Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Time to Epinephrine and Survival After Pediatric In-Hospital Cardiac Arrest

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IMPORTANCE Delay in administration of the first epinephrine dose is associated with decreased survival among adults after in-hospital, nonshockable cardiac arrest. Whether this association is true in the pediatric in-hospital cardiac arrest population remains unknown.

OBJECTIVE To determine whether time to first epinephrine dose is associated with outcomes in pediatric in-hospital cardiac arrest.

DESIGN, SETTING. AND PARTICIPANTS We performed an analysis of data from the Get With the Guidelines–Resuscitation registry. We included US pediatric patients (age <18 years) with an in-hospital cardiac arrest and an initial nonshockable rhythm who received at least 1 dose of epinephrine. A total of 1558 patients (median age, 9 months [interquartile range [IQR], 13 days–5 years]) were included in the final cohort.

EXPOSURE Time to epinephrine, defined as time in minutes from recognition of loss of pulse to the first dose of epinephrine.

MAIN OUTCOMES AND MEASURES The primary outcome was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation (ROSC), survival at 24 hours, and neurological outcome. A favorable neurological outcome was defined as a score of 1 to 2 on the Pediatric Cerebral Performance Category scale.

RESULTS Among the 1558 patients, 487 (31.3%) survived to hospital discharge. The median time to first epinephrine dose was 1 minute (IQR, 0-4; range, 0-20; mean [SD], 2.6 [3.4] minutes). Longer time to epinephrine administration was associated with lower risk of survival to discharge in multivariable analysis (multivariable-adjusted risk ratio [RR] per minute delay, 0.95 [95% CI, 0.93-0.98]). Longer time to epinephrine administration was also associated with decreased risk of ROSC (multivariable-adjusted RR per minute delay, 0.97 [95% CI, 0.96-0.99]), decreased risk of survival at 24 hours (multivariable-adjusted RR per minute delay, 0.97 [95% CI, 0.95-0.99]), and decreased risk of survival with favorable neurological outcome (multivariable-adjusted RR per minute delay, 0.95 [95% CI, 0.91-0.99]). Patients with time to epinephrine administration of longer than 5 minutes (233/1558) compared with those with time to epinephrine of 5 minutes or less (1325/1558) had lower risk of in-hospital survival to discharge (21.0% [49/233] vs 33.1% [438/1325]; multivariable-adjusted RR, 0.75 [95% CI, 0.60-0.93]; $P = .01$).

CONCLUSIONS AND RELEVANCE Among children with in-hospital cardiac arrest with an initial nonshockable rhythm who received epinephrine, delay in administration of epinephrine was associated with decreased chance of survival to hospital discharge, ROSC, 24-hour survival, and survival to hospital discharge with a favorable neurological outcome.

Editorial page 776

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Approximately 16 000 children in the United States have a cardiac arrest each year, predominantly in a hospital setting.[1,2] An initial rhythm of pulseless electrical activity or asystole (ie, a nonshockable rhythm) is most common and carries a significant mortality, with 25% to 40% of patients surviving to hospital discharge.[1,3-5] Despite efforts in resuscitation research and improvement in outcomes after in-hospital pediatric resuscitation during the last 30 years,[4,6] there are few evidence-based interventions besides supportive care for the pediatric patient in cardiac arrest with a nonshockable rhythm.[6,7]

Epinephrine (or adrenaline), a potent α- and β-adrenergic agonist, is recommended by both the American Heart Association (AHA) and the European Resuscitation Council in pediatric cardiac arrest. Current guidelines recommend giving epinephrine at 0.01 mg/kg (maximum, 1 mg) as soon as vascular or intraosseous access is obtained and subsequently every 3 to 5 minutes for patients with a nonshockable rhythm.[6,8] Epinephrine's beneficial effects are thought to be mediated predominantly through α-adrenergic increase in aortic diastolic pressure and increased coronary perfusion pressure—an important determinant of return of spontaneous circulation (ROSC).[9-11] Despite this, to our knowledge, no randomized trial comparing epinephrine with placebo has been conducted in this population,[7] and the ethics of such a trial may currently be questionable.

Prior studies have addressed the dosage of epinephrine (standard vs high dose) in pediatric cardiac arrest.[12-14] We have not identified any studies examining the association between delay in epinephrine dose and outcomes in pediatric cardiac arrest. A recent report found that delay in epinephrine administration for adult in-hospital, nonshockable cardiac arrest was associated with decreased chance of ROSC, survival to discharge, and good neurological outcome.[15] We hypothesized that delay in epinephrine administration for pediatric in-hospital, nonshockable cardiac arrest would likewise be associated with decreased survival.

Methods

We used the Get With the Guidelines–Resuscitation (GWTG-R) registry, an AHA-sponsored, national, prospective, quality improvement registry of US in-hospital cardiac arrests. The details of data collection and reliability have been described previously.[3,16] Cardiac arrest is defined as pulselessness, or a pulse with inadequate perfusion, requiring chest compressions, defibrillation, or both, with a hospital-wide or unit-based emergency response by acute care facility personnel. In-hospital cardiac arrest patients with prior do-not-resuscitate orders or cardiopulmonary resuscitation (CPR) events that began outside the hospital are excluded. Cases are identified and data extracted by trained personnel from cardiac arrest flow sheets, hospital paging system logs, routine checks of code carts, pharmacy drug records, and hospital billing charges for resuscitation medication.[16] The registry uses Utstein-style templates for cardiac arrest, standardized reporting guidelines used to define patient variables and outcomes, to facilitate uniform reporting across hospitals.[17,18] Integrity of the data is optimized through rigorous certification of data entry personnel and the use of standardized software that checks the data for completeness and accuracy.[19]

All participating hospitals are required to comply with local regulatory guidelines. Because data are used primarily at the local site for quality improvement, sites are granted a waiver of informed consent under the common rule.

Study Population

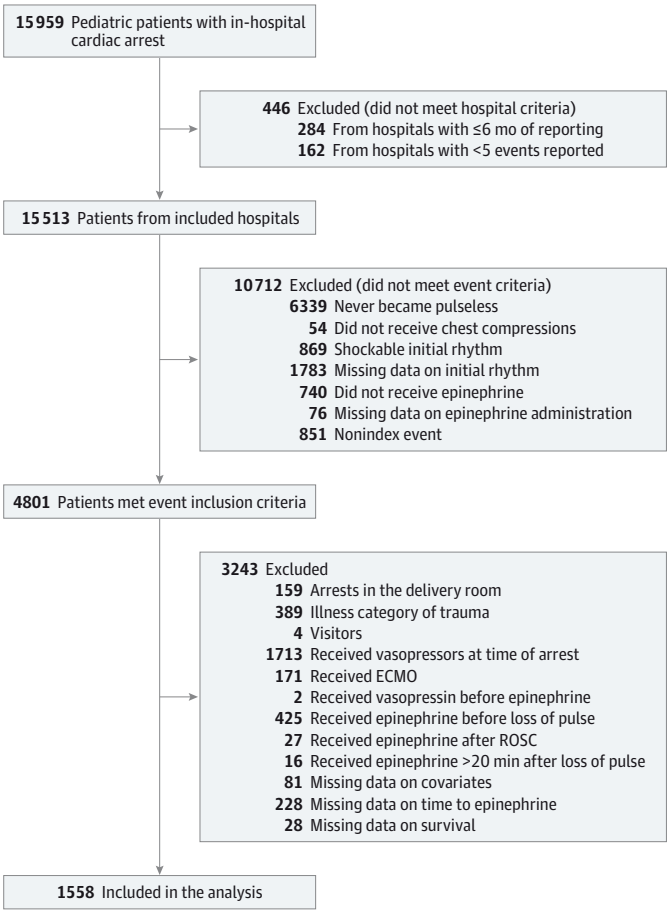
The cohort included data submitted to the GWTG-R registry between January 2000 and December 2014. We included all patients younger than 18 years who received chest compressions while pulseless with a documented nonshockable initial rhythm and who received at least 1 epinephrine bolus during resuscitation. We included index events only from hospitals with at least 6 months of reporting and at least 5 cases reported. We excluded patients with the following: (1) cardiac arrest in the delivery room, (2) an illness category of trauma or an illness category of hospital visitor, (3) vasopressor (epinephrine, norepinephrine, phenylephrine, and/or dopamine [for dopamine, at least 3 μg/kg/min]) infusion at the time of cardiac arrest, (4) treatment with extracorporeal membrane oxygenation during the event, (5) vasopressin received before epinephrine, (6) epinephrine given before loss of pulse, (7) epinephrine received after ROSC, (8) epinephrine given more than 20 minutes after loss of pulse, (9) missing data on covariates, (10) missing data on time to first epinephrine dose, and (11) missing data on in-hospital survival (**Figure 1**).

Time to Epinephrine and Study Outcomes

Time to epinephrine was defined as the interval in minutes from recognition of loss of pulse to the first bolus dose of epinephrine. The recording of the time of pulselessness and the first dose of epinephrine was done in whole minutes. As such, a time to epinephrine of 0 minutes represents that epinephrine was given within the same whole minute that the patient lost their pulse, a time of 1 minute represents that epinephrine was given within the next whole minute, etc.

The primary outcome was survival to discharge from the hospital. Secondary outcomes were ROSC, defined as at least 20 minutes with a palpable pulse; survival at 24 hours; and favorable neurological outcome at hospital discharge. Neurological outcome was assessed with the Pediatric Cerebral Performance Category (PCPC) scale,[20] in which a score of 1 indicates no neurological deficit; 2, mild cerebral disability; 3, moderate cerebral disability; 4, severe cerebral disability; 5, coma or vegetative state; and 6, brain death. A PCPC score of 1 to 2 was considered a favorable neurological outcome, and a PCPC score of 3 to 6 (death) was considered a poor neurological outcome. However, there is currently no universal definition of a favorable neurological outcome in pediatric cardiac arrest patients using the PCPC score, and multiple definitions have been used previously.[4,21,22] To account for this, we did sensitivity analyses using 3 different definitions: (1) a PCPC score of 1 or 2 or no increase from baseline; (2) a PCPC score of 1, 2, or 3; and (3) a PCPC score of 1, 2, or 3 or no increase from baseline. Outcome assessors were unaware of the hypoth-

Figure 1. Patient Flowchart for Study of Timing of Epinephrine and Pediatric In-Hospital Nonshockable Cardiac Arrest



The database contained data on 15 959 pediatric in-hospital cardiac arrests. Of these, 1558 met all inclusion criteria and no exclusion criteria and were included in the analysis. ECMO indicates extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation.

eses of the current study. Data abstractors were not blinded to the outcomes.

Statistical Analyses

The study population was characterized using descriptive statistics. Categorical variables are presented with counts and frequencies and continuous variables in means with standard deviations or medians with interquartile ranges (IQRs) depending on the normality of the data. The χ^2 test was used to compare frequencies.

To assess the independent association between time to epinephrine administration during cardiac arrest resuscitation and survival to discharge, we applied a multivariable regression model with generalized estimating equations with an exchangeable (compound symmetry) correlation matrix to account for hospital clustering. We used modified Poisson regression models with robust variance estimates to estimate risk ratios (RRs)[23,24] as previously used in the adult GWTG cohort.[4,25,26] For our primary analysis, we treated time to epinephrine as a linear, continuous variable.

The following variables were entered into the multivariable model: age group (neonate [<1 month], infant [1 month to <1 year], child [1-12 years], or adolescent [>12 years]), sex, year of the arrest (treated as a categorical variable with year 2000 as the reference), illness category (medical cardiac, medical noncardiac, surgical cardiac, surgical noncardiac, or newborn [ie, born this admission]), preexisting mechanical ventilation, whether the patient was monitored (presence of electrocardiography, pulse oximetry, and/or apnea monitor), whether the event was witnessed, location of arrest (intensive care unit [including postanesthesia care unit and the operating room], emergency department, floor without telemetry, floor with telemetry, or other), time of week (weekday [Monday 7 AM-Friday 11 PM] vs weekend [Friday 11 PM-Monday 7 AM]), time of day (day [7:00 AM-10:59 PM] vs night [11:00 PM-6:59 AM]), first documented pulseless rhythm (asystole vs pulseless electrical activity), and insertion or reinsertion of an airway during the event. We also included whether the hospital was primarily a pediatric hospital and hospital teaching status (major [with fellowship program], minor [with residency program], or nonteaching [no residency program]). We entered time (in minutes) to initiation of chest compressions from loss of pulse into each multivariable model to account for any delay in resuscitation. If time to CPR was negative (ie, the patient lost his or her pulse after initiation of CPR), a value

of 0 minutes was imputed. All variables were chosen a priori based on prior work and clinical reasoning.[22,27,28]

Similar multivariable regression models were used to analyze secondary outcomes (ROSC, 24-hour survival, and survival to discharge with favorable neurological outcome), including different definitions of favorable neurological outcome. Results from the multivariable regression models are reported as RRs with 95% CIs. For both primary and secondary outcomes, the RRs represent the RR for the outcome per minute increase in time to epinephrine.

To further characterize the relationship between time to epinephrine and outcomes, we conducted a preplanned analysis in which time to epinephrine was categorized into 5 minutes or less or longer than 5 minutes, as previously used as a quality metric in the adult cardiac arrest population.[29] Using this definition, we conducted similar analyses as described earlier in this section.

Outcome variables were complete for ROSC, survival at 24 hours, and survival to discharge in the included cohort. For all definitions of neurological outcome, approximately 11% of patients had missing data. For the analysis of neurological outcome, we included only patients who had these outcomes reported.

We performed a number of post hoc sensitivity analyses, including propensity score analyses, nonlinearity analyses, and multiple imputations with imputation of missing values for time to epinephrine, covariates, and the various outcomes. (Details of these analyses are provided in the eMethods in the Supplement.) We also performed post hoc tests of the following interactions with time to epinephrine in the main multivariable analysis: location of the arrest, initial rhythm, and age.

Statistical analyses were conducted with SAS version 9.4 (SAS Institute). All hypothesis tests were 2-sided, with a significance level of $P < .05$. No adjustments were made for multiple testing, and, as such, our secondary end points should be considered exploratory.

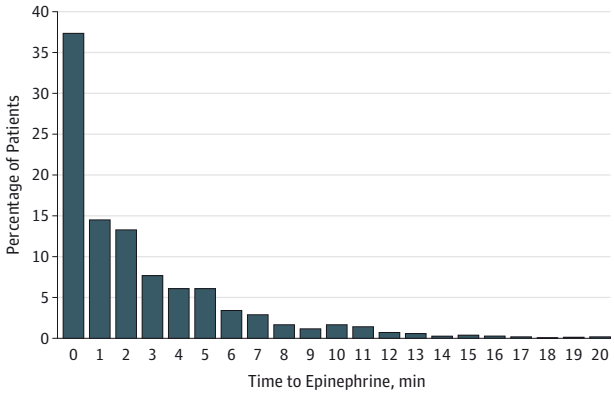
Results

The final cohort included 1558 patients (Figure 1). Median age was 9 months (IQR, 13 days-5 years), and 46% were female. The median time to first epinephrine dose was 1 minute (IQR, 0-4; range, 0-20; mean [SD], 2.6 [3.4] minutes) (**Figure 2**). Median time to chest compressions was 0 minutes (IQR, 0-0). Additional patient, event, and hospital characteristics are presented in **Table 1** and in eTable 1 in the Supplement.

Primary Outcome

Survival to discharge was 31.3% (487/1558). Longer time to epinephrine was significantly associated with lower risk of survival to discharge in unadjusted analysis (RR per minute delay, 0.94 [95% CI, 0.91-0.97]; $P < .001$) (**Figure 3**). This association remained significant in multivariable analysis (RR per minute delay, 0.95 [95% CI, 0.93-0.98]; $P < .001$) (eFigure 1 in the Supplement), accounting for potentially confounding variables, displayed in **Table 2**.

Figure 2. Distribution of Time to Epinephrine in Pediatric In-Hospital Nonshockable Cardiac Arrest (N=1558)



The majority of the included patients received epinephrine early, with 37% receiving epinephrine within the first minute; 15% received the first dose of epinephrine more than 5 minutes after the cardiac arrest. (See Methods for definition of time to epinephrine.) No time point had zero observations.

Secondary Outcomes

Of 1558 patients, 993 (63.7%) had ROSC, and 745 (47.8%) were alive 24 hours after the arrest; 217 of 1395 patients (15.6%) had a documented favorable neurological outcome at hospital discharge (an additional 10.5% [163/1558] survived to hospital discharge but without a documented PCPC score). Increasing time to epinephrine was associated with a decreased risk of ROSC (RR per minute delay, 0.96 [95% CI, 0.94-0.97]; $P < .001$), lower survival at 24 hours (RR per minute delay, 0.96 [95% CI, 0.94-0.98]; $P < .001$), and less survival with favorable neurological outcome (RR per minute delay, 0.94 [95% CI, 0.91-0.97]; $P < .001$) in unadjusted analysis. These associations remained statistically significant in multivariable analysis for ROSC (RR per minute delay, 0.97 [95% CI, 0.96-0.99]; $P < .001$), for survival at 24 hours (RR per minute delay, 0.97 [95% CI, 0.95-0.99]; $P = .003$), and for survival with favorable neurological outcome (RR per minute delay, 0.95 [95% CI, 0.91-0.99]; $P = .02$) using our primary definition. The results of the multivariable analyses when using the 3 different sensitivity definitions of favorable neurological outcome were similar to the main definition (eTable 2 in the Supplement).

We found no sign of nonlinear (ie, quadratic or cubic) associations between time to epinephrine and survival to hospital discharge (all $P > .05$). None of the tested interactions as described in the Methods section were significant (all $P > .05$). The results of the post hoc sensitivity analyses are presented in eTable 3 in the Supplement. The association between time to epinephrine and the various outcomes remained statistically significant when using propensity score analyses and when using multiple imputation techniques for missing data.

Time to Epinephrine as a Categorical Variable

As an additional analysis, we divided patients into 2 groups: time to epinephrine of 5 minutes or less vs longer than 5 minutes. The 5-minutes-or-less group (1325/1558 patients [85%]) had in-hospital survival to discharge of 33.1% (438/1325), compared with 21.0% (49/233) in the longer-than-5-minutes group

Table 1. Characteristics of the Population for Study of Timing of Epinephrine and Pediatric In-Hospital Nonshockable Cardiac Arrest[a]

	No. (%)			
	All Patients (N = 1558)	Survivors to Hospital Discharge (n = 487)	Nonsurvivors (n = 1071)	*P* Value
Sex				
Female	709 (46)	218 (45)	491 (46)	.69
Male	849 (55)	269 (55)	580 (54)	
Age group				
Neonate, <1 mo	421 (27)	117 (24)	304 (28)	<.001
Infant, 1 mo-<1 y	406 (26)	147 (30)	259 (24)	
Child, 1-12 y	501 (32)	173 (36)	328 (31)	
Adolescent, >12 y	230 (15)	50 (10)	180 (17)	
Type of admission				
Medical cardiac	258 (17)	71 (15)	187 (17)	<.001
Medical noncardiac	777 (50)	221 (45)	556 (52)	
Surgical cardiac	179 (11)	80 (16)	99 (9)	
Surgical noncardiac	139 (9)	69 (14)	17 (7)	
Newborn[b]	205 (13)	46 (9)	159 (15)	
Location of arrest				
Emergency department	266 (17)	56 (12)	210 (20)	<.001
ICU/PACU/OR	1001 (64)	338 (69)	663 (62)	
Floor with telemetry	41 (3)	9 (2)	32 (3)	
Floor without telemetry	144 (9)	35 (7)	109 (10)	
Other	106 (7)	49 (10)	57 (5)	
Time of week of arrest				
Weekend[c]	480 (31)	123 (25)	357 (33)	.001
Weekday	1078 (69)	364 (75)	714 (67)	
Time of day of arrest				
Nighttime[d]	457 (29)	118 (24)	339 (32)	.003
Daytime	1101 (71)	369 (76)	732 (68)	
Arrest witnessed				
Yes	1401 (90)	462 (95)	939 (88)	<.001
No	157 (10)	25 (5)	132 (12)	
Arrest monitored				
Yes	1313 (84)	430 (88)	883 (82)	.003
No	245 (16)	57 (11)	188 (18)	
Preexisting mechanical ventilation				
Yes	768 (49)	243 (50)	525 (49)	.75
No	709 (51)	244 (50)	546 (51)	
Insertion of an airway				
Yes	759 (49)	240 (49)	519 (48)	.06
No	799 (51)	247 (51)	552 (52)	
Initial rhythm				
Asystole	812 (52)	217 (45)	595 (56)	.001
Pulseless electrical activity	746 (48)	270 (55)	476 (44)	
Time to epinephrine, min				
Median (IQR)	1 (0-4)	1 (0-3)	2 (0-4)	<.001
Mean (SD)	2.6 (3.4)	2.0 (2.8)	2.8 (2.6)	
Time to chest compressions, min				
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	.14
Mean (SD)	0.1 (1.0)	0.1 (0.4)	0.2 (1.1)	

(continued)

Table 1. Characteristics of the Population for Study of Timing of Epinephrine and Pediatric In-Hospital Nonshockable Cardiac Arrest[a] (continued)

	No. (%)			
	All Patients (N = 1558)	Survivors to Hospital Discharge (n = 487)	Nonsurvivors (n = 1071)	*P* Value
Type of hospital				
Primarily children	564 (36)	202 (41)	362 (34)	.004
Primarily adult	994 (64)	285 (58)	709 (66)	
Teaching status				
Major	1079 (69)	359 (74)	420 (67)	.02
Minor	366 (23)	103 (21)	263 (25)	
Nonteaching	113 (7)	25 (5)	88 (8)	
Year of the arrest				
2000-2002	109 (7)	20 (4)	89 (8)	.07
2003-2004	133 (11)	47 (10)	122 (11)	
2005-2006	254 (16)	81 (17)	173 (16)	
2007-2008	272 (18)	93 (19)	182 (17)	
2009-2010	270 (17)	88 (18)	182 (17)	
2011-2012	260 (17)	87 (18)	173 (16)	
2013-2014	221 (14)	71 (16)	150 (14)	

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PACU, postanesthesia care unit; OR, operating room.

[a] Continuous variables are presented as medians with interquartile ranges and categorical variables as counts (frequencies).

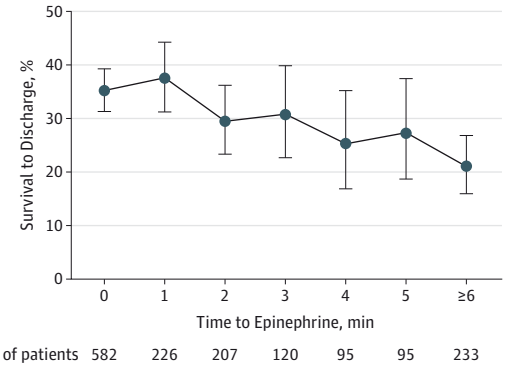
[b] Defined as being born on the current admission.

[c] Friday 11 PM to Monday 7 AM.

[d] 11:00 PM to 6:59 AM.

(233/1558 patients [15%]). The crude secondary outcomes are reported in eTable 4 in the Supplement. In unadjusted analysis, the longer-than-5-minutes group had significantly lower risk of ROSC (RR, 0.73 [95% CI, 0.64-0.84]; *P* < .001), 24-hour survival (RR, 0.69 [95% CI, 0.58-0.83]; *P* < .001), survival to discharge (RR, 0.64 [95% CI, 0.49-0.83]; *P* = .001), and survival to hospital discharge with favorable neurological outcome (RR, 0.58 [95% CI, 0.38-0.88]; *P* = .01). This association remained significant in multivariable analysis for ROSC (RR, 0.85 [95% CI, 0.75-0.95]; *P* = .006), 24-hour survival (RR, 0.79 [95% CI, 0.69-0.92]; *P* = .002), and survival to discharge (RR, 0.75 [95% CI, 0.60-0.93]; *P* = .01). There was no significant association with survival to hospital discharge with favorable neurological outcome (RR, 0.77 [95% CI, 0.47-1.25]; *P* = .29).

Figure 3. Time to Epinephrine and Survival to Hospital Discharge After Pediatric In-Hospital Nonshockable Cardiac Arrest (N = 1558)



Longer time to epinephrine administration was associated with lower risk of survival to discharge in multivariable analysis (risk ratio per minute delay, 0.95 [95% CI, 0.93-0.98]; *P* < .001). Error bars indicate exact binomial 95% confidence intervals.

Discussion

In this multicenter cohort study of in-hospital pediatric cardiac arrest, delay in administration of epinephrine was associated with a decreased chance of ROSC, 24-hour survival, survival to hospital discharge, and survival to hospital discharge with a favorable neurological outcome among patients with an initial nonshockable rhythm. These associations remained when accounting for multiple predetermined potentially confounding patient, event, and hospital characteristics and in multiple different sensitivity analyses. Although the observational design precludes ascertainment of causality, the strong association with outcomes suggests that early epinephrine may be beneficial in pediatric cardiac arrest.

The physiological rationale for epinephrine is primarily through α-adrenergic increase in coronary perfusion pressure, which has been shown to be an important determinant of ROSC.[9-11,30] The association between epinephrine administration and a better chance of ROSC is a consistent finding across studies.[31-34] Because duration of CPR is associated with outcome[21] and ROSC is a necessary first step to a meaningful recovery, the rationale for epinephrine administration as a time-sensitive intervention to improve long-term outcome becomes apparent. The lack of long-term survival data with epinephrine has previously been attributed to late drug administration in clinical trials of out-of-hospital cardiac arrest.[35] Whether decreasing time to epinephrine during in-hospital and out-of-hospital cardiac arrest will improve outcomes in the pediatric or adult population remains to be clarified. Our findings do suggest, however, that there is room for improvement, with 15% of pediatric patients getting their first epinephrine dose more than 5 minutes after loss of pulse.

Table 2. Multivariable Model With Survival to Discharge as the Outcome of Pediatric In-Hospital Cardiac Arrest[a]

Variable	Risk Ratio (95% CI)	*P* Value
Time to epinephrine, per min	0.95 (0.93-0.98)	<.001
Time to chest compressions, per min	0.88 (0.71-1.08)	.21
Sex		
Male	1 [Reference]	
Female	0.97 (0.56-1.09)	.57
Age group		
Child, 1-12 y	1 [Reference]	
Neonate, <1 mo	0.88 (0.71-1.09)	.24
Infant, 1 mo-<1 y	1.08 (0.92-1.27)	.35
Adolescent, >12 y	0.64 (0.49-0.84)	.001
Type of admission		
Medical noncardiac	1 [Reference]	
Medical cardiac	0.88 (0.71-1.08)	.22
Surgical cardiac	1.26 (1.02-1.54)	.03
Surgical noncardiac	1.55 (1.30-1.85)	<.001
Newborn	0.79 (0.58-1.08)	1.14
Location of arrest		
ICU/PACU/OR	1 [Reference]	
Emergency department	0.75 (0.56-1.00)	.05
Floor with telemetry	0.64 (0.41-1.00)	.05
Floor without telemetry	0.83 (0.57-1.21)	.34
Other	1.41 (1.12-1.76)	.003
Time of week of arrest		
Weekday	1 [Reference]	
Weekend[b]	0.85 (0.74-0.98)	.02
Time of day of arrest		
Nighttime[c]	1 [Reference]	
Daytime	1.10 (0.93-1.32)	.27
Arrest characteristics		
Witnessed	1.56 (1.12-2.17)	.009
Monitored	0.97 (0.72-1.32)	.86
Preexisting mechanical ventilation	0.87 (0.71-1.05)	.15
Insertion of an airway	1.20 (0.98-1.47)	.08
Initial rhythm		
Asystole	1 [Reference]	
Pulseless electrical activity	1.17 (1.02-1.35)	.02
Hospital characteristics		
Primary hospital status		
Adult	1 [Reference]	
Pediatric	1.12 (0.92-1.36)	.28
Teaching status		
Major	1 [Reference]	
Minor	0.98 (0.80-1.21)	.88
Nonteaching	0.91 (0.66-1.27)	.59

Abbreviations: ICU, intensive care unit; PACU, postanesthesia care unit; OR, operating room.

[a] We encourage the readers to interpret the results in the table carefully as the study and statistical analysis were not designed to specifically assess the association between these variables (except time to epinephrine) and survival. The model included all variables in the table as well as year of the arrest.

[b] Friday 11 PM to Monday 7 AM.

[c] 11:00 PM to 6:59 AM.

Epinephrine is currently recommended in pediatric cardiac arrests as the first-line pharmacological intervention despite no randomized placebo-controlled trials in this patient population.[6,8] One randomized placebo-controlled study in the adult out-of-hospital cardiac arrest population found improved ROSC and short-term survival with administration of epinephrine.[31] However, the study was underpowered to detect any difference in long-term outcome because of unanticipated lack of enrollment.[36] Similar results were reported in a study comparing intravenous drug administration (with 79% receiving epinephrine) vs no intravenous drug administration in out-of-hospital cardiac arrest.[37] In addition to these randomized studies, a number of large observational studies have been published about the adult out-of-hospital cardiac arrest population with conflicting results, even within the same data set, because of different statistical approaches.[32-34] These conflicting studies have added to the complexity of clinical decision making.[36,38]

The aim of the current study was not to answer the question of whether or not epinephrine should be given but to clarify whether there was an association between delay in epinephrine administration and outcome when epinephrine was given during in-hospital pediatric cardiac arrest. We found that a delay in epinephrine administration was associated with a significantly decreased chance of good outcomes. There are notable differences between pediatric and adult cardiac arrest in etiology, epidemiology, and treatment, including that more children have a nonshockable rhythm.[3] Despite this, the current findings in the pediatric population are in line with those previously reported for adults.[15] The current study included only patients who initially had a nonshockable rhythm. We decided to analyze data only from this patient population to avoid confounding by defibrillation, which has previously been found to be a time-sensitive component of cardiac arrest resuscitation in adult patients with a shockable rhythm.[39] As such, the findings should not be extrapolated to patients with a shockable rhythm; neither should they be extrapolated to out-of-hospital cardiac arrest, for which the time to initiation of therapy is often much longer.

A number of limitations should be considered when interpreting the current study. The data are observational, and the possibility of unmeasured confounding remains. We tried to account for this by multivariable regression modeling, including adjusting for time to CPR and hospital center as well as multiple patient and event characteristics. We excluded a small number of patients based on missing values for covariates, time to epinephrine, or the outcomes, which might decrease the generalizability of our results. However, the majority of patients had complete data, which allowed us to adjust for several variables, and the results did not change when using multiple imputation to account for missing data. However, the possibility remains that time to epinephrine is a marker of other aspects of the resuscitation processes and not the causal mediator.

The GWTG-R data registry is designed as a data quality improvement tool, not specifically designed to answer the current research question. The quality of data across sites may therefore vary. However, the AHA provides standardized

reporting guidelines and training of all entry personnel to ensure accuracy of entered data. We furthermore included only hospitals with at least 6 months of data and at least 5 cases reported to ensure high quality of the data. Data abstractors were not blinded to the outcome of the patients, although they were unaware of the hypothesis of the current study. As such, we consider it unlikely that this limitation would bias our results. The classification of the time variables was done in whole minutes, and the actual time might therefore have been slightly misclassified. Furthermore, time variables may have been classified incorrectly on the code sheets from which data were abstracted. We believe that this potential misclassification is likely undifferentiated and that, in most cases, this would lead to bias toward the null.

The current study was not designed to evaluate whether epinephrine should be administered. Patients who did not receive epinephrine were therefore excluded. Seven hundred forty patients did not receive epinephrine (Figure 1). Although some of these patients met other exclusion criteria, 362 patients were excluded solely on the basis of not having received epinephrine. These 362 patients had a very high rate of ROSC (94%) and a short median downtime (2 minutes [IQR, 1-5]), compared with the included cohort (64% ROSC and median downtime of 14 minutes [IQR, 6-28]). Based on this difference, we consider this patient population to be substantially different from the one included and believe that a meaningful comparison would be problematic, especially given the relatively low overall sample size.

Conclusions

Among children with in-hospital cardiac arrest with an initial nonshockable rhythm who received epinephrine, delay in administration of epinephrine was associated with decreased chance of survival to hospital discharge, ROSC, 24-hour survival, and survival to hospital discharge with a favorable neurological outcome.

ARTICLE INFORMATION

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