Epinephrine Dosing Intervals Are Associated With Pediatric In-Hospital Cardiac Arrest Outcomes: A Multicenter Study*

OBJECTIVES: Data to support epinephrine dosing intervals during cardiopulmonary resuscitation (CPR) are conflicting. The objective of this study was to evaluate the association between epinephrine dosing intervals and outcomes. We hypothesized that dosing intervals less than 3 minutes would be associated with improved neurologic survival compared with greater than or equal to 3 minutes.

DESIGN: This study is a secondary analysis of The ICU-RESUScitation Project (NCT028374497), a multicenter trial of a quality improvement bundle of physiology-directed CPR training and post-cardiac arrest debriefing.

SETTING: Eighteen PICUs and pediatric cardiac ICUs in the United States.

PATIENTS: Subjects were 18 years young or younger and 37 weeks old or older corrected gestational age who had an index cardiac arrest. Patients who received less than two doses of epinephrine, received extracorporeal CPR, or had dosing intervals greater than 8 minutes were excluded.

INTERVENTIONS: The primary exposure was an epinephrine dosing interval of less than 3 vs. greater than or equal to 3 minutes.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was survival to discharge with a favorable neurologic outcome defined as a Pediatric Cerebral Performance Category score of 1–2 or no change from baseline. Regression models evaluated the association between dosing intervals and: 1) survival outcomes and 2) CPR duration. Among 382 patients meeting inclusion and exclusion criteria, median age was 0.9 years (interquartile range 0.3–7.6 yr) and 45% were female. After adjustment for confounders, dosing intervals less than 3 minutes were not associated with survival with favorable neurologic outcome (adjusted relative risk [aRR], 1.10; 95% CI, 0.84–1.46; $p = 0.48$) but were associated with improved sustained return of spontaneous circulation (ROSC) (aRR, 1.21; 95% CI, 1.07–1.37; $p < 0.01$) and shorter CPR duration (adjusted effect estimate, −9.5 min; 95% CI, −14.4 to −4.84 min; $p < 0.01$).

CONCLUSIONS: In patients receiving at least two doses of epinephrine, dosing intervals less than 3 minutes were not associated with neurologic outcome but were associated with sustained ROSC and shorter CPR duration.

KEYWORDS: cardiac arrest; cardiopulmonary resuscitation; epinephrine; intensive care unit; pediatrics

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In-hospital cardiac arrest (IHCA) affects 15,000 children in the United States each year (1, 2). While the majority obtain return of spontaneous circulation (ROSC), only half survive to hospital discharge, and neurologic morbidity is common among survivors. Furthermore, survival has plateaued, highlighting the need for further investigation into intra-arrest therapies (3–5).

Epinephrine is the only drug uniformly recommended across Advanced Cardiac Life Support and Pediatric Advanced Life Support (PALS)

KEY POINTS

Question: The objective of this study was to evaluate the association between epinephrine dosing intervals and outcomes in a multicenter cohort. We hypothesized that dosing intervals less than 3 minutes would be associated with improved neurologic survival compared with greater than or equal to 3 minutes.

Findings: Epinephrine dosing intervals less than 3 minutes were not associated with survival with favorable neurologic outcome but were associated with improved return of spontaneous circulation and shorter cardiopulmonary resuscitation duration. In patients on a vasoactive infusion, intervals less than 3 minutes were associated with favorable neurologic outcome.

Meaning: Shorter dosing intervals than currently recommended may be appropriate in some patients. Prospective studies of epinephrine dosing intervals are needed.

cardiopulmonary resuscitation (CPR) algorithms, with a recommended dosing interval of 3–5 minutes (6, 7). The mechanism of action is an increase in aortic diastolic blood pressure (DBP) and thus coronary perfusion pressure, which has been associated with achieving ROSC (8–10). While observational studies suggest a time-dependent benefit to the first dose of epinephrine for both adult and pediatric IHCA and out-of-hospital cardiac arrest (OHCA) (11–19), data to support a dosing interval for subsequent doses are conflicting (12, 20–25).

Pharmacologic studies suggest that epinephrine administered more frequently than currently recommended may be beneficial (26–29). A recent single-center study showed improved survival with favorable neurologic outcome when epinephrine was given at intervals less than or equal to 2 minutes compared with greater than 2 minutes. CPR duration was shorter when epinephrine was given more frequently, and DBP was higher, providing mechanisms by which frequent epinephrine may limit neurologic injury (20).

Our primary objective was to investigate the association between epinephrine dosing intervals and survival outcomes from pediatric IHCA using data from a prospective multicenter interventional trial (The ICU-RESUScitation Project [ICU-RESUS]; NCT02837497). We hypothesized that in patients receiving at least two doses of epinephrine, epinephrine dosing intervals less than 3 minutes would be associated with improved survival to hospital discharge with a favorable neurologic outcome compared with greater than or equal to 3-minute intervals.

MATERIALS AND METHODS

Study Setting and Oversight

The ICU-RESUS study was a multicenter, hybrid stepped-wedge cluster-randomized trial of a quality improvement bundle of physiology-directed bedside CPR training and structured post-cardiac arrest debriefing (30). It was conducted in 18 PICUs and pediatric cardiac ICUs in the United States. The institutional review board (IRB) at the University of Utah served as the single IRB and approved the ICU-RESUS study protocol with waiver of informed consent (protocol IRB_00093320; July 18, 2016). Procedures were followed in accordance with the ethical standards of the central IRB and with the Helsinki Declaration of 1975. An independent data safety and monitoring board appointed by the National Heart, Lung, and Blood Institute (NHLBI) provided regulatory oversight.

This secondary study was designed during ICU-RESUS patient enrollment without prior examination of the data. Only data prospectively collected per the ICU-RESUS protocol were included.

Patient Population

The ICU-RESUS study enrolled patients 18 years young or younger and 37 weeks old or older post-gestational age who received chest compressions for index (first of admission) IHCA in any of the participating ICUs. Subjects were excluded if, before the arrest, they: 1) were not expected to survive the hospitalization due to a terminal illness or had a documented lack of commitment to aggressive ICU therapies; 2) were brain dead; or 3) had an OHCA associated with the current hospitalization. Patients were excluded from the present study if they received less than two doses epinephrine, achieved return of circulation via extracorporeal CPR (ECPR), or had estimated dosing intervals greater than 8 minutes (due to presumed periods of nonsustained ROSC such that estimated

dosing intervals would be inaccurate). Specifically, ECPR patients were excluded because our postulated mechanism by which more frequent epinephrine dosing leads to improved neurologic outcomes is more prompt ROSC, which does not apply to ECPR patients.

Data Collection and Physiologic Waveform Analyses

Trained research coordinators at each study site collected standard cardiac arrest and CPR data elements consistent with the Utstein Resuscitation Registry Template for IHCA (31). Data elements pertinent to this study included the total number of doses of code-dose epinephrine administered during CPR, timing (to the nearest minute) of the first dose of epinephrine, and duration of CPR (code events were bound by CPR start and stop times, which were extracted from the medical record). As part of an NHLBI ancillary study to the main trial, epinephrine administration times beyond the first dose were also recorded in a subset of patients. As a component of the ICU-RESUS study, physiologic waveforms were collected for patients with invasive arterial blood pressure (BP) data available. These waveforms were reviewed and analyzed by blinded investigators (R.W.M., K.G., R.M.S.) at the Children's Hospital of Philadelphia as previously described (9, 30, 32).

Study Variables and Outcomes

The primary predictor variable was an estimated epinephrine dosing interval of less than 3 minutes vs. greater than or equal to 3 minutes. This differed from the 2-minute threshold used in previous work because preliminary data in the present study identified estimated intervals to overestimate documented intervals, and because 3 minutes represents the lower limit of the interval recommended by existing guidelines. Specifically, in the subset of patients with documented epinephrine dosing times (n = 103), times were used to create an event-level average dosing interval ("documented dosing interval") as performed in previous work (20). The estimated dosing interval was calculated by the following equation: (CPR duration after the first dose of epinephrine)/(total doses of epinephrine–1). The relationship between estimated and documented dosing intervals was explored visually with a scatterplot of estimated vs. documented dosing interval and with Spearman correlation. The average absolute difference between estimated and documented dosing interval was 0.90 minutes; the median absolute difference was 0.67 (minimum difference, 0 min; maximum difference, 5 min; **Fig. 1**). Estimated dosing interval was used instead of documented interval as it was available for more patients (n = 382 vs. 103), and thus increased the power to test our hypothesis.

The primary outcome was survival to discharge with a favorable neurologic outcome defined as a Pediatric Cerebral Performance Category score of 1–2 or no change from the patient's baseline (33). Secondary outcomes included sustained ROSC (≥ 20 min) (31), CPR duration, survival to hospital discharge, and, among survivors, change in Functional Status Scale (FSS) at hospital discharge from baseline ("delta FSS") (34).

Statistical Methods

Patient and event characteristics were reported as frequencies and percentages or medians with interquartile range (IQR). Univariate analysis of associations

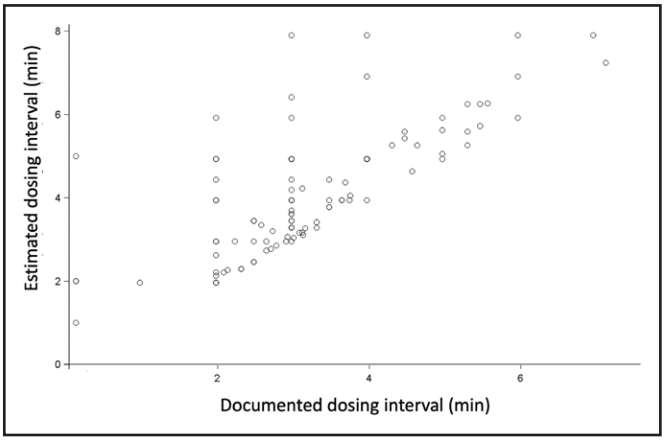

Figure 1. Exploring the relationship between documented and estimated epinephrine dosing intervals. In patients with documented epinephrine dosing times after the first dose (n = 103), times were used to create an event-level average dosing interval or "documented dosing interval." The estimated dosing interval was calculated by the following equation: (cardiopulmonary resuscitation duration after the first dose of epinephrine)/(total doses of epinephrine−1). The relationship between estimated and documented dosing intervals was explored visually with a *scatterplot* of estimated vs. documented dosing interval and with Spearman correlation. The average absolute difference between estimated and documented dosing interval was 0.90 min; the median absolute difference was 0.67 (minimum difference, 0 min; maximum difference, 5 min). Spearman correlation = 0.74.

with dosing interval were examined using Fisher exact test for categorical variables and Wilcoxon rank-sum test for ordinal variables.

Poisson regression with robust error estimates assessed the relationship between dosing interval and survival outcomes. Ordinary linear regression assessed the relationship between dosing interval and CPR duration, and delta FSS. Models included a priori covariates hypothesized to be associated with both dosing interval and outcomes: illness category (35), first documented rhythm (36), weekday vs. night/weekend (37), hospital/site, and time to first epinephrine dose (11). Regression models were repeated after stratification by presence of a vasoactive infusion at the time of arrest, a variable hypothesized to be an effect modifier between the exposure and outcomes.

All analyses were performed with SAS, Version 9.4 (SAS Institute, Cary, NC) and two-sided *p* values of less than 0.05 were considered statistically significant.

Secondary Analyses

Secondary analyses using the aforementioned regression models included: 1) a predictor of intervals of less than or equal to 2 vs. greater than 2 minutes for comparison with prior work (20) and 2) a trichotomous predictor (< 3, 3–5, > 5 min) for comparison to current guidelines

In patients from the primary analysis with ROSC, we examined post-cardiac arrest patient-level data up to six hours following ROSC to identify differences between groups that may have influenced outcomes. Highest arterial lactate (mmol/L) (38), lowest Po_2 (mm Hg) (39), and proportions of patients with post-arrest systolic and/or diastolic hypotension (40, 41) (defined as the minimum recorded BP < 5th percentile), highest core temperature greater than 38°C (42), highest Pao_2 greater than 300 (mm Hg), lowest Pco_2 less than 30 (mm Hg) (43), highest Pco_2 greater than 50 (mm Hg), lowest glucose less than 60 (mg/dL) (44), and highest glucose greater than 200 (mg/dL) (45) were investigated. Associations with dosing interval were examined using Fisher exact test for dichotomous variables and Wilcoxon rank-sum test for continuous variables.

In an exploratory analysis, the change in DBP and systolic BP (SBP) from "baseline" (before the second epinephrine dose based on estimated dosing intervals) to after the second dose was compared between groups using the Wilcoxon rank-sum test.

RESULTS

Of 1129 patients with index IHCA, 614 received at least two doses of epinephrine. After sequential exclusions, 382 patients were available for analysis (**Fig. 2**). Median age was 0.9 years (IQR, 0.3–7.6 yr) and 45% were female. Ninety-six patients (25%) had estimated dosing intervals of less than 3 minutes (**Table 1**). Two hundred seventy-three (71%) achieved ROSC, 167 (44%) survived to hospital discharge, and 143 (37%) survived with a favorable neurologic outcome (**Table 2**).

Patient demographics by dosing interval are described in **Supplementary Table 1** (http://links.lww.com/CCM/H548). There were no differences between exposure groups (< 3 vs. ≥ 3 min) on univariate analysis. Event characteristics are described in Table 1. There were no differences between exposure groups on univariate analysis of interventions in place before arrest, immediate cause of arrest, or first documented rhythm; CPR duration was shorter in the less than 3-minute group (9 min [4.5–18.0 min] vs. 13 min [7.0–26.0 min]; $p < 0.001$).

Primary Exposure Analyses

After adjustment for confounders, estimated dosing intervals less than 3 minutes were not associated with the primary outcome of survival to hospital discharge with favorable neurologic outcome (adjusted relative risk [aRR], 1.10; 95% CI, 0.84–1.46; $p = 0.48$) but were associated with higher risk of ROSC (aRR, 1.21; 95% CI, 1.07–1.37; $p = 0.002$) and shorter CPR duration (adjusted effect estimate, –9.5 min; 95% CI, –14.1 to –4.8; $p < 0.001$) (**Table 3**).

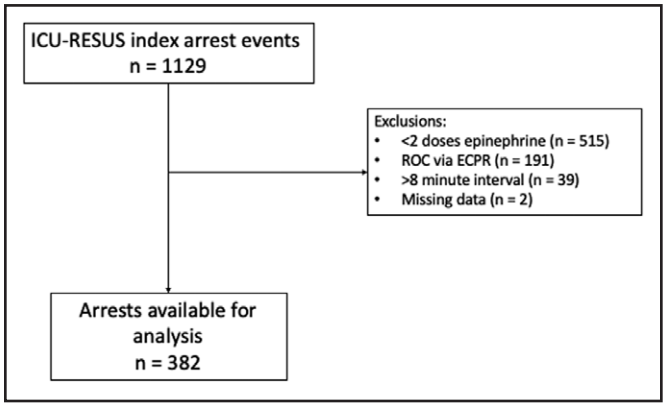

Figure 2. Flow diagram of patient selection. ECPR = extracorporeal cardiopulmonary resuscitation, ICU-RESUS = The ICU-RESUScitation Project, ROC = return of circulation.

TABLE 1.
Event Characteristics

Event Characteristic	Epinephrine Dosing Interval (min)		p
	≥ 3 (*n* = 286)	< 3 (*n* = 96)	
Interventions in place before event, *n* (%)			
Central venous catheter	193 (67.5)	66 (68.8)	0.900[a]
Vasoactive infusion	146 (51.0)	54 (56.3)	0.410[a]
Invasive mechanical ventilation	204 (71.3)	73 (76.0)	0.429[a]
Noninvasive ventilation	51 (17.8)	19 (19.8)	0.650[a]
End-tidal CO_2 monitoring	186 (65.0)	59 (61.5)	0.540[a]
Immediate cause(s) of event, *n* (%)			
Arrhythmia	51 (17.8)	14 (14.6)	0.532[a]
Cyanosis without respiratory decompensation	11 (3.8)	3 (3.1)	1.000[a]
Hypotension	167 (58.4)	60 (62.5)	0.548[a]
Respiratory decompensation	152 (53.1)	54 (56.3)	0.637[a]
First documented rhythm, *n* (%)			0.156[a]
Pulseless electrical activity/asystole	115 (40.2)	49 (51.0)	
Ventricular fibrillation/tachycardia	24 (8.4)	8 (8.3)	
Bradycardia with poor perfusion	147 (51.4)	39 (40.6)	
Duration of CPR (min), median (IQR)	13.0 (7.0–26.0)	9.0 (4.5–18.0)	< 0.001[b]
Duration of CPR (min), *n* (%)			< 0.001[a]
< 6	35 (12.2)	34 (35.4)	
6–15	123 (43.0)	33 (34.4)	
16–35	81 (28.3)	22 (22.9)	
> 35	47 (16.4)	7 (7.3)	
CPR time, *n* (%)			0.762[a]
Weekday (7 AM TO 11 PM, Monday to Friday)	150 (52.4)	49 (51.0)	
Weeknight (after 11 PM, Monday to Thursday)	53 (18.5)	21 (21.9)	
Weekend (11 PM on Friday through 7 AM on the following Monday)	83 (29.0)	26 (27.1)	
Defibrillation attempted, *n* (%)	47 (16.4)	5 (5.2)	0.005[a]
Pharmacologic interventions during event			
Minutes to first epinephrine bolus, median (IQR)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	0.285[b]
Number of epinephrine boluses, median (IQR)	4.0 (2.0–7.0)	4.5 (3.0–7.0)	0.090[b]
Epinephrine dosing interval (min), median (IQR)	4.5 (3.6–5.5)	2.0 (1.3–2.5)	< 0.001[b]
Atropine, *n* (%)	45 (15.7)	10 (10.4)	0.241[a]
Calcium, *n* (%)	172 (60.1)	54 (56.3)	0.549[a]
Sodium bicarbonate, *n* (%)	210 (73.4)	61 (63.5)	0.070[a]
Vasopressin, *n* (%)	18 (6.3)	6 (6.3)	1.000[a]
Amiodarone, *n* (%)	17 (5.9)	3 (3.1)	0.427[a]
Lidocaine, *n* (%)	12 (4.2)	5 (5.2)	0.775[a]
Fluid bolus, *n* (%)	107 (37.4)	33 (34.4)	0.626[a]

CPR = cardiopulmonary resuscitation, IQR = interquartile range.
[a]Fisher exact test.
[b]Wilcoxon rank-sum test.

TABLE 2.
Summary of Outcomes

Outcome	Epinephrine Dosing Interval (min)		p
	≥ 3 (*n* = 286)	< 3 (*n* = 96)	
Survival to hospital discharge with favorable neurologic outcome[a], *n* (%)	102 (36)	41 (43)	0.225[b]
Favorable neurologic outcome[a] at hospital discharge among survivors, *n* (%)	102/124 (82)	41/43 (95)	0.042[b]
Sustained return of spontaneous circulation (≥ 20 min), *n* (%)	195 (68)	78 (81)	0.013[b]
Survival to hospital discharge, *n* (%)	124 (43)	43 (45)	0.813[b]
Change from baseline to hospital discharge in Functional Status Scale, median (interquartile range)	1 (0–3)	0 (0–2)	0.044[c]

[a]Favorable neurologic outcome is defined as discharge Pediatric Cerebral Performance Category of 1–2 or no change from patient's baseline.
[b]Fisher exact test.
[c]Wilcoxon rank-sum test.

Stratified Analysis. In patients administered a vasoactive infusion at the time of arrest (*n* = 200), estimated dosing intervals less than 3 minutes were associated with improved survival to hospital discharge with favorable neurologic outcome (aRR, 1.48; 95% CI, 1.0–2.1; $p = 0.035$), as well as ROSC (aRR, 1.27; 95% CI, 1.06–1.53; $p = 0.011$), shorter CPR duration (adjusted effect estimate, –11.6 min; 95% CI, –17.9 to –5.3; $p < 0.001$), and smaller delta FSS (adjusted effect estimate, –1.70; 95% CI, –3.16 to –0.24; $p = 0.023$). In patients without a vasoactive infusion, dosing intervals less than 3 minutes did not achieve statistical significance for any outcome (Table 3).

Post-Arrest Care Variables. Among patients with ROSC (*n* = 273), there was no difference between exposure groups for post-arrest care variables except for hyperoxia: Thirty percent of patients exposed to estimated intervals less than 3 minutes (*n* = 18) experienced Pao_2 greater than 300 mm Hg compared with 16% (*n* = 23) of patients exposed to intervals greater than or equal to 3 minutes ($p = 0.03$) (**Supplementary Table 2**, http://links.lww.com/CCM/H548).

Secondary Exposure Analyses

In the analysis of estimated dosing intervals less than or equal to 2 minutes (*n* = 53) vs. greater than 2 minutes (*n* = 329), intervals less than or equal to 2 minutes were associated with higher relative risk of ROSC (aRR, 1.34; 95% CI, 1.20–1.49; $p < 0.001$) and shorter CPR duration (adjusted effect estimate, –15.9 min; 95% CI, –21.7 to –10.1; $p < 0.001$) in the full cohort and after stratification by vasoactive infusion. Intervals less than or equal to 2 minutes were also associated with a smaller delta FSS in patients on a vasoactive infusion (**Supplementary Table 3**, http://links.lww.com/CCM/H548).

In the analysis using a trichotomous predictor to compare the PALS-recommended interval of 3–5 minutes (*n* = 199) with greater than 5 minutes (*n* = 87) and a reference interval of less than 3 minutes (*n* = 96), estimated intervals of 3–5 and greater than 5 minutes were associated with longer CPR duration in the full cohort and after stratification by vasoactive infusion. Intervals of 3–5 and greater than 5 minutes were also associated with decreased risk of ROSC in the full cohort and in patients on a vasoactive infusion, and with a greater delta FSS in the full cohort (**Supplementary Table 4**, http://links.lww.com/CCM/H548).

Exploratory Physiologic Analysis

Among 164 patients with arterial catheters in place during CPR, 77 had evaluable BP data for the exploratory analysis of BP response to epinephrine using estimated intervals (reasons for nonanalyzable data: poor waveform signal, absence of CPR, inability to determine bounds of CPR, truncated DBP, and scale/shift issues). There was no association between estimated dosing interval less than 3 minutes

TABLE 3.
Association of Epinephrine Dosing Interval Less Than 3 Minutes With Outcomes

Outcome	Difference (95% CI)	Relative Risk (95% CI)	*p*
Survival to hospital discharge with favorable neurologic outcome			
All subjects		1.10 (0.84–1.46)	0.482
Subjects with vasoactive infusion		1.48 (1.03–2.12)	0.035
Subjects without vasoactive infusion		0.86 (0.59–1.25)	0.427
Duration of cardiopulmonary resuscitation (min)			
All subjects	−9.49 (−14.14 to −4.84)		< 0.001
Subjects with vasoactive infusion	−11.63 (−17.92 to −5.34)		< 0.001
Subjects without vasoactive infusion	−6.42 (−13.14 to 0.30)		0.061
Sustained return of spontaneous circulation (≥ 20 min)			
All subjects		1.21 (1.07–1.37)	0.002
Subjects with vasoactive infusion		1.27 (1.06–1.53)	0.011
Subjects without vasoactive infusion		1.10 (0.95–1.27)	0.216
Survival to hospital discharge			
All subjects		1.03 (0.79–1.35)	0.814
Subjects with vasoactive infusion		1.39 (0.97–1.99)	0.070
Subjects without vasoactive infusion		0.81 (0.57–1.14)	0.233
Change from baseline to hospital discharge in Functional Status Scale			
All subjects	−1.28 (−2.59 to 0.04)		0.056
Subjects with vasoactive infusion	−1.70 (−3.16 to −0.24)		0.023
Subjects without vasoactive infusion	−1.00 (−3.06 to 1.07)		0.341

Ordinary linear regression was used for Functional Status Scale, Pediatric Cerebral Performance Category, and duration of cardiopulmonary resuscitation while Poisson regression with robust error estimates was used for survival outcomes. All models control for illness category, first documented rhythm, weekday vs. night/weekend, hospital, and time to first epinephrine dose.
The few subjects with vasoactive infusion and illness category of surgical noncardiac or trauma died; these subjects are excluded from the vasoactive-infusion-specific modeling to allow estimates to be defined.

and absolute DBP or SBP nor the change in DBP or SBP after the second estimated dose compared with baseline (change in DBP: 6 mm Hg [0–12 mm Hg] vs. 5 mm Hg [0–10 mm Hg]; $p = 0.70$ and change in SBP: 16 mm Hg [6–28 mm Hg] vs. 8 mm Hg [−5 to 24 mm Hg]; $p = 0.13$) (**Supplementary Table 5**, http://links.lww.com/CCM/H548).

DISCUSSION

In this multicenter cohort study of PICU patients with IHCA who received at least two doses of epinephrine, estimated dosing intervals less than 3 minutes were not associated with improved survival with favorable neurologic outcome but were associated with improved ROSC and shorter CPR duration. Findings were driven by patients on a vasoactive infusion in whom intervals less than 3 minutes were associated with improved survival with a favorable neurologic outcome, as well as improved ROSC, shorter CPR duration, and smaller delta FSS. In secondary analyses of less than or equal to 2 vs. greater than 2 minutes and less than 3 vs. 3 to 5 and greater than 5 minutes, more frequent epinephrine than currently recommended was again associated with better rates of ROSC, shorter CPR duration, and smaller delta FSS. Building on previous work, these findings challenge current epinephrine dosing recommendations.

These findings are consistent with those of a recent nonoverlapping single-center study of 125 pediatric IHCA (20), as well as a 2019 study of adult OHCA (24). Findings of improved ROSC and shorter CPR duration in our primary analysis were seen throughout our stratified and secondary analyses, which were also notable for improved neurologic survival in patients with a vasoactive infusion in place at the time of arrest. However, in contrast to the aforementioned study, we failed to detect an association between "frequent" epinephrine and improved neurologic survival in the full cohort (20). It is worth noting that in unadjusted analysis of survivors in the present study, a larger proportion survived with a favorable neurologic status in the less than 3-minute group than in the greater than or equal to 3-minute group (95% vs. 82%; $p = 0.04$) (Table 2). Furthermore, there was a significant difference in the unadjusted analysis of delta FSS, with patients in the less than 3-minute group showing a smaller delta (1 [0–3] vs. 0 [0–2]; $p = 0.04$) (Table 2). Thus, it is possible that we were underpowered to find a difference in neurologic outcome in the full cohort given these other analyses suggesting potential benefit. CPR quality among this cohort was excellent (Supplementary Table 5, http://links.lww.com/CCM/H548), which may have caused a "ceiling effect," preventing detection of a difference in neurologic survival related to epinephrine administration in the full cohort, as even those patients receiving longer durations of CPR had adequate DBP during resuscitation, a variable associated with improved neurologic outcomes (9). Additionally, post-cardiac arrest data largely showed avoidance of vital sign and/or acid-base disturbances associated with worse outcomes in observational studies to posit as a possible explanation of our findings. Whether the association between dosing intervals and post-ROSC hyperoxia is mechanistically related (e.g., differences in perfusion or degree of post-cardiac arrest syndrome) may deserve further exploration.

Interestingly, patients on a vasoactive infusion at the time of arrest displayed better neurologic survival when exposed to less than 3-minute intervals compared with those not on a vasoactive infusion. It is possible that patients not dependent on exogenous catecholamines before arrest did not need frequent epinephrine to achieve adequate hemodynamics needed for ROSC and a favorable long-term outcome. This subgroup finding contrasts with previous single-center work, which showed greater benefit of frequent epinephrine in those without a vasoactive infusion in place at the time of arrest (20). As ICU-RESUS patients on a vasoactive infusion had low Vasoactive-Inotrope Scores (Supplementary Table 1, http://links.lww.com/CCM/H548), it is possible that patients with a modest degree of vasoactive requirement at the time of arrest benefit from frequent epinephrine administration during arrest while those in the single-center study may have had catecholamine-refractory shock that failed to respond as robustly to further catecholamines during CPR. Alternatively, vasoactive infusions may be a surrogate for different patient and/or event characteristics between the single-center cohort and this multicenter cohort, and not a predictor of response to bolus dose epinephrine during CPR.

Administering epinephrine more frequently than recommended was not only associated with increased likelihood of ROSC in both the single-center cohort and the present cohort but was common during these IHCAs, occurring in about 25% in both studies. Although the findings of the present study provide evidence of generalizability, the reader should not conclude that epinephrine dosed more frequently than recommended is appropriate for all patients. A recently published secondary analysis of the ICU-RESUS trial as well as several large animal studies show interindividual variation in response to epinephrine, and those subjects with greater increases in BP following epinephrine are more likely to attain ROSC and to attain ROSC more promptly (29, 46–49). Epinephrine responsiveness is likely a complex phenomenon involving modifiable and nonmodifiable factors, and it is probable that some benefit from more frequent epinephrine while others do not.

Previous registry studies showing better outcomes with longer intervals deserve mention. These studies controlled for CPR duration. Kienzle et al (20) hypothesized and showed that CPR duration was not a confounder but rather an effect mediator in the association between frequent epinephrine and good neurologic outcome. Grunau et al (24) used a similar approach in a 2019 study of adult OHCA, which showed shorter time to ROSC and neurologic survival benefit in patients with estimated dosing intervals less than 3 minutes. Ultimately, there are limitations to using observational

studies to identify appropriate dosing of a medication during cardiac arrest. Epinephrine dosing intervals should be investigated with prospective, randomized studies.

Kienzle et al (20) also hypothesized and provided evidence that more frequent epinephrine than recommended promotes more robust DBP earlier in the arrest, which may make conditions more favorable for prompt ROSC and good neurologic survival. In the present study, there was no difference in BP before and after the estimated second dose of epinephrine. Perhaps a second dose administered quickly after the first prevented a BP nadir and thus an identifiable delta between them. Of note, baseline DBP was lower for the less than 3-minute group, but this did not reach statistical significance. However, for some patients, this may have been why clinicians dosed epinephrine more frequently than PALS recommendations, perhaps a bias by indication. Alternatively, as DBP was robust across both exposure groups, perhaps more frequent epinephrine provided additional benefit though a different mechanism (e.g., by increasing inotropy/chronotropy in the large proportion of patients with nonpulseless arrests.)

This study has limitations. First, it is observational. Second, it uses estimated dosing intervals derived from CPR duration and number of epinephrine doses, similar to previous studies (12, 22). However, this dataset has a large subset of patients with documented intervals allowing the relationship between them to be explored and a priori predictor variables to be validated. Third, we are unable to discern patterns of epinephrine administration throughout arrests (50). Fourth, we lack information on specific supportive therapies (e.g., peri-arrest bolus epinephrine), which may have contributed to outcomes. Fifth, participating centers in the ICU-RESUS trial are large academic children's hospitals interested in CPR quality, potentially limiting generalizability. Differences in patient populations and CPR quality at other centers may impact the effectiveness of epinephrine and its relationship with outcomes.

CONCLUSIONS

In pediatric IHCA patients receiving at least two doses of epinephrine, dosing intervals less than 3 minutes were not associated with improved survival with favorable neurologic outcome but were associated with improved ROSC and shorter CPR duration. In the subset of patients on a vasoactive infusion at the onset of CPR, intervals less than 3 minutes were associated with improved survival with a favorable neurologic outcome.

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