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

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Abstract

Background—Based on laboratory cardiopulmonary resuscitation (CPR) investigations and limited adult data demonstrating that survival depends on attaining adequate arterial diastolic blood pressure (DBP) during CPR, American Heart Association recommends using BP to guide pediatric CPR. However, evidence-based BP 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 prior to 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 mmHg during CPR in infants and ≥30 mmHg 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 neurologic outcome, defined as Pediatric Cerebral Performance Categories 1–3 or no worse than pre-arrest baseline. Multivariable Poisson regression models with robust error estimates were used to estimate the relative risk of outcomes.

Results—Blinded investigators analyzed BP waveforms during CPR from 164 children, including 60% <1 year old, 60% with congenital heart disease, and 54% post-cardiac surgery. 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 minutes, 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 neurologic outcome. Maintaining mean DBP ≥25 mmHg in infants and ≥30 mmHg in children ≥1 year old occurred in 101/164 children (62%) and was associated with survival (adjusted Relative Risk [aRR] 1.7; 95% CI, 1.2–2.6; P=0.007) and survival with favorable neurologic outcome (aRR 1.6; 95% CI, 1.1–2.5; P=0.02).

Conclusion—These data demonstrate that mean DBP ≥25 mmHg during CPR in infants and ≥30 mmHg in children ≥1 year old was associated with greater likelihood of survival to hospital discharge and survival with favorable neurologic outcome.

Keywords

Cardiopulmonary resuscitation (CPR); cardiac arrest; pediatric; in-hospital; survival; outcomes

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Introduction

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: "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," based primarily on data from animal studies.[4, 5] However, "because the precise numerical targets for these parameters during resuscitation [for adults or children] have not yet been established, these were not specified."[4, 5]

Among the 5–10,000 American children who require in-hospital CPR annually, >95% occur 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 is 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 AHA pediatric CPR guidelines. Based on animal data and clinical experience, the hypothesis was that a relaxation phase ("diastolic") BP ≥25 mmHg during CPR in infants and ≥30 mmHg 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 neurologic outcome.[9–12] In addition, the overall relationships of diastolic BPs with outcomes were evaluated using cubic splines in infants and children ≥1 year old. Because brain perfusion depends on both compression phase ("systolic") BP and diastolic BP and because many deaths after ROSC are due to neurologic injuries, the relationship of systolic BP during CPR with outcomes was also evaluated.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. Study datasets will be publicly available through CPCCRN.org three years after study completion.[13]

The Pediatric Intensive Care Quality of CPR (PICqCPR) Study 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 blood pressure monitoring prior to and during CPR in a CPCCRN Pediatric ICU or Pediatric Cardiac ICU were eligible. Patients were enrolled from eleven institutions between July 1, 2013 and June 30, 2016. Cardiac arrests were identified at each site using a 24-hour paging system and/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 (DCC).

Inclusion criteria were patients with: 1) invasive arterial BP monitoring prior to and during CPR; 2) first compression of CPR captured on transmitted arterial BP waveform data; 3) at least one minute of continuous arterial BP waveforms; and 4) central venous pressure, respiratory plethysmography or ECG artifact available on transmitted arterial BP waveform data to allow determination of CPR starts and stops. Exclusion criteria were: 1) unable to determine diastolic blood pressure (DBP) (e.g., lack of arterial waveform due to line interruption for blood draw or truncation of BP waveform obscuring DBP) or 2) unable to determine when CPR started and stopped.

The overall goal was to evaluate the association of BP during the relaxation phase of CPR ("diastolic" BP) with outcomes of ROSC >20 minutes, survival to hospital discharge, and survival to hospital discharge with a favorable neurologic outcome. The primary hypothesis was that mean DBP ≥25 mmHg during CPR in infants and ≥30 mmHg 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 more than one CPR event because a patient can only survive once per hospitalization.[14] Secondary hypotheses were: 1) that these DBPs during CPR would be associated with higher rates of ROSC and survival to discharge with a favorable neurologic outcome; and 2) that mean compression phase ("systolic") blood pressure (SBP) ≥60 mmHg during CPR in infants and ≥80 mmHg 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: 1) patient factors such as demographics, preexisting conditions, and illness categories, 2) arrest characteristics such as interventions in place at time of arrest, first documented rhythm, immediate cause of arrest, duration of CPR, defibrillation shocks, and pharmacologic interventions, and 3) outcome data such as ROSC >20 minutes, survival to hospital discharge and survival to hospital discharge with a favorable neurologic outcome. Pre-arrest blood pressures were obtained during the 10 minutes prior to initiation of CPR. Pediatric Cerebral Performance Categories (PCPC) pre-arrest and at hospital discharge were documented, as well as pediatric Functional Status Scale (FSS) scores at baseline and hospital discharge. Survival to hospital discharge with a favorable neurologic outcome was defined as PCPC 1–3 or no worse than pre-arrest PCPC.[14, 15] Substantive new functional morbidity was defined as an increase in the FSS 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, de-identified, and then transmitted and stored at the DCC. De-identified 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. Systolic BP was sampled at the peak of the arterial pressure tracing for each compression; DBP was sampled during mid-diastole for each compression (Figure 1). This process allowed extraction of numerical X (time in seconds) and Y (arterial BP) data.[17] Central venous pressure, left atrial pressure, ECG 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 was the average BP 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 using frequencies and percentages or the median and quartiles. Differences in these characteristics between patients who did and did not survive to hospital discharge were examined using Fisher's 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 based on 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 ten minutes of CPR.[18] These models were adjusted for age category, initial cardiac rhythm, and location of CPR (cardiac versus general pediatric ICU), which were specified *a priori* based on 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] Relative risks are presented with their 95% confidence intervals (CIs).

The robustness of the main findings was addressed in several ways. First, multivariable models were constructed using 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 pre-arrest characteristics associated with survival. Second, the appropriateness of the *a priori* thresholds for DBP was assessed. Data-driven thresholds were obtained based on receiver operating characteristic (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 allow 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. 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 20^{th}, 40^{th}, 60^{th} and 80^{th} percentiles. The fitted spline is a smooth curve of the estimated survival rate as a continuous function of DBP, adjusting for covariables (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 in order to verify that the mean DBP in the first 10 minutes is still predictive of survival. All analyses were performed using SAS software v9.4 (Cary, NC).

Based on 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 6–10, the Poisson regression model analyses for relationships of mean DBP ≥25 mmHg during CPR in infants and ≥30 mmHg in children ≥1 year with hospital discharge outcomes were repeated, using exclusively mean DBP data during the first 5 minutes of CPR. Because pre-arrest DBP was higher among infants who survived to hospital discharge versus infants who did not survive, adjustment for pre-arrest 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 mean DBP ≥20 mmHg during CPR in infants and ≥25 mmHg 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 regarding the number of cardiac arrests or number of children with CPR ≥1 minute was not available. Figure 3 is an Utstein-style diagram of patients included and excluded. Maintaining mean DBP during CPR ≥25 mmHg in infants and ≥30 mmHg in children ≥1 year old occurred in 101/164 children (62%). Pre-arrest patient characteristics of this overall cohort are described in Table 1, as are comparisons of these characteristics among children who survived to hospital discharge versus 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 (i.e., post-operative 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 pre-arrest characteristics, pre-existing 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 excluded patients (Supplemental Table 1).

Event characteristics of the index CPR events in the overall cohort are described in Table 2, as are comparisons of these characteristics among children who survived to hospital discharge versus those who died. Immediate causes of the arrest were hypotension in 67%, respiratory decompensation in 44%, and arrhythmia in 19%. During CPR, the median SBP was 74 mmHg, median DBP was 29 mmHg, median chest compression rate was 112 beats/minute, and median chest compression fraction was 0.9. Median duration of CPR was 8 minutes; 42% received 1–5 minutes, 21% received 6–15 minutes, 18% received 16–35 minutes, and 19% received >35 minutes. The duration of CPR was ≤10 minutes for 55% of these CPR events. The pre-arrest mean systolic and diastolic BP at 6–10 minutes prior to CPR did not differ between all patients who survived to hospital discharge and patients who did not survive, but the mean DBP at 6–10 minutes prior to CPR was significantly higher among infants <1 year old who survived versus infants who did not survive (42 [quartiles 36, 52] mmHg versus 35 [31, 45] mmHg, $P<0.005$). 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 the administration of either calcium or sodium bicarbonate during CPR.

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 neurologic outcome. Among patients surviving to hospital discharge, 91% survived with a favorable neurologic outcome and 71% survived without substantive new functional morbidities by FSS scores.

Maintaining DBP ≥25 mmHg in infants and ≥30 mmHg in children ≥1 year old during the early (up to first 10) minutes of CPR was significantly associated with survival (adjusted relative risk [aRR] 1.7; 95% CI, 1.2–2.6; P=0.007) and survival with favorable neurologic outcome (aRR 1.6; 95% CI, 1.1–2.5; P=0.02), using multivariable Poisson regression (Table 4). The adjusted relative risk of ROSC >20 minutes when maintaining DBP ≥25 mmHg in infants and ≥30 mmHg in children ≥1 year old during the early minutes of CPR was 1.2 (0.9, 1.5), P = 0.20. Maintaining SBP ≥60 mmHg during CPR in infants and ≥80 mmHg 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 neurologic outcome (aRR 1.0; 95% CI, 0.7–1.4), or ROSC >20 minutes (aRR 1.1; 95% CI, 0.9–1.3).

Similar to the primary multivariable Poisson regression modelling, backward stepwise models showed that maintaining DBP ≥25 mmHg in infants and ≥30 mmHg 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 neurologic outcome (aRR 1.5; 95% CI, 1.0–2.2; P=0.04) (Supplemental Table 2 and Supplemental Table 3). Because pre-arrest DBP was not different among overall survivors versus non-survivors and was missing on 19/164 children, the pre-arrest DBP was not included for adjustment in either the primary Poisson model or the backward stepwise model. After forcing adjustment for pre-arrest DBP into the Poisson model, the resultant aRR of survival to hospital discharge associated with DBP ≥25 mmHg in infants and ≥30 mmHg in children was 1.4 (0.9, 2.2), P=0.155. In addition, maintaining SBP ≥60 mmHg during CPR in infants and ≥80 mmHg 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 neurologic outcome (RR 0.9; 95% CI, 0.6–1.3).

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

The post-hoc Poisson regression model analysis using the alternative mean DBP targets of ≥20 mmHg for infants and ≥25 mmHg 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 6/19 (32%) when mean DBP was <20 mmHg compared with 14/34 (41%) when mean DBP was <25 mmHg in infants (difference in survival rate -10% with 95% bootstrap CI -26%, 6%). Similarly, the rate of survival to hospital discharge was 4/16 (25%) when mean DBP was <25 mmHg compared with 8/29 (28%) when mean DBP was <30 mmHg in children <1 year (difference in survival rate -3% with 95% bootstrap CI -19%, 13%).

Table 5 illustrates the association of DBP with survival outcomes in the subgroup with CPR >10 minutes, using multivariable Poisson regression modelling. For this subgroup, maintaining DBP ≥25 mmHg in infants and ≥30 mmHg 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 neurologic outcome (aRR 2.5; 95% CI, 1.1–5.8; P=0.02).

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 neurologic outcome among patients with invasive arterial blood pressure monitoring at the time of cardiac arrest. Specifically, when mean DBP was maintained ≥25 mmHg during the early minutes of CPR in infants <1 year old and ≥30 mmHg 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 neurologic outcome compared with patients not attaining these mean DBP thresholds. These findings were further supported by stepwise multivariable modelling, receiver operating characteristics (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 mmHg in infants <1 year old and ≥25 mmHg in children ≥1 year old.

Animal studies have established that survival following CPR depends on attaining adequate myocardial blood flow during CPR, and the primary determinant of myocardial blood flow is the coronary perfusion pressure (arterial DBP minus right atrial diastolic pressure).[9–11, 25, 26] In multiple animal models, survival is associated with coronary perfusion pressure (CoPP) >20 mmHg and DBP >30 mmHg 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 mmHg and 35±12 mmHg compared with mean maximum CoPP and DBP of 8±10 mmHg and 24±15 mmHg among 76 patients without ROSC.[12] Similar to laboratory findings, CoPP >15 mmHg during CPR was necessary to attain ROSC, CoPP >25 mmHg was much more likely to result in ROSC, and none of the patients had ROSC with DBP <18 mmHg. 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 prior to commencement of CPR and prompt provision of CPR had far superior rates of survival to hospital discharge.

Present 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 mmHg 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 regarding appropriate BP targets during CPR.[4, 5] These PICqCPR data support a target DBP ≥25 mmHg during the early minutes of CPR in infants and ≥30 mmHg in children ≥1 year old.

The PICqCPR findings raise the question of whether a DBP ≥25 mmHg during CPR in infants <1 year old and ≥30 mmHg in children ≥1 year 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 PICqCPR investigators chose to test the a priori hypothesis that mean DBP ≥25 mmHg during CPR in infants and ≥30 mmHg in children ≥1 year old would be associated with survival to hospital discharge. The Poisson multivariable modelling, stepwise multivariable modelling, receiver operating characteristics (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 maintaining DBP ≥20 mmHg in infants <1 year old and ≥25 mmHg 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 mmHg in infants and DBP <25 mmHg 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 emanate from the potential to titrate CPR processes and thereby improve outcomes. For the many children with arterial catheters during CPR whose DBP is below the target, the resuscitating team can focus their efforts to increase the DBP by improving basic life support, adding vasoactive medications, and/or addressing potentially reversible causes. Basic life support efforts to improve DBP during CPR include providing 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

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hypoglycemia, hyperkalemia, toxins, or myocardial pathology that precludes ROSC (e.g., post-surgical 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 neurologic outcomes based on underlying causes of their cardiac arrests and pre-existing co-morbidities. 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 neurologic outcomes, and 71% survived without a substantive new functional morbidity. The excellent outcomes reflect the overall outstanding quality of CPR with median SBP of 74 mmHg [55, 99], median DBP of 29 mmHg [28, 38], median chest compression rate of 112 beats/minute [98, 123], and median chest compression fraction of 0.9 [0.8, 1.0].[3, 34, 35]

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 commencement 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 more than 10 minutes of CPR; therefore, hemodynamic data was not available for the entirety of their CPR because of study design 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 using exclusively mean DBP data during the first 5 minutes of CPR that 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, co-morbidities and the pre-arrest and post-arrest care. The CPCCRN sites are all large academic pediatric ICUs, and the quality of care provided before and after cardiac arrests may differ from 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 was inadequate for determination of mean DBP per study protocol. Notably, characteristics and outcomes of included patients were similar to excluded patients (Supplemental Table 1), and the survival rate was similar to a previous CPCCRN ICU CPR study that included children with and without arterial BP data.[35] Nevertheless, this is a highly selected population: all had pre-arrest invasive arterial BP monitoring, thus their providers assumed that they differed from other ICU patients and they clearly differ from children who receive CPR in other settings (e.g., hospital wards, emergency departments, out-of-hospital settings). Notably, this population is precisely the group that can benefit from a BP target because they have continuous invasive BP monitoring available for titration during CPR. Although the pre-arrest BP at 6–10 minutes prior to CPR did not differ overall between patients who survived to hospital discharge and patients who did not survive, the mean DBP at 6–10 minutes prior to CPR was significantly higher among infants <1 year old who survived versus infants who did not survive (42 [36, 52] mmHg versus 35 [31,45] mmHg), raising the possibility that the association of DBP during CPR with outcomes in infants may be related to differences in pre-arrest DBP. As a frame of reference, the 50th percentile DBP for a normal 1 year old boy is 37 [34, 39] mmHg.[37] After additionally controlling for pre-arrest DBP, the resultant aRR of survival to hospital discharge associated with DBP ≥25 mmHg was 1.4 (0.9, 2.2), P<0.155. The aRR was similar to the model without adjusting for pre-arrest DBP, but the confidence interval crossed 1.0, presumably due to the reduction in power as the n decreased from 164 to 145 because of unavailable pre-arrest 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. Importantly, the data available had adequate variability in mean DBP to evaluate its association with outcome.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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All of the listed authors satisfy the ICMJE 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.

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Appendix

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In addition to the listed collaborators, the following PICqCPR Investigators were involved in study design and/or data acquisition: Athena F. Zuppa M.D. M.S.C.E.,[1] Katherine Graham B.S.,[1] Carolann Twelves R.N,[1] William Landis B.S.E.,[1] Mary Ann DiLiberto R.N.,[1] Elyse

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ABBREVIATIONS

CPR	cardiopulmonary resuscitation
CPCCRN	Collaborative Pediatric Critical Care Research Network
PICqCPR study	Pediatric Intensive Care Quality of CPR study

DBP	Diastolic blood pressure
SBP	Systolic blood pressure
ROSC	Return of spontaneous circulation
ICU	intensive care unit
CoPP	coronary perfusion pressure
PCPC	Pediatric cerebral performance category
DCC	Data Coordinating Center

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Clinical Perspective

What is new?

- In this multi-center population of children with invasive arterial blood pressure monitoring during in-hospital ICU cardiac arrests, mean diastolic blood pressure ≥25 mmHg during CPR in infants and ≥30 mmHg 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 neurologic outcome.
- Survival rates decreased markedly with mean diastolic blood pressure <20 mmHg in infants and <25 mmHg in children ≥1 year old.

What are the clinical implications?

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

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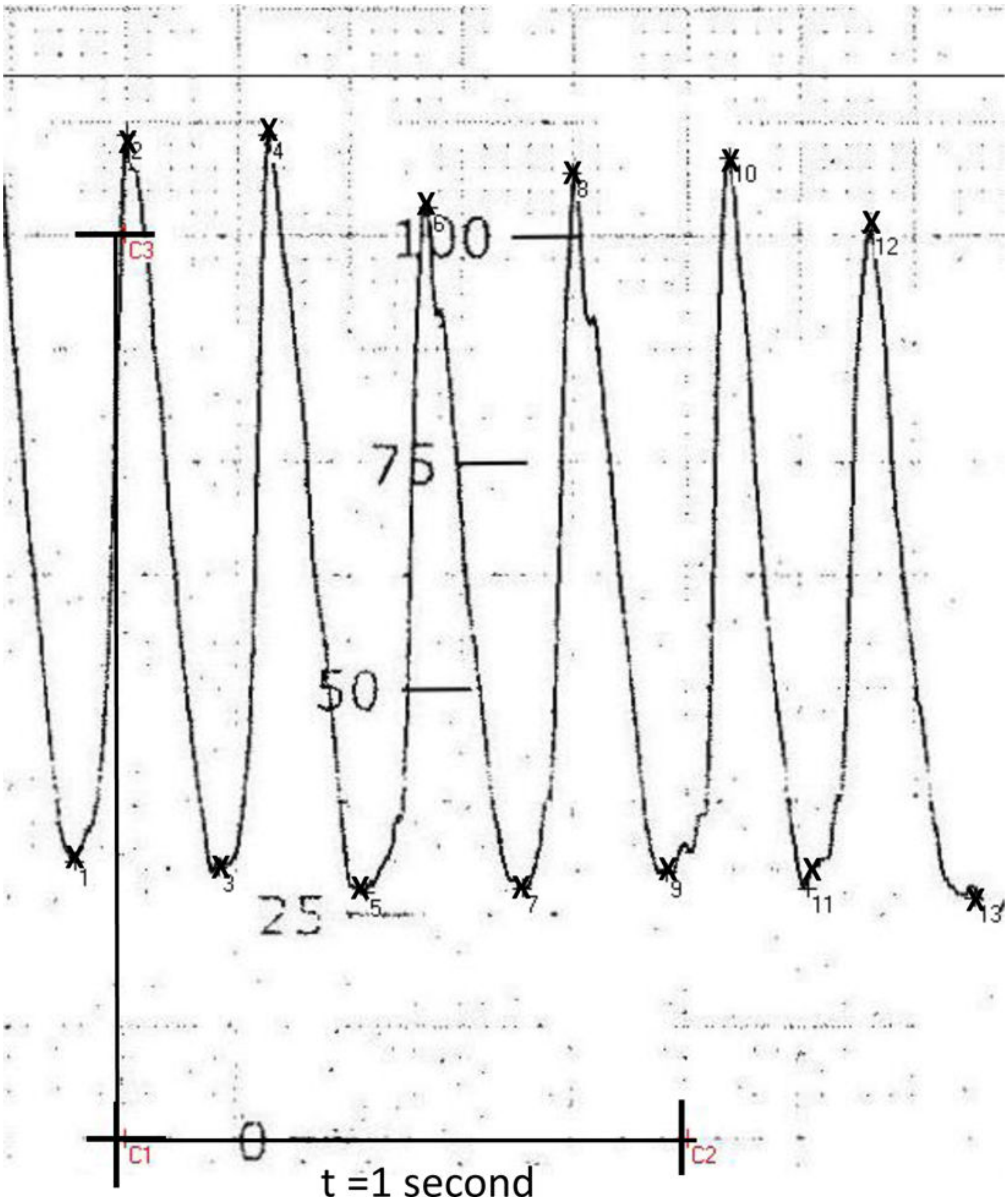
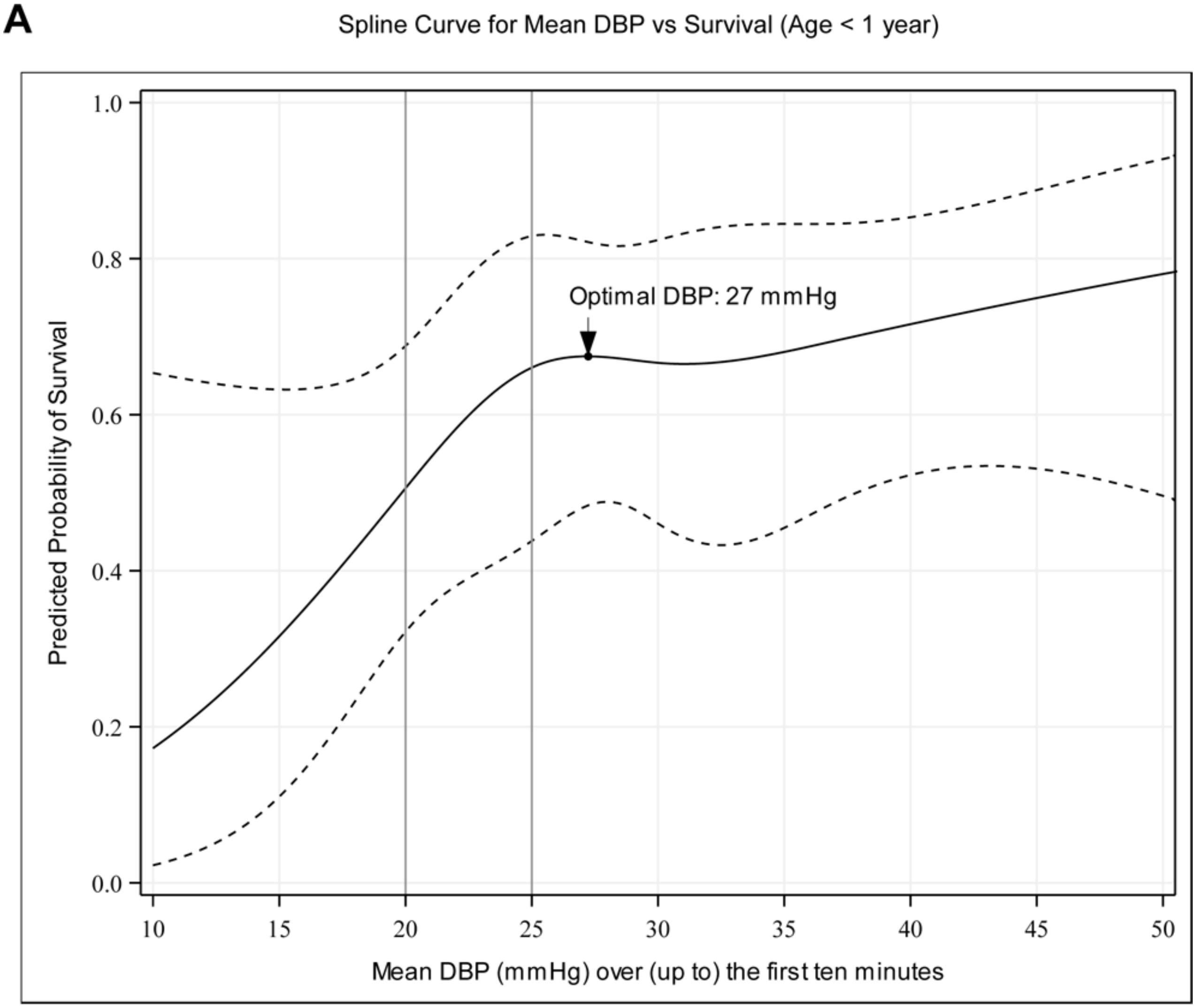


Figure 1.
De-identified arterial blood pressure waveform from a patient in this study with manually digitized systolic and diastolic pressures sampled at the peak and mid-diastole of individual compressions, respectively, as indicated by x.

A


Spline Curve for Mean DBP vs Survival (Age < 1 year)
Optimal DBP: 27 mmHg
Predicted Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
10
15
20
25
30
35
40
45
50
Mean DBP (mmHg) over (up to) the first ten minutes

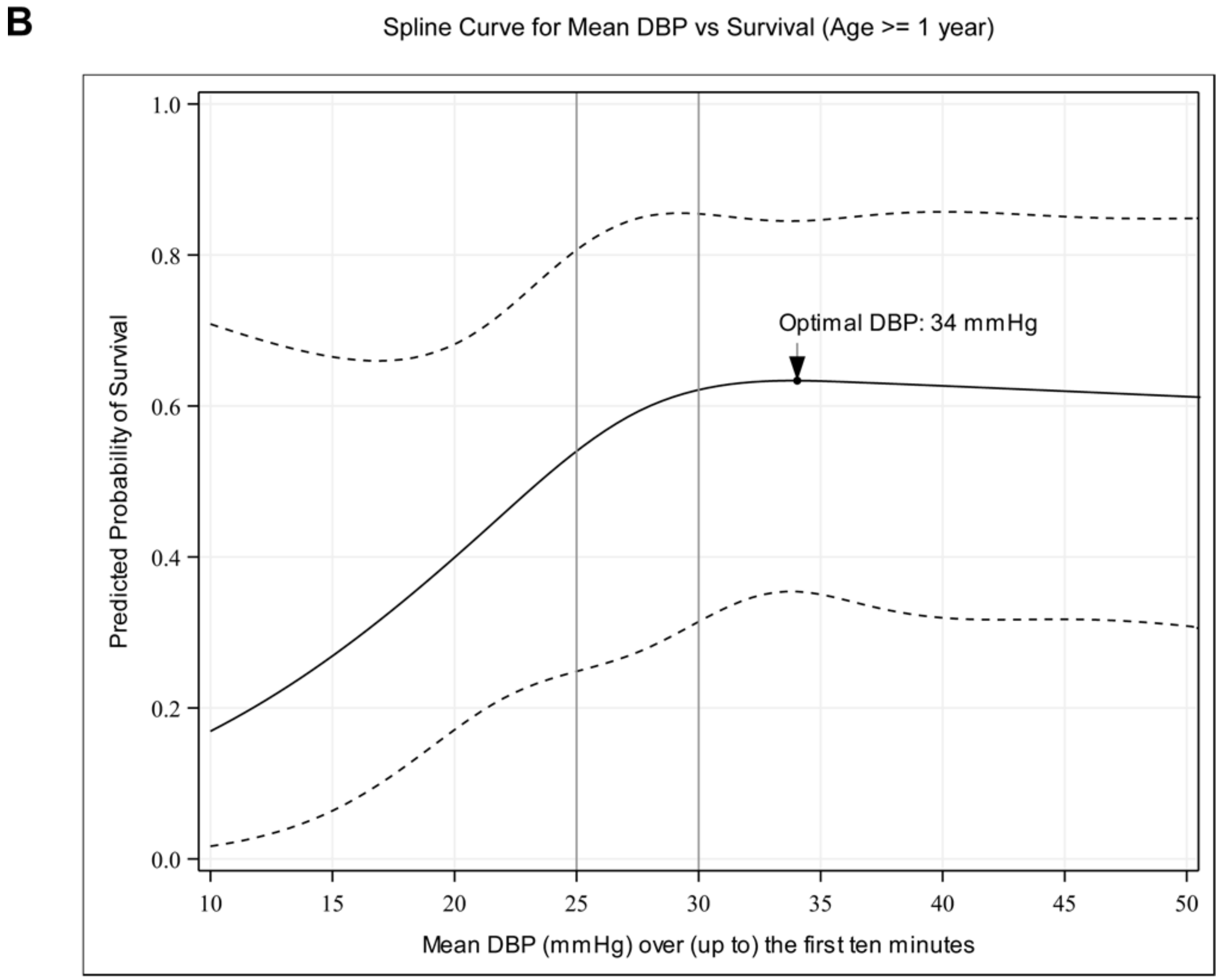


Figure 2.

Spline curves showing association of mean DBP over (up to) the first 10 minutes of CPR with survival to hospital discharge in infants (Figure 2A) and children ≥1 year old (2B). Upper and lower dashed curves in Figures 2A and 2B represent 95% and 5% confidence interval bands. Arrow at point of optimal predicted survival (defined as maximum predicted survival over the interval 15 to 30 mmHg for infants, and 15 to 35 for children) and vertical lines at mean DBP targets of interest (25 mmHg and 20 mmHg for infants; and 30 mmHg and 25 mmHg for children ≥1 year old). Curves were generated using restricted cubic splines for mean DBP with knots at the 20th, 40th, 60th, and 80th percentiles. For infants, DBP with maximum predicted survival was 27mmHg; predicted survival: 63% (35%, 84%). For children, DBP with maximum predicted survival was 34mmHg; predicted survival: 67% (48%, 82%).

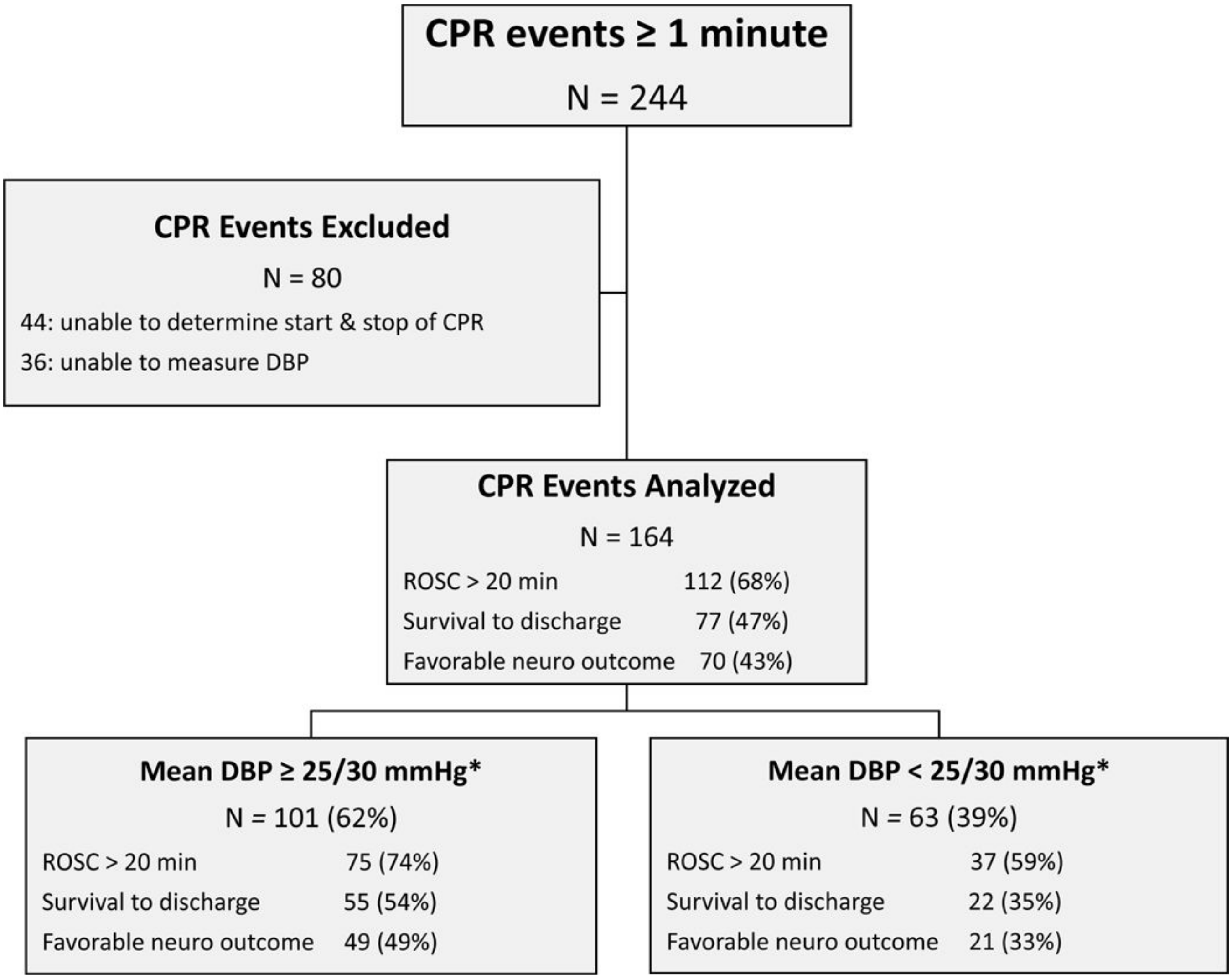


Figure 3.

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

Table 1

Pre-arrest Characteristics by Survival to Hospital Discharge

		Survival to hospital discharge		
	Overall (N = 164)	Yes (N = 77)	No (N = 87)	P-value
Age (Years)	0.7 [0.1, 3.1]	0.4 [0.0, 1.6]	1.0 [0.1, 5.2]	0.057 *
Age				0.162 †
< 1 month	41 (25%)	22 (29%)	19 (22%)	
1 month - < 1 year	57 (35%)	31 (40%)	26 (30%)	
1 year - < 8 years	41 (25%)	14 (18%)	27 (31%)	
8 years - < 19 years	25 (15%)	10 (13%)	15 (17%)	
Male	90 (55%)	47 (61%)	43 (49%)	0.158 †
Race				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				
Respiratory insufficiency	132 (80%)	59 (77%)	73 (84%)	0.324 †
Hypotension	128 (78%)	51 (66%)	77 (89%)	<.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				0.090 †
Surgical cardiac	88 (54%)	49 (64%)	39 (45%)	
Medical cardiac	25 (15%)	8 (10%)	17 (20%)	
Surgical non-cardiac	13 (8%)	5 (6%)	8 (9%)	
Medical non-cardiac	37 (23%)	14 (18%)	23 (26%)	
Unknown	1 (1%)	1 (1%)	0 (0%)	
Baseline Pediatric Cerebral Performance Category				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	8 [6, 11]	8 [6, 11]	7 [6, 11]	0.120 *

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

† Fisher's exact test is used for categorical variables.

‡ The CochranArmitage test for trend is used for Baseline Pediatric Cerebral Performance Category. Percentages are based on row totals.

Table 2

Event Characteristics by Survival to Hospital Discharge

	Overall (N = 164)	Survival to hospital discharge: Yes (N = 77)	Survival to hospital discharge: No (N = 87)	P-value
Avg. Hemodynamics over (up to) the first 10 minutes				
DBP (mmHg)	29.3 [22.8, 37.9]	30.9 [25.0, 38.7]	27.6 [21.0, 36.5]	0.097 *
< 1 year	28.0 [22.4, 35.2]	30.0 [24.0, 37.0]	25.3 [18.6, 33.0]	0.038 *
≥ 1 year	31.9 [25.0, 42.0]	33.0 [26.2, 40.0]	30.0 [22.9, 44.5]	0.514 *
SBP (mmHg)	74.4 [54.9, 98.2]	69.0 [53.8, 93.0]	77.6 [55.5, 101.4]	0.180 *
< 1 year	65.9 [50.8, 87.0]	65.0 [53.8, 85.8]	68.0 [49.6, 88.1]	0.648 *
≥ 1 year	84.8 [65.9, 121.0]	81.0 [55.6, 116.2]	93.5 [70.1, 121.6]	0.198 *
Compression rate (/minute)	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 §	101 (62%)	55 (71%)	46 (53%)	0.016 †
Mean SBP above target //	93 (57%)	44 (57%)	49 (56%)	1.000 †
Avg. Hemodynamics 6–10 minutes prior to the arrest (N=145)				
DBP (mmHg)	41.5 [34.0, 50.2]	43.0 [36.0, 52.0]	40.0 [32.8, 48.6]	0.098 *
< 1 year	39.0 [32.4, 46.4]	41.6 [36.0, 52.0]	35.2 [31.2, 45.0]	0.005 *
≥ 1 year	46.0 [37.2, 56.4]	48.0 [38.7, 52.0]	45.8 [36.0, 57.2]	1.000 *
SBP (mmHg)	75.0 [59.2, 92.0]	77.8 [57.6, 94.0]	74.0 [59.2, 89.6]	0.364 *
< 1 year	68.3 [55.6, 86.6]	75.2 [55.6, 93.8]	64.0 [56.0, 75.4]	0.055 *
≥ 1 year	80.4 [62.8, 102.0]	80.2 [63.0, 113.6]	82.2 [62.8, 100.0]	0.893 *
Mean Arterial Pressure (mmHg)	51.6 [43.0, 65.6]	54.3 [46.0, 69.6]	50.0 [42.0, 62.4]	0.170 *
< 1 year	49.4 [40.2, 60.8]	51.8 [42.4, 65.0]	45.6 [40.0, 57.0]	0.053 *
≥ 1 year	59.7 [47.0, 71.6]	61.2 [47.6, 76.4]	57.0 [46.4, 71.6]	0.686 *
Location of CPR Event				0.026 †
PICU	64 (39%)	23 (30%)	41 (47%)	
CICU	100 (61%)	54 (70%)	46 (53%)	
Immediate cause				
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)				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%)	

	Overall (N = 164)	Survival to hospital discharge: Yes (N = 77)	Survival to hospital discharge: No (N = 87)	P-value
Unknown	6 (4%)	5 (6%)	1 (1%)	
Duration or CPR (minutes)	8.0 [3.0, 27.0]	5.0 [2.0, 13.0]	17.5 [4.0, 38.0]	<0.001 *
Duration of CPR (minutes)				<0.001‡
1–5	69 (42%)	43 (56%)	26 (30%)	
6–15	34 (21%)	19 (25%)	15 (17%)	
16–35	29 (18%)	8 (10%)	21 (24%)	
>35	31 (19%)	7 (9%)	24 (28%)	
Unknown	1 (1%)	0 (0%)	1 (1%)	
Interventions in place				
Central venous catheter	142 (87%)	66 (86%)	76 (87%)	0.821†
Vasoactive infusion	128 (78%)	53 (69%)	75 (86%)	0.008†
Invasive mechanical ventilation	134 (82%)	57 (74%)	77 (89%)	0.025†
Non-invasive ventilation	19 (12%)	11 (14%)	8 (9%)	0.338†
Time **				0.157†
Weekday	102 (62%)	51 (66%)	51 (59%)	
Weeknight	34 (21%)	11 (14%)	23 (26%)	
Weekend	28 (17%)	15 (19%)	13 (15%)	
Pharmacologic interventions				
Epinephrine	143 (87%)	65 (84%)	78 (90%)	0.355†
# of doses (when used)	3 [1, 5]	2 [1, 3]	3 [2, 7]	<0.001 *, #
Calcium	78 (48%)	28 (36%)	50 (57%)	0.008†
Sodium bicarbonate	93 (57%)	36 (47%)	57 (66%)	0.018†

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

†Fisher's exact test is used for categorical variables.

‡The Cochran-Armitage test for trend is used for duration of CPR category variables.

§Target DBP is ≥25 for infants and ≥30 for children.

//Target SBP is ≥60 for infants and ≥80 for children.

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

**Weekdays are Mon - Fri, 07:00 - 22:59; weeknights are Mon - Fri, 23:00 - 06:59; and weekends are Sat - Sun.

Table 3

Summary of Outcomes

	Overall (N = 164)
Immediate outcome	
ROC *	148 (90%)
ROSC † ≥ 20 minutes	112 (68%)
ROC with E-CPR ‡	36 (22%)
Died	16 (10%)
Hospital discharge outcomes	
Survival §	77 (47%)
Survival with favorable neurologic outcome //	70 (43%)
Pediatric Cerebral Performance Category	
Normal	24 (15%)
Mild disability	27 (16%)
Moderate disability	17 (10%)
Severe disability	8 (5%)
Coma/vegetative state	1 (1%)
Brain death	87 (53%)
Functional Status Score (FSS) in survivors	9 [8, 12]
FSS change from baseline in survivors	0 [0, 3]
New Morbidity at Hospital Discharge #	22 (29%)

* ROC, Return of Circulation.

† ROSC, Return of Spontaneous Circulation.

‡ E-CPR, Extracorporeal cardiopulmonary resuscitation.

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

// Favorable neurologic outcome defined as discharge PCPC of normal, mild disability, or moderate disability or a discharge PCPC no worse than baseline PCPC.

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

Table 4

Multivariable Poisson Models of BP during CPR with Survival Outcomes

	Survival to hospital discharge		Survival to hospital discharge with favorable neurologic outcome	
Predictor	**Adjusted relative risk‡ (95% CI)**	**P-value**	**Adjusted relative risk‡ (95% CI)**	**P-value**
Average DBP above target * over (up to) the first ten minutes	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 five minutes	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 ten minutes	1.1 (0.8, 1.6)	0.491	1.0 (0.7, 1.4)	0.955

*DBP is considered meeting target if ≥ 25 mmHg neonates and infants and ≥ 30 mmHg for children.

†SBP is considered meeting target if ≥ 60 mmHg for neonates and ≥ 80 mmHg for children.

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

Table 5

Multivariable Poisson models of BP during CPR with Survival Outcomes (Subjects with CPR Duration ≥ 10 min)

	Survival to hospital discharge		Survival to hospital discharge with favorable neurologic outcome	
Predictor	**Adjusted relative risk‡ (95% CI)**	**P-value**	**Adjusted relative risk‡ (95% CI)**	**P-value**
Mean DBP above target* over (up to) the first ten minutes	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 ten minutes	1.3 (0.7, 2.6)	0.355	1.2 (0.6, 2.3)	0.570

*DBP is considered meeting target if ≥ 25 mmHg neonates and infants and ≥ 30 for children.

†SBP is considered meeting target if ≥ 60 for neonates and ≥ 80 mmHg for children.

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