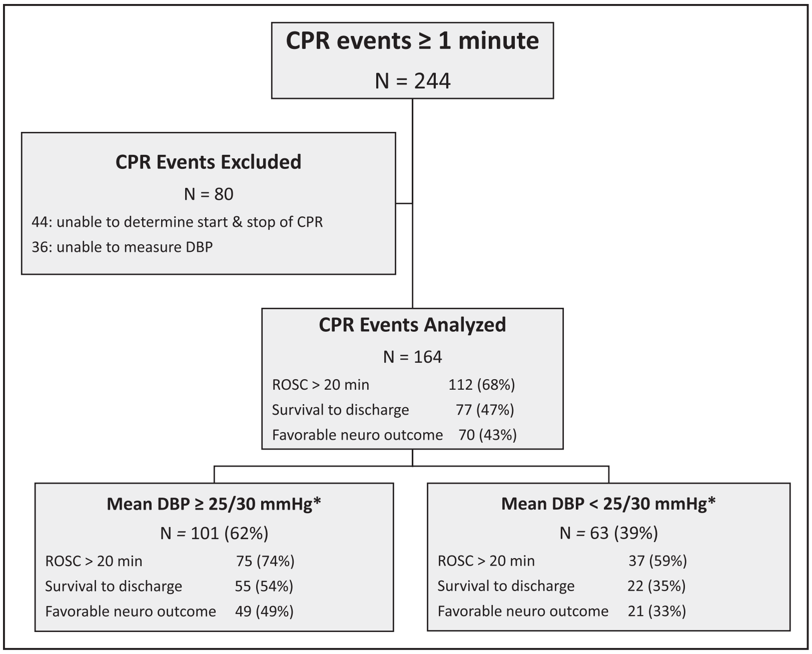

Figure 3. Utstein-style flow diagram of patients included in the PICqCPR study (Pediatric Intensive Care Quality of Cardiopulmonary Resuscitation).
Cardiopulmonary resuscitation (CPR) events ≥1 minute refer to patients included with arterial blood pressure waveform data who had ≥1 minute of CPR. Favorable neuro outcome refers to patients who survived to hospital discharge with Pediatric Cerebral Performance Category of 1 to 3 or no change from baseline. ROSC indicates return of spontaneous circulation. *Mean diastolic blood pressure (DBP) ≥25/30 mm Hg refers to patients whose mean diastolic blood pressure over (up to) the first 10 minutes of CPR was ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old.

in 19%. During CPR, the median SBP was 74 mm Hg, median DBP was 29 mm Hg, median chest compression rate was 112 bpm, and median chest compression fraction was 0.9. Median duration of CPR was 8 minutes; 42% received 1 to 5 minutes, 21% received 6 to 15 minutes, 18% received 16 to 35 minutes, and 19% received >35 minutes of CPR. The duration of CPR was ≤10 minutes for 55% of these CPR events. The prearrest mean SBP and DBP at 6 to 10 minutes before CPR did not differ between all patients who survived to hospital discharge and patients who did not survive, but the mean DBP at 6 to 10 minutes before CPR was significantly higher among infants <1 year old who survived versus infants who did not survive (42 [quartiles, 36, 52] mm Hg versus 35 [quartiles, 31, 45] mm Hg; $P<0.005$). Among the index event characteristics, lower survival rates were associated with vasoactive infusions and invasive mechanical ventilation in place at the time of event, longer duration of CPR, number of epinephrine doses during CPR, and administration of either calcium or sodium bicarbonate during CPR. AQ12

T3 Outcomes are summarized in Table 3. Ninety percent of patients survived the event, 68% with ROSC and 22% by the provision of extracorporeal life support during CPR. Forty-seven percent survived to hospital discharge, and 43% survived to discharge with favorable neurological outcome. Among patients surviving to hospital discharge, 91% survived with a favorable neurological outcome, and 71% survived without substantive new functional morbidities by Functional Status Scale scores.

Maintaining DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old during the early (up to first 10) minutes of CPR was significantly associated with survival (adjusted RR [aRR], 1.7; 95% CI, 1.2–2.6; $P=0.007$) and survival with favorable neurological outcome (aRR, 1.6; 95% CI, 1.1–2.5; $P=0.02$) with multivariable Poisson regression (Table 4). The aRR of ROSC >20 minutes when maintaining DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old during the early minutes of CPR was 1.2 (95% CI, 0.9–1.5; $P=0.20$). Maintaining SBP ≥60 mm Hg during CPR in infants and ≥80 mm Hg in children ≥1 year old was not significantly associated with survival to discharge (aRR, 1.1; 95% CI, 0.8–1.6), survival with favorable neurological outcome (aRR, 1.0; 95% CI, 0.7–1.4), or ROSC >20 minutes (aRR, 1.1; 95% CI, 0.9–1.3). T4

Similar to the primary multivariable Poisson regression modeling, backward stepwise models showed that maintaining DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old during the early (up to first 10) minutes of CPR was significantly associated with survival to discharge (aRR, 1.6; 95% CI, 1.1–2.3; $P=0.01$) and survival with favorable neurological outcome (aRR, 1.5; 95% CI, 1.0–2.2; $P=0.04$; Tables II and III in the online-only Data Supplement). Because prearrest DBP was not different among overall survivors versus nonsurvivors and was missing for 19 of 164 children, the prearrest DBP was not included for adjustment in either the primary Poisson model or the backward stepwise model. After adjustment for prearrest DBP was forced into the Poisson model, the resultant aRR of survival to hospital discharge associated with DBP ≥25 mm Hg in infants and ≥30 mm Hg in children was 1.4 (95% CI, 0.9–2.2; $P=0.155$). In addition, maintaining SBP ≥60 mm Hg during CPR in infants and ≥80 mm Hg in children ≥1 year old was again not significantly associated with survival to discharge (RR, 1.0; 95% CI, 0.7–1.4) or survival with favorable neurological outcome (RR, 0.9; 95% CI, 0.6–1.3).

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Table 1. Prearrest Characteristics by Survival to Hospital Discharge

	Overall (n=164)	Survival to Hospital Discharge		*P* Value
		Yes (n=77)	No (n=87)	
Age, y	0.7 (0.1, 3.1)	0.4 (0.0, 1.6)	1.0 (0.1, 5.2)	0.057*
Age, n (%)				0.162†
<1 mo	41 (25)	22 (29)	19 (22)	
1 mo–<1 y	57 (35)	31 (40)	26 (30)	
1–<8 y	41 (25)	14 (18)	27 (31)	
8–<19 y	25 (15)	10 (13)	15 (17)	
Male, n (%)	90 (55)	47 (61)	43 (49)	0.158†
Race, n (%)				0.248†
White	82 (50)	37 (48)	45 (52)	
Black or African American	37 (23)	12 (16)	25 (29)	
Other	8 (5)	5 (6)	3 (3)	
Not reported	37 (23)	23 (30)	14 (16)	
Preexisting conditions, n (%)				
Respiratory insufficiency	132 (80)	59 (77)	73 (84)	0.324†
Hypotension	128 (78)	51 (66)	77 (89)	<0.001†
Congestive heart failure	19 (12)	7 (9)	12 (14)	0.465†
Pneumonia	13 (8)	8 (10)	5 (6)	0.386†
Sepsis	44 (27)	20 (26)	24 (28)	0.861†
Renal insufficiency	24 (15)	8 (10)	16 (18)	0.186†
Malignancy	5 (3)	1 (1)	4 (5)	0.372†
Congenital heart disease	99 (60)	55 (71)	44 (51)	0.007†
Illness category, n (%)				0.090†
Surgical cardiac	88 (54)	49 (64)	39 (45)	
Medical cardiac	25 (15)	8 (10)	17 (20)	
Surgical noncardiac	13 (8)	5 (6)	8 (9)	
Medical noncardiac	37 (23)	14 (18)	23 (26)	
Unknown	1 (1)	1 (1)	0 (0)	
Baseline PCPC, n (%)				0.940‡
Normal	77 (47)	32 (42)	45 (52)	
Mild disability	47 (29)	26 (34)	21 (24)	
Moderate disability	23 (14)	13 (17)	10 (11)	
Severe disability	13 (8)	6 (8)	7 (8)	
Coma/vegetative state	4 (2)	0 (0)	4 (5)	
Baseline Functional Status Scale score	8 (6, 11)	8 (6, 11)	7 (6, 11)	0.120*

PCPC indicates Pediatric Cerebral Performance Category.
*The Wilcoxon rank-sum test was used for continuous variables.
†The Fisher exact test was used for categorical variables.
‡The Cochran-Armitage test for trend was used for baseline PCPC. Percentages are based on row totals.

The ROC curves identified optimal thresholds for mean DBP based on Euclidean distance without consideration of covariables: 27 mm Hg in infants and 31.75 mm Hg in children ≥1 year old. In addition, the restricted cubic spline curves demonstrate precipitous decreases in the survival rate with a mean DBP <20 mm Hg in infants and <25 mm Hg in children ≥1 year old (Figure 2). The lowest mean DBP with survival to hospital discharge was 16 mm Hg for infants and 18 mm Hg for children ≥1 year old.

The post hoc Poisson regression model analysis using the alternative mean DBP targets of ≥20 mm Hg for infants and ≥25 mm Hg in children also demonstrated an association with survival to hospital discharge (aRR, 2.2; 95% CI, 1.2–4.2; *P*=0.01). The rate of survival to hospital discharge was 6 of 19 (32%) when mean DBP was <20 mm Hg compared with 14 of 34 (41%) when mean DBP was <25 mm Hg in infants (difference in survival rate, −10% with 95% bootstrap CI of −26 to 6). Similarly, the rate of survival to hospital discharge was 4 of 16 (25%) when mean DBP was <25 mm Hg compared with 8 of 29 (28%) when mean DBP was <30 mm Hg in children <1 year (difference in survival rate, −3% with 95% bootstrap CI of −19 to 13).

Table 5 illustrates the association of DBP with survival outcomes in the subgroup with CPR >10 minutes with multivariable Poisson regression modeling. For this subgroup, maintaining DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old during the early (up to first 10) minutes of CPR was again significantly associated with survival to discharge (aRR, 2.1; 95% CI, 1.0–4.6; *P*=0.03) and survival with favorable neurological outcome (aRR, 2.5; 95% CI, 1.1–5.8; *P*=0.02). T5

Post hoc Poisson regression model analyses using exclusively mean DBP data during the first 5 minutes of CPR led to results that were nearly identical to the original Poisson regression model analyses that included DBP data up to 10 minutes (Table 4).

DISCUSSION

These data support the hypothesis that mean DBP during the early minutes of pediatric in-hospital CPR is associated with survival to hospital discharge and survival to hospital discharge with favorable neurological outcome among patients with invasive arterial BP monitoring at the time of cardiac arrest. Specifically, when mean DBP was maintained ≥25 mm Hg during the early minutes of CPR in infants <1 year old and ≥30 mm Hg in children ≥1 year old, patients were 70% more likely to survive to hospital discharge and 60% more likely to survive to hospital discharge with favorable neurological outcome compared with patients not attaining these mean DBP thresholds. These findings were further supported by stepwise multivariable modeling,

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Table 2. Event Characteristics by Survival to Hospital Discharge

		Survival to Hospital Discharge		
	Overall (n=164)	Yes (n=77)	No (n=87)	*P* Value
Average hemodynamics over (up to) the first 10 min				
DBP, mm Hg	29.3 (22.8, 37.9)	30.9 (25.0, 38.7)	27.6 (21.0, 36.5)	0.097*
<1 y	28.0 (22.4, 35.2)	30.0 (24.0, 37.0)	25.3 (18.6, 33.0)	0.038*
≥1 y	31.9 (25.0, 42.0)	33.0 (26.2, 40.0)	30.0 (22.9, 44.5)	0.514*
SBP, mm Hg	74.4 (54.9, 98.2)	69.0 (53.8, 93.0)	77.6 (55.5, 101.4)	0.180*
<1 y	65.9 (50.8, 87.0)	65.0 (53.8, 85.8)	68.0 (49.6, 88.1)	0.648*
≥1 y	84.8 (65.9, 121.0)	81.0 (55.6, 116.2)	93.5 (70.1, 121.6)	0.198*
Compression rate, bpm	112.4 (98.1, 123.4)	113.4 (92.8, 129.2)	111.5 (102.9, 123.1)	0.617*
Chest compression fraction	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.437*
Mean DBP above target, n (%)†	101 (62)	55 (71)	46 (53)	0.016‡
Mean SBP above target, n (%)§	93 (57)	44 (57)	49 (56)	1.000‡
Average hemodynamics 6–10 min before the arrest (n=145)				
DBP, mm Hg	41.5 (34.0, 50.2)	43.0 (36.0, 52.0)	40.0 (32.8, 48.6)	0.098*
<1 y	39.0 (32.4, 46.4)	41.6 (36.0, 52.0)	35.2 (31.2, 45.0)	0.005*
≥1 y	46.0 (37.2, 56.4)	48.0 (38.7, 52.0)	45.8 (36.0, 57.2)	1.000*
SBP, mm Hg	75.0 (59.2, 92.0)	77.8 (57.6, 94.0)	74.0 (59.2, 89.6)	0.364*
<1 y	68.3 (55.6, 86.6)	75.2 (55.6, 93.8)	64.0 (56.0, 75.4)	0.055*
≥1 y	80.4 (62.8, 102.0)	80.2 (63.0, 113.6)	82.2 (62.8, 100.0)	0.893*
Mean arterial pressure, mm Hg	51.6 (43.0, 65.6)	54.3 (46.0, 69.6)	50.0 (42.0, 62.4)	0.170*
<1 y	49.4 (40.2, 60.8)	51.8 (42.4, 65.0)	45.6 (40.0, 57.0)	0.053*
≥1 y	59.7 (47.0, 71.6)	61.2 (47.6, 76.4)	57.0 (46.4, 71.6)	0.686*
Location of CPR event, n (%)				0.026‡
PICU	64 (39)	23 (30)	41 (47)	
CICU	100 (61)	54 (70)	46 (53)	
Immediate cause, n (%)				
Hypotension	110 (67)	49 (64)	61 (70)	0.408‡
Respiratory decompensation	72 (44)	34 (44)	38 (44)	1.000‡
Arrhythmia	31 (19)	14 (18)	17 (20)	0.845‡
First documented rhythm at time CPR initiated (collapsed), n (%)				0.068‡
Asystole/PEA	48 (29)	19 (25)	29 (33)	
VF/VT	19 (12)	5 (6)	14 (16)	
Bradycardia with poor perfusion	91 (55)	48 (62)	43 (49)	
Unknown	6 (4)	5 (6)	1 (1)	
Duration or CPR, min	8.0 (3.0, 27.0)	5.0 (2.0, 13.0)	17.5 (4.0, 38.0)	<0.001*
Duration of CPR, n (%)				<0.001‖
1–5 min	69 (42)	43 (56)	26 (30)	
6–15 min	34 (21)	19 (25)	15 (17)	
16–35 min	29 (18)	8 (10)	21 (24)	
>35 min	31 (19%	7 (9)	24 (28)	
Unknown	1 (1)	0 (0)	1 (1)	
Interventions in place, n (%)				
Central venous catheter	142 (87)	66 (86)	76 (87)	0.821‡
Vasoactive infusion	128 (78)	53 (69)	75 (86)	0.008‡

(*Continued*)

Table 2. Continued

	Overall (n=164)	Survival to Hospital Discharge		*P* Value
		Yes (n=77)	No (n=87)	
Invasive mechanical ventilation	134 (82)	57 (74)	77 (89)	0.025‡
Noninvasive ventilation	19 (12)	11 (14)	8 (9)	0.338‡
Time, n (%)¶				0.157‡
Weekday	102 (62)	51 (66)	51 (59)	
Weeknight	34 (21)	11 (14)	23 (26)	
Weekend	28 (17)	15 (19)	13 (15)	
Pharmacological interventions				
Epinephrine, n (%)	143 (87)	65 (84)	78 (90)	0.355‡
Doses (when used), n	3 (1, 5)	2 (1, 3)	3 (2, 7)	<0.001*#
Calcium, n (%)	78 (48)	28 (36)	50 (57)	0.008‡
Sodium bicarbonate, n (%)	93 (57)	36 (47)	57 (66)	0.018‡

CICU indicates cardiac intensive care unit; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; PEA, pulseless electric activity; PICU, pediatric intensive care unit; SBP, systolic blood pressure; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*The Wilcoxon rank-sum test was used for continuous variables.

†Target DBP is ≥25 mm Hg for infants and ≥30 mm Hg for children.

‡The Fisher exact test was used for categorical variables.

§Target SBP is ≥60 mm Hg for infants and ≥80 mm Hg for children.

‖The Cochran-Armitage test for trend was used for duration of CPR category variables.

¶Weekdays are Monday through Friday, 7 AM to 10:59 PM; weeknights are Monday through Friday, 11 PM to 6:59 AM; and weekends are Saturday and Sunday.

#The comparison of number of epinephrine doses is based only on index events for which epinephrine was used.

ROC curves, cubic spline analyses, and subgroup analyses of patients with CPR duration >10 minutes. Post hoc analyses showed similar associations with survival to hospital discharge when mean DBP during CPR was maintained ≥20 mm Hg in infants <1 year old and ≥25 mm Hg in children ≥1 year old.

Animal studies have established that survival after CPR depends on attaining adequate myocardial blood flow during CPR, and the primary determinant of myocardial blood flow is the coronary perfusion pressure (CoPP; arterial DBP minus right atrial diastolic pressure).[9–11,25,26] In multiple animal models, survival is associated with CoPP >20 mm Hg and DBP >30 mm Hg during CPR.[9–11,27,28] In a single-center study of adult out-of-hospital cardiac arrests, 24 patients with ROSC had a mean maximum CoPP and DBP of 26±8 and 35±12 mm Hg compared with mean maximum CoPP and DBP of 8±10 and 24±15 mm Hg among 76 patients without ROSC.[12] Similar to laboratory findings, CoPP >15 mm Hg during CPR was necessary to attain ROSC, CoPP >25 mm Hg was much more likely to result in ROSC, and none of the patients had ROSC with DBP <18 mm Hg. However, none of their 100 patients survived to hospital discharge, in part because these out-of-hospital cardiac arrests were quite prolonged when arterial catheters were placed in the emergency department for BP measurement. In contrast, our PICqCPR cohort with arterial catheters in place before CPR was started and prompt provision of CPR had far superior rates of survival to hospital discharge.

Current CPR training programs focus on standardizing CPR using a provider-centric paradigm with prescriptive chest compression depths and rates, as well as timing and dosing of epinephrine, without consideration of individual patient-level hemodynamic effects.[29,30] A standardized provider-centric paradigm allows simpler, algorithmic care in the high-intensity, time-sensitive clinical scenario of cardiac arrest. However, laboratory studies in multiple animal models of cardiac arrest have established that "personalized" hemodynamic-directed CPR to maintain CoPP >20 mm Hg through titration of chest compression force and vasoactive medication dosing improves outcomes compared with the traditional provider-centric approach.[27,28,31,32] In 2015, the American Heart Association guidelines suggested that it is reasonable for rescuers to use BP monitoring to guide CPR yet noted the important gap in knowledge about appropriate BP targets during CPR.[4,5] These PICqCPR data support a target DBP ≥25 mm Hg during the early minutes of CPR in infants and ≥30 mm Hg in children ≥1 year old.

The PICqCPR findings raise the question of whether a DBP ≥25 mm Hg during CPR in infants <1 year old and ≥30 mm Hg in children ≥1 year old is the optimal target. Unfortunately, these data do not provide a definitive answer to this important question. Although this study was designed to be the largest published clinical investigation with invasive BP monitoring during CPR to date, the investigators were aware a priori that the number of patients would not support adequately powered separate derivation and validation data sets. Therefore, the

Table 3. Summary of Outcomes

	Overall (n=164)
Immediate outcome, n (%)	
ROC	148 (90)
ROSC ≥20 min	112 (68)
ROC with E-CPR	36 (22)
Died	16 (10)
Hospital discharge outcomes	
Survival, n (%)*	77 (47)
Survival with favorable neurological outcome, n (%)†	70 (43)
PCPC	
Normal	24 (15)
Mild disability	27 (16)
Moderate disability	17 (10)
Severe disability	8 (5)
Coma/vegetative state	1 (1)
Brain death	87 (53)
FSS score in survivors	9 (8, 12)
FSS score change from baseline in survivors	0 (0, 3)
New morbidity at hospital discharge‡	22 (29)

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E-CPR indicates extracorporeal cardiopulmonary resuscitation; FSS, Functional Status Score; PCPC, Pediatric Cerebral Performance Category; ROC, return of circulation; and ROSC, return of spontaneous circulation.

*Survival was assumed for 1 subject alive who remained in the hospital 6 months after cardiopulmonary resuscitation at the end of the study. FSS and PCPC were obtained at that time for this assumed survivor.

†Favorable neurological outcome was defined as discharge PCPC of normal, mild disability, or moderate disability or a discharge PCPC no worse than baseline PCPC.

‡New morbidity was defined as an increase of at least 3 between baseline and discharge FSS score.

PICqCPR investigators chose to test the a priori hypothesis that mean DBP ≥25 mm Hg during CPR in infants and ≥30 mm Hg in children ≥1 year old would be associated with survival to hospital discharge. The Poisson multivariable modeling, stepwise multivariable modeling, ROC curves, cubic spline analyses, and subgroup analyses of patients with CPR duration >10 minutes all support this hypothesis. Because the cubic spline analyses suggested that lower DBP thresholds might be appropriate, post hoc analyses were performed and demonstrated that maintaining DBP ≥20 mm Hg in infants <1 year old and ≥25 mm Hg in children ≥1 year old is similarly associated with survival to hospital discharge. However, the cubic spline data further suggest that survival rates decrease markedly with mean DBP <20 mm Hg in infants and DBP <25 mm Hg in children ≥1 year old. Therefore, it may be prudent to choose DBP targets that are not too close to pressures that result in inadequate coronary perfusion and worse outcomes. Thus, further refinement of optimal DBP targets for CPR guidelines is a fertile area for future investigation.

The importance of hemodynamic targets during CPR emanates from the potential to titrate CPR processes and thereby to improve outcomes. For the many children with arterial catheters during CPR whose DBP is below the target, the resuscitating team can focus its efforts to increase the DBP by improving basic life support, adding vasoactive medications, or addressing potentially reversible causes. Basic life support efforts to improve DBP during CPR include providing an adequate chest compression rate and force/depth, avoiding interruptions in compressions, and encouraging adequate venous return by allowing full chest recoil and avoiding hyperventilation.[3,5] Administering a vasopressor medication such as epinephrine can further increase DBP, especially in the setting of excellent CPR.[3,33] In addition, the resuscitating team should consider potentially reversible causes of low DBP during CPR such as pulmonary thromboembolism, tension pneumothorax, cardiac tamponade, toxins, or hypovolemia. Conversely, attaining target DBP during CPR is reassuring about the adequacy of CPR hemodynamics. The resuscitating team may then focus on reasons that adequate CPR hemodynamics have not resulted in ROSC such as hypoglycemia, hyperkalemia, toxins, or myocardial pathology that precludes ROSC (eg, postsurgical cardiomyopathy, acute myocarditis, or end-stage heart failure).

The CPR for these critically ill children in the PICqCPR study was remarkably effective despite inherent limitations on survival and neurological outcomes based on underlying causes of their cardiac arrests and preex-

Table 4. Multivariable Poisson Models of BP During CPR With Survival Outcomes

	Survival to Hospital Discharge		Survival to Hospital Discharge With Favorable Neurological Outcome	
Predictor	aRR* (95% CI)	*P* Value	aRR* (95% CI)	*P* Value
Average DBP above target† over (up to) the first 10 min	1.7 (1.2–2.6)	0.007	1.6 (1.1–2.5)	0.022
Average DBP above target† over (up to) the first 5 min	1.7 (1.2–2.6)	0.007	1.6 (1.1–2.5)	0.020
Average SBP above target‡ over (up to) the first 10 min	1.1 (0.8–1.6)	0.491	1.0 (0.7–1.4)	0.955

aRR indicates adjusted relative risk; BP, blood pressure; CI, confidence interval; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Multivariable models adjusted for age category (<1 year, ≥1 year), initial rhythm, location of CPR, and study site.

†DBP is considered meeting target if ≥25 mm Hg for neonates and infants and ≥30 mm Hg for children.

‡SBP is considered meeting target if ≥60 mm Hg for neonates and ≥80 mm Hg for children.

Table 5. Multivariable Poisson Models of BP During CPR With Survival Outcomes (Subjects With CPR Duration ≥ 10 Minutes)

	Survival to Hospital Discharge		Survival to Hospital Discharge With Favorable Neurological Outcome	
Predictor	aRR* (95% CI)	*P* Value	aRR* (95% CI)	*P* Value
Mean DBP above target† over (up to) the first 10 min	2.1 (1.0–4.6)	0.031	2.5 (1.1–5.8)	0.016
Mean SBP above target‡ over (up to) the first 10 min	1.3 (0.7–2.6)	0.355	1.2 (0.6–2.3)	0.570

aRR indicates adjusted relative risk; BP, blood pressure; CI, confidence interval; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*Multivariable models adjust for age category (<1 year, ≥1 year), initial rhythm, and location of CPR.

†DBP is considered meeting target if ≥25 mm Hg for neonates and infants and ≥30 mm Hg for children.

‡SBP is considered meeting target if ≥60 mm Hg for neonates and ≥80 mm Hg for children.

isting comorbidities. Ninety percent of these patients survived the CPR event, 68% by attaining ROSC and 22% by provision of extracorporeal life support during CPR. In addition, 47% survived to hospital discharge, 91% of these survivors had favorable neurological outcomes, and 71% survived without a substantive new functional morbidity. The excellent outcomes reflect the overall outstanding quality of CPR with a median SBP of 74 mm Hg (quartiles, 55, 99), median DBP of 29 mm Hg (quartiles, 28, 38), median chest compression rate of 112 bpm (quartiles, 98, 123), and median chest compression fraction of 0.9 (quartiles, 0.8, 1.0).[3,34,35]

The generalizability of findings from this multicenter study should be cautiously interpreted in light of several limitations. The definition of mean DBP during the early minutes of CPR required that arterial BP was measured continuously at the start of CPR. It is possible that the relationship of DBP with outcome may differ at a later time during CPR. Forty-five percent of the patients had >10 minutes of CPR; therefore, hemodynamic data were not available for the entirety of their CPR because the study design was based on practical limitations in data acquisition. Nevertheless, the relationship of mean DBP with outcomes was similarly demonstrable among patients with >10 minutes of CPR (Table 5). Mean DBP during the early minutes of CPR was defined as mean DBP during the first 10 minutes of CPR. Because of concerns that the effect of CPR hemodynamics on outcome may be more important during the first 5 minutes of CPR, post hoc multivariable analyses were performed that used exclusively mean DBP data during the first 5 minutes of CPR and revealed nearly identical findings as the first 10-minute analyses (Table 4). Survival rates from CPR depend on many other factors besides DBP during CPR, including underlying causes of the cardiac arrest, comorbidities, and the prearrest and postarrest care. The CPCCRN sites are all large academic pediatric ICUs, and the quality of care provided before and after cardiac arrests may differ from that of other institutions. Forty percent of children with CPR in an ICU have arterial catheters at the time of CPR; therefore, DBP targets may not be applicable to the other 60%. Among children who met inclusion criteria, 33% were excluded because waveform data were inadequate for determination of mean DBP per study protocol. Notably, characteristics and outcomes of included patients were similar to those of excluded patients (Table I in the online-only Data Supplement), and the survival rate was similar to a previous CPCCRN ICU CPR study that included children with and without arterial BP data.[36] AQ15 Nevertheless, this is a highly selected population: all had prearrest invasive arterial BP monitoring; thus, their providers assumed that they differed from other patients in the ICU, and they clearly differ from children who receive CPR in other settings (eg, hospital wards, emergency departments, out-of-hospital settings). Notably, this population is precisely the group who can benefit from a BP target because they have continuous invasive BP monitoring available for titration during CPR. Although the prearrest BP at 6 to 10 minutes before CPR did not differ overall between patients who survived to hospital discharge and patients who did not survive, the mean DBP at 6 to 10 minutes before CPR was significantly higher among infants <1 year old who survived versus infants who did not survive (42 [quartiles, 36, 52] mm Hg versus 35 [quartiles, 31, 45] mm Hg), raising the possibility that the association of DBP during CPR with outcomes in infants may be related to differences in prearrest DBP. As a frame of reference, the 50th percentile DBP for a normal 1-year-old boy is 37 (quartiles, 34, 39) mm Hg.[37] After additionally controlling for prearrest DBP, the resultant aRR of survival to hospital discharge associated with DBP ≥25 mm Hg was 1.4 (95% CI, 0.9–2.2; *P*<0.155). The aRR was similar to the model without adjustment for prearrest DBP, but the CI crossed 1.0, presumably as a result of the reduction in power as the number decreased from 164 to 145 because of unavailable prearrest BP data. The quality of CPR for chest compression fraction and chest compression rate was excellent in this study by established standards and previously published data.[3,34,35] Perhaps the relationship of DBP during CPR with outcome may differ if the chest compression fraction is much less or the chest compression rate is much lower. The data available had adequate variability in mean DBP to evaluate its association with outcome.

CONCLUSIONS

This multicenter prospective observational study supports the hypothesis that a mean DBP ≥25 mm Hg during the early minutes of CPR in infants and ≥30 mm Hg in children ≥1 year old is associated with substantially greater likelihood of survival to hospital discharge and survival with favorable neurological outcome. These PICqCPR data provide evidence to support targeting DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year old during pediatric CPR in a pediatric ICU when invasive arterial pressure is monitored, and they highlight the importance of avoiding DBP <20 mm Hg in infants and DBP <25 mm Hg in children ≥1 year old.

ARTICLE INFORMATION

Received October 19, 2017; accepted December 7, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.032270/-/DC1.

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Acknowledgments

All of the listed authors satisfy the *International Committee of Medical Journal Editors* authorship criteria and have access to the data. Neither this manuscript nor one with substantially similar content has been published or is being considered for publication elsewhere. We agree to provide access to our data. AQ16

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Sources of Funding

This PICqCPR study was conducted by the CPCCRN, and all sites were funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. There was no compensation for persons who have made substantial contributions but are not authors. This work was supported in part by the following cooperative agreements from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, and Department of Health and Human Services: UG1HD050096, UG1HD049981, UG1HD049983, UG1HD063108, UG1HD083171, UG1HD083166, UG1HD083170, U10HD050012, U10HD063106, U10HD063114, and U01HD049934.

Disclosures

None.

APPENDIX

CPCCRN PICqCPR Investigators

In addition to the listed collaborators, the following PICqCPR Investigators were involved in study design and/or data acquisition: Athena F. Zuppa, MD, MSCE; Katherine Graham, BS; Carolann Twelves, RN; William Landis, BSE; Mary Ann DiLiberto, RN; Elyse Tomanio, RN; Jeni Kwok, JD, Michael J. Bell, MD; Alan Abraham, MBA; Anil Sapru, Mustafa F. Alkhouli, BA, Sabrina Heidemann, MD, Ann Pawluszka, RN, Mark W. Hall, MD, Lisa Steele, RN, Thomas P. Shanley, MD, Monica Weber, RN, Heidi J. Dalton, MD, Aimee La Bell, RN, Peter M. Mourani, MD, Kathryn Malone, RN, Russell Telford, MS, Whitney Coleman, Alecia Peterson, MS, Julie Thelen, Allan Doctor, MDCPCCRN PICqCPR Investigators AQ20 AQ21

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