

# Early Postresuscitation Hypotension Is Associated With Increased Mortality Following Pediatric Cardiac Arrest

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**Objective:** To describe the association of systolic hypotension during the first 6 hours after successful resuscitation from pediatric cardiopulmonary arrest with in-hospital mortality.

**Design:** Retrospective cohort study.

**Setting:** Fifteen children's hospitals associated with the Pediatric Emergency Care Applied Research Network.

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**Patients:** Patients between 1 day and 18 years old who had a cardiopulmonary arrest, received chest compressions more than 1 minute, had a return of spontaneous circulation more than 20 minutes, and had a systolic blood pressure documented within 6 hours of arrest.

**Interventions:** None.

**Measurements and Main Results:** Three hundred eighty-three patients had complete data for analysis. Patients with a documented minimum systolic blood pressure less than fifth percentile for age and sex within the first 6 hours following return of spontaneous circulation were considered to have early postresuscitation hypotension. Two hundred fourteen patients (56%) had early postresuscitation hypotension. One hundred eighty-four patients (48%) died prior to hospital discharge. After controlling for patient and cardiopulmonary arrest characteristics, hypotension in the first 6 hours following return of spontaneous circulation was associated with a significantly increased odds of in-hospital mortality (adjusted odds ratio = 1.71; 95% CI, 1.02–2.89;  $p = 0.042$ ) and odds of unfavorable outcome (adjusted odds ratio = 1.83; 95% CI, 1.06–3.19;  $p = 0.032$ ).

**Conclusions:** In the first 6 hours following successful resuscitation from pediatric cardiac arrest, systolic hypotension was documented in 56% and was associated with a higher rate of in-hospital mortality and worse hospital discharge neurologic outcomes. (*Crit Care Med* 2014; XX:00–00)

**Key Words:** children; heart arrest; hypotension; resuscitation; shock

Cardiac arrest (CA) is a major public health problem with more than 500,000 CAs in adults and more than 10,000 children each year in the United States (1–4). Survival rates are less than 10% following out-of-hospital CAs in adults and children (1–4). During the decade from 2000 to 2009, risk-adjusted survival rates following in-hospital CAs have increased in adults from 14% to 22% and in children from 14% to 44% (5, 6).

After successful initial resuscitation following a CA, most patients die in the post-CA period prior to hospital

discharge (1, 4, 6–10). Over the last two decades, a post-CA syndrome characterized by myocardial dysfunction, systemic ischemia-reperfusion response, brain injury, and multiple organ dysfunction has been described (9, 11, 12). Recent adult data suggest that early hypotension after CA is associated with a higher mortality rate (8, 10).

In a large multicenter observational cohort study of children with successful resuscitation following either out-of-hospital CA or in-hospital CA, most children in each group died prior to hospital discharge (13). Using this rich investigational database, our goals are to 1) determine the prevalence of hypotension in the first 6 hours among children following successful resuscitation from CA and 2) evaluate whether systolic hypotension in the first 6 hours following resuscitation from CA was associated with a higher rate of post-CA in-hospital mortality and/or unfavorable neurologic outcome.

## METHODS

### Study Population

Our study was conducted using an existing public access dataset from the Pediatric Emergency Care Applied Research Network (PECARN). The PECARN database was created with support from the NICHD (HD044955) to plan the current NHLBI-funded Therapeutic Hypothermia for Pediatric Cardiac Arrest Trials (NCT00880087 and NCT00878644). The database was derived from a retrospective cohort study of in-hospital and out-of-hospital CA conducted between July 1, 2003, and December 31, 2004, at 15 children's hospitals associated with the PECARN. Patients from 1 day (24 hr) to 18 years old (inclusive) who experienced CA requiring at least 1 minute of chest compressions and who had return of spontaneous circulation (ROSC) for a minimum of 20 minutes were eligible for inclusion. Out-of-hospital classification was assigned if chest compressions were initiated prior to hospital arrival; in-hospital classification was assigned if chest compressions were initiated in the emergency department or other hospital setting. Patients with CAs in a neonatal ICU and those who had planned CA in the operating room as part of congenital heart disease surgical repair were excluded. Identification of patients and database management for the PECARN database have been previously described (13–15).

Variables collected in the original database included the following: patient characteristics, such as age, sex, race, ethnicity, and preexisting chronic conditions; pre-event characteristics, such as presence and types of vascular access, endotracheal intubation, and monitoring devices; event characteristics, such as location and timing of CA, first and subsequent monitored cardiac rhythms, defibrillation, and drugs administered during the arrest; etiology of CA; hospital course characteristics, such as use of extracorporeal membrane oxygenation (ECMO), therapeutic hypothermia, other intensive care monitoring devices and interventions, drug therapies, seizures, and subsequent CAs; physiologic and laboratory data, such as prearrest lactate and blood pH, glucose blood urea nitrogen, and creatinine concentrations in the first 6 hours post arrest;

and outcome data, such as survival to hospital discharge and Pediatric Cerebral Performance Category (PCPC) scores at hospital discharge.

Dates and times of important clinical events were recorded, and relevant time intervals were determined. Utstein-style definitions were used for variables for which such definitions exist (16, 17). Time 0 represented the time that chest compressions were initiated. Both physiologic and laboratory data were collected as minimum and maximum values obtained from 0 to 6 hours. If there was only one value provided for a time interval, it was assigned to both the minimum and maximum. If there was no documented value within a given time period, it was considered missing.

This study was exempted by The Children's Hospital of Philadelphia Institutional Review Board because it was a de-identified, publicly available dataset.

### Inclusion and Exclusion Criteria

Patients were excluded from analysis if they were missing information on age, sex, or systolic blood pressure (SBP) during the 0- to 6-hour interval following ROSC (see *Exposures and Outcomes* section). Patients treated with ECMO or patients without clear documentation regarding ECMO use in the first 2 hours following ROSC were excluded because of the limited time for hypotension in light of full mechanical support so soon after arrest. Patients who died within the first 6 hours were also excluded because they may have had persistent hypotension that was untreated or undertreated (e.g., if they were moribund). Patients were excluded from the secondary analysis of neurologic outcome if they were unable to have a functional outcome category assigned to them based on missing PCPC scores (see *Exposures and Outcomes* section).

### Exposures and Outcomes

Hypotension was defined as a minimum SBP less than fifth percentile derived from normative age and sex data (Table 1) (18). Arrest times were categorized as night or weekend versus weekdays (13, 19). Arrest location was stratified by location (in-hospital vs out-of-hospital) and witnessed status.

The primary outcome was in-hospital mortality. The secondary outcome was neurologic outcome, determined by the PCPC. The PCPC is a 6-point classification system to define cognitive function: 1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, and 6 = death (20). Favorable neurologic outcome was defined as a PCPC score of 1 or 2 at hospital discharge or no change from prearrest to hospital discharge (21). Unfavorable neurologic outcome was defined as a discharge PCPC score of 3, 4, 5, or 6 and a change from prearrest PCPC score more than or equal to 1. If patients were missing a prearrest PCPC score, but had a discharge PCPC score of 1 or 2, they were determined to have a favorable neurologic outcome. If patients were missing a prearrest PCPC score but died, they were included in the unfavorable neurologic outcome group. If patients were missing a prearrest PCPC score but had a discharge PCPC score of 3, 4, or 5, they were excluded from the analysis of functional

**TABLE 1. Fifth Percentile Systolic Blood Pressures by Age and Gender for the 50th Height Percentile**

Age (yr)	Fifth Percentile Male	Fifth Percentile Female
1	71	72
2	73	74
3	75	75
4	77	77
5	78	78
6	80	80
7	82	81
8	84	82
9	85	83
10	86	85
11	88	88
12	89	90
13	92	91
14	94	92
15	96	92
16	97	93
17	99	94

Available at: <https://sites.google.com/a/channing.harvard.edu/bernardrosner/pediatric-blood-press>.

outcome because the appropriate group (favorable vs unfavorable neurologic outcome) could not be determined.

### Statistical Analysis

Standard descriptive statistics were used to summarize patient and CA event characteristics, stratified by hypotension status and survival to discharge. Fisher exact test or Wilcoxon rank-sum test was used to determine differences between groups. Univariable logistic regression models were used to estimate the association between hypotension over the first 6 hours after CA and odds of in-hospital mortality (primary) and odds of unfavorable neurologic outcome (secondary). Multivariable models included patient and CA event characteristics based on a priori clinical rationale or a posteriori evidence for potential confounding. Variables included were age (cubic splines), preexisting conditions (lung or airway; hematologic, oncologic, or immune compromised; genetic metabolic; and neurologic), total number of vasopressors before arrest, night or weekend arrest, arrest location, first documented rhythm, and total doses of epinephrine at arrest. A final parsimonious model eliminated variables from the multivariable model using a stepwise variable-selection procedure that minimized the Akaike information criterion. The potential for modification of the effect of hypotension on in-hospital mortality by vasopressor use

during the first 6 hours after ROSC was evaluated by including an interaction term between hypotension and an indicator variable for any vasopressor use in the parsimonious model. For the primary outcome, *p* value of less than 0.05 was used to determine statistical significance; for the secondary outcome, *p* value of less than 0.05 was considered to suggest significance; and for interaction analyses, *p* value of less than 0.1 was considered to suggest significance. All analyses were completed using R 2.15.2 (R Development Core Team, Vienna, Austria).

### RESULTS

Four hundred ninety-one patients were enrolled in the database. After applying exclusion criteria, 383 patients were eligible for analysis (**Fig. 1**). Patients were stratified by minimum SBP in the first 6 hours following arrest by age and sex-derived percentiles. Two hundred fourteen patients (56%) had documented hypotension (minimum SBP < fifth percentile for age and sex) in the first 6 hours following ROSC.

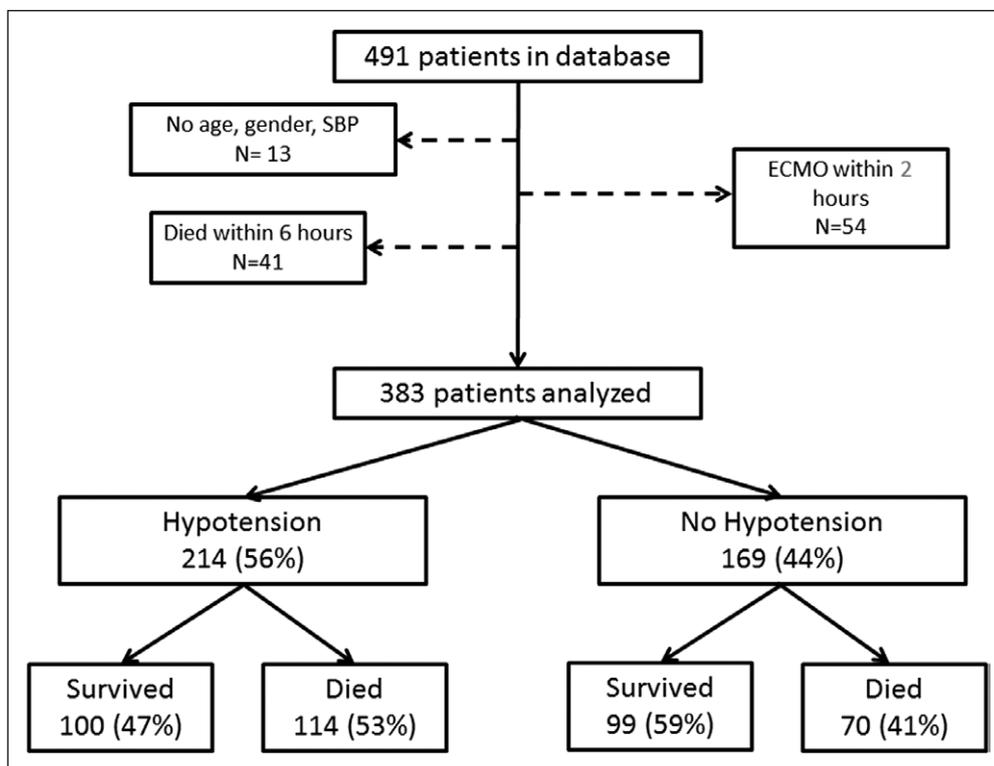
In a sensitivity analysis, we treated minimum SBP as a continuous variable, indexed to the 50th percentile for age and sex. The strong association of hypotension with mortality remained (*p* = 0.003), but there was some evidence that the association was nonlinear (*p* = 0.036).

Patients with documented early postresuscitation hypotension were less likely to have preexisting lung or airway disease but more likely to be on prearrest vasopressors and less likely to have had an out-of-hospital CA. Patients with early postresuscitation hypotension received more epinephrine during resuscitation and were on more vasopressors following ROSC (**Supplemental Table 1**, Supplemental Digital Content 1, <http://links.lww.com/CCM/A845>). Patients with postresuscitation hypotension had lower postresuscitation median minimum pH and higher postresuscitation median maximum creatinine.

One hundred eight-four patients died prior to hospital discharge. Patients who died were more likely to have an out-of-hospital arrest, an initial rhythm of pulseless electrical activity or asystole, a longer duration of cardiopulmonary resuscitation, and more doses of epinephrine (**Supplemental Table 2**, Supplemental Digital Content 2, <http://links.lww.com/CCM/A846>). Nonsurvivors also had a lower postresuscitation median minimum pH, a lower postresuscitation median minimum plasma bicarbonate concentration, and higher postresuscitation median maximum glucose.

Patients who had hypotension were more likely to die prior to hospital discharge (53% vs 41%; odds ratio [OR] = 1.61; *p* = 0.022) (**Table 2**). After controlling for patient and event characteristics, hypotension in the first 6 hours following ROSC was associated with a significantly increased odds of in-hospital death (adjusted OR = 1.71; 95% CI, 1.02–2.89; *p* = 0.042) and odds of unfavorable neurologic outcome (adjusted OR = 1.83; 95% CI, 1.06–3.19; *p* = 0.032).

Of the fifty-two patients excluded due to receiving early ECMO support, in-hospital death occurred in 19 of 38 hypotensive patients (50%) and 9 of 14 nonhypotensive patients (64%).



**Figure 1.** The distribution of patients with post–cardiac arrest hypotension and outcomes. SBP = systolic blood pressure, ECMO = extracorporeal membrane oxygenation.

An unfavorable outcome occurred in 20 of 29 hypotensive patients (69%) and 9 of 12 nonhypotensive patients (75%).

The impact of post-ROSC vasopressor use during the first 6 hours after ROSC on the association between hypotension and in-hospital mortality was also evaluated. Of children with early postresuscitation hypotension, 88 of 214 (41%) received vasopressor infusions within the first 6 hours after ROSC. Among patients who received post-ROSC vasopressors, there was no difference in discharge outcomes between hypotension and no hypotension groups ( $p = 0.18$ ). However, among patients who did not receive vasopressors within 6 hours post ROSC, those with no post-ROSC hypotension were less likely to die than those with hypotension (OR = 2.12; 95% CI, 1.18–3.81).

Thirty-three patients (8.6%) were initiated on a new vasopressor following resuscitation. Three hundred fifty patients did not have the initiation or addition of a new vasopressor

following ROSC. The mortality rate for both groups was 48%. Of the 214 with early postresuscitation hypotension, 73 continued to receive preexisting vasopressor support, whereas 15 were initiated on vasopressor support. More than half (126 of 214) were not treated with a continuous vasopressor infusion.

## DISCUSSION

This study establishes that early postresuscitation hypotension is associated with increased hospital discharge mortality in children after successful resuscitation from CA. Among children with documented early post-ROSC hypotension, 53% died in the hospital compared with 41% without documented early post-ROSC hypotension. Importantly, early postresuscitation hypotension was common: 56% had documented

hypotension in the first 6 hours post ROSC. Interestingly, only 41% of the children with early post-ROSC hypotension received post-ROSC vasopressor infusions during those first 6 hours post ROSC in this high-risk cohort with a 53% in-hospital mortality rate. Post-CA syndrome is a recently described clinical entity, manifested by myocardial dysfunction, systemic ischemia/reperfusion response, brain injury, and multiple organ dysfunction (9). The cardiovascular pathophysiology includes a sepsis-like syndrome associated with elevations in circulating cytokines and concomitant myocardial dysfunction. This combination can cause hypotension and systemic hypoperfusion, resulting in further postarrest end-organ injury (22). Notably, the children with early post-ROSC hypotension in this study had a lower minimum pH in the first 6 hours after ROSC and higher serum creatinine concentrations. This association may

**TABLE 2. Associations of Hypotension During First 6 Hours Post Cardiac Arrest With Outcomes**

Variable	No Hypotension, n (%)	Hypotension, n (%)	Unadjusted OR (95% CI); p	Fully Adjusted OR <sup>a</sup> (95% CI); p	Parsimonious OR <sup>b</sup> (95% CI); p
In-hospital mortality	70/169 (41)	114/214 (53)	1.61 (1.07, 2.43); 0.022	1.71 (1.02, 2.89); 0.042	1.71 (1.07, 2.76); 0.026
Unfavorable outcome	82/160 (51)	128/207 (62)	1.54 (1.02, 2.34); 0.043	1.83 (1.06, 3.19); 0.032	1.78 (1.08, 2.95); 0.024

OR = odds ratio.

<sup>a</sup>Adjusted for age (cubic splines), preexisting conditions (lung or airway; hematologic, oncologic, or immune compromised; genetic metabolic; neurologic), total number of vasopressors before arrest, night or weekend arrest, arrest location, first documented rhythm, and total doses of epinephrine at arrest; 26 patients removed due to missing data.

<sup>b</sup>Adjusted for arrest location, preexisting conditions (hematologic, oncologic, or immune compromised; genetic metabolic), and total doses of epinephrine at arrest; 24 patients removed due to missing data.

Hypotension defined as a minimum systolic blood pressure < fifth percentile; percentiles derived from normative age and sex data.

be due to a more severe CA or the hypotension itself may be associated with secondary organ injury. Postresuscitation myocardial dysfunction following adult out-of-hospital CA is a myocardial stunning process that begins within hours of ROSC and resolves by 72 hours (23). Although optimal management of post-ROSC myocardial dysfunction and hypotension has not been established, vasopressor support is recommended as part of the bundle of care to improve hemodynamic status, avoid secondary insults, and attempt to improve long-term survival and neurologic outcomes (24–27).

In this cohort of children successfully resuscitated from CA, 56% had documented hypotension in the first 6 hours post ROSC. These findings in children are similar to the 47–65% prevalence of documented hypotension among adults admitted to an ICU after ROSC from CA (8, 10, 23). The adult studies included both out-of-hospital and in-hospital CAs, as does our study. Many of the adults had out-of-hospital CAs and may have had acute coronary syndromes. However, children and adults with in-hospital CAs have similar causes for their CAs: acute respiratory failure and acute circulatory shock (21). For all of these groups of adults and children with an initially successful resuscitation, the message is clear: post-ROSC hypotension is common. Therefore, frequent post-CA hemodynamic assessment should be provided for these patients.

Most importantly, early post-ROSC hypotension is associated with worse outcomes. In our cohort, 53% of children with early post-ROSC hypotension died in the hospital compared with only 41% of children without early post-ROSC hypotension, and the adjusted OR for in-hospital mortality was 1.71 (95% CI, 1.02–2.89). Similarly, 38% of children with early post-ROSC hypotension had an unfavorable neurologic outcome compared with 49% of these children without early post-ROSC, and the adjusted OR for unfavorable neurologic outcome was 1.83 (95% CI, 1.06–3.19). Our study extends the observation that early post-ROSC hypotension is associated with worse outcomes in adults to children without pre-existing coronary artery disease and acute coronary artery syndrome (8, 10, 14).

This observational study cannot distinguish whether early post-ROSC hypotension resulted in worse outcomes versus the possibility that children with more severe prearrest and/or in-arrest insults were more likely to have both early post-ROSC hypotension and higher mortality rates. However, the dangers of secondary injuries after initial hypoxic-ischemic insults are well established (9). In addition, Trzeciak et al (10) showed that post-ROSC hypotension was common in adults (47% of 8,736) and was associated with a higher in-hospital mortality rate (65% vs 27%; adjusted OR, 2.7; 95% CI, 2.5–3). They speculated that treatment to avoid this secondary insult might improve outcomes. Our findings among the subgroup of children in our study without early vasopressor therapy show that early hypotension was associated with worse outcomes. In contrast, among the subgroup with early vasopressor therapy, early hypotension was not significantly associated with worse outcomes. Perhaps, the vasopressor therapy mitigated the severity of hypoperfusion, myocardial dysfunction,

or allowed clinicians to simply titrate the vasopressor infusions to limit the duration and severity of hypotension. Similar to the findings by Trzeciak et al (10), our data raise the possibility that closer hemodynamic monitoring, avoidance of hypotension, and prompt treatment of post-ROSC hypotension may improve postresuscitation hemodynamics, may minimize secondary injuries, and may improve outcomes.

Our study had several limitations. Data were retrospectively collected and therefore limited to what was documented in the medical record. It was not documented in the database whether specific blood pressure measurements were obtained invasively or noninvasively, although 75% of patients were managed with an arterial catheter at some point during their postresuscitation care. Normal blood pressure for children depends on age and sex, and blood pressure percentiles for age and sex are only available at threshold values. Therefore, it is difficult to evaluate blood pressure as a continuous variable across percentile groups. We do not have specific data regarding management of hypotension with respect to fluid resuscitation, electrolyte repletion, or vasopressor titration in relation to specific blood pressure values. The database included lowest SBP during the first 6 hours following ROSC but did not indicate the duration of low blood pressure or when these lowest blood pressures occurred during the 6-hour post-ROSC time interval. Therefore, a patient categorized as having hypotension could have had only one documented low blood pressure without sustained hypotension. Nevertheless, post-ROSC hypotension was demonstrably associated with in-hospital mortality. Furthermore, we excluded patients who were initiated on ECMO within 2 hours of ROSC or who died in the first 6 hours following ROSC and patients who did not have data for age, sex, or ECMO treatment. Exclusion of early ECMO patients limits the generalizability of this study to this population. There were no available echocardiographic data or further details regarding myocardial function or vasopressor dosing. Finally, this retrospective study demonstrating associations of hypotension with increased mortality is hypothesis generating and potentially clinically important, but the experimental design precludes establishment of causality.

## CONCLUSIONS

Following successful resuscitation from pediatric CA, hypotension was documented in 56% of patients during the first 6 hours post ROSC. Early post-ROSC hypotension was associated with a higher rate of in-hospital mortality and worse neurologic outcome at hospital discharge. These data raise the possibility that avoidance of post-ROSC hypotension and treatment of post-ROSC hypotension may improve post-ROSC hemodynamics and improve clinically important outcomes.

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