The Association of the Average Epinephrine Dosing Interval and Survival With Favorable Neurologic Status at Hospital Discharge in Out-of-Hospital Cardiac Arrest

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Study objective: For patients with out-of-hospital cardiac arrest, the recommended dosing interval of epinephrine is 3 to 5 minutes, but this recommendation is based on expert opinion without data to guide optimal management. We seek to evaluate the association between the average epinephrine dosing interval and patient outcomes.

Methods: In a secondary analysis of the Resuscitation Outcomes Consortium continuous chest compression trial, we identified consecutive patients treated with greater than or equal to 2 doses of epinephrine. We defined average epinephrine dosing interval as resuscitation duration after the first dose of epinephrine divided by the total administered epinephrine, and categorized the dosing interval in minutes as less than 3, 3 to less than 4, 4 to less than 5, and greater than or equal to 5. We fit a logistic regression model to estimate the association of the average epinephrine dosing interval category with survival with favorable neurologic status (modified Rankin Scale score $\leq$3) at hospital discharge.

Results: We included 15,909 patients (median age 68 years [interquartile range 56 to 80 years], 35% women, 13% public location, 46% bystander cardiopulmonary resuscitation, and 19% initial shockable rhythm). The median epinephrine dosing interval was 4.3 minutes (interquartile range 3.5 to 5.3 minutes). Survival with favorable neurologic status occurred in 4.7% of patients. Compared with the reference dosing interval of less than 3 minutes, longer epinephrine dosing intervals were associated with lower survival with favorable neurologic status: dosing interval 3 to less than 4 minutes, adjusted odds ratio 0.44 (95% confidence interval 0.32 to 0.60); 4 to less than 5 minutes, adjusted odds ratio 0.26 (95% confidence interval 0.18 to 0.36); and greater than or equal to 5 minutes, adjusted odds ratio 0.21 (95% confidence interval 0.15 to 0.30).

Conclusion: In this out-of-hospital cardiac arrest series, a shorter average epinephrine dosing interval was associated with improved survival with favorable neurologic status. [Ann Emerg Med. 2019;74:797-806.]

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SEE EDITORIAL, P. 807.

INTRODUCTION

Background

Emergency medical services (EMS) attend to greater than 300,000 adult out-of-hospital cardiac arrests in the United States annually.[1] Epinephrine has been a mainstay of out-of-hospital cardiac arrest treatment for greater than 50 years.[2] It increases coronary perfusion during chest compressions (cardiopulmonary resuscitation [CPR]) to facilitate return of spontaneous circulation.[3] Administration of epinephrine is currently recommended at 1 mg every 3 to 5 minutes. However, this dosing interval is based solely on expert opinion.[2] Acquiring further evidence for the best application of epinephrine may be particularly important for individuals with nonshockable initial cardiac rhythms, for whom survival remains poor, with few proven effective treatments beyond early and high-quality chest compressions.[4]

Importance

For out-of-hospital cardiac arrest resuscitations, there are currently no data linking epinephrine dosing intervals with

Editor's Capsule Summary

What is already known on this topic

Guidelines recommend giving epinephrine every 3 to 5 minutes during cardiac arrest.

What question this study addressed

Are shorter epinephrine dosing intervals associated with improved out-of-hospital cardiac arrest outcomes?

What this study adds to our knowledge

In this analysis of 15,909 out-of-hospital cardiac arrests from the Resuscitation Outcomes Consortium, compared with longer intervals (3 to 4 minutes, 4 to 5 minutes, and ≥5 minutes), shorter epinephrine dosing intervals (<3 minutes) were associated with better survival with favorable neurologic status.

How this is relevant to clinical practice

Although practitioners may consider shorter dosing intervals, the optimal dose and clinical effectiveness of epinephrine remain unknown.

survival or survival with favorable neurologic status. There are also no data indicating the optimal epinephrine dosing interval. For patients with inhospital cardiac arrest, 3 observational studies have reported consistent associations between less frequent epinephrine dosing and improved survival at hospital discharge.[5-7] Whether these findings can be extended to individuals with out-of-hospital cardiac arrest is unclear.

Goals of This Investigation

Our objective was to determine the association between the average epinephrine dosing interval and survival with favorable neurologic status after out-of-hospital cardiac arrest.

MATERIALS AND METHODS

Study Design

This was a secondary analysis of adult out-of-hospital cardiac arrest patients enrolled in the Resuscitation Outcomes Consortium Continuous or Interrupted Chest Compressions During CPR trial. The trial was conducted with exception from informed consent under US and Canadian regulations.[8,9] We designed this study and wrote the article according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10]

The Resuscitation Outcomes Consortium comprised 10 regional centers across North America and their respective EMS systems, with a data coordinating center at the University of Washington. The geographic footprint spanned 218 out-of-hospital agencies covering 35,000 square miles and 24 million persons. The design and results of the Continuous or Interrupted Chest Compressions During CPR trial have been previously reported.[8] The trial enrolled out-of-hospital cardiac arrest patients who received EMS chest compressions, and excluded traumatic, asphyxial, or hemorrhagic arrests; EMS-witnessed arrests; pregnant patients or prisoners; patients with advanced directives to forgo resuscitation; patients treated with a mechanical chest-compression device; individuals with a tracheostomy or advanced airway management before EMS agency arrival; or individuals known to have previously opted out of resuscitation research. During the preintubation resuscitation phase, patients were randomized to receive either continuous chest compressions with unsynchronized ventilations or chest compressions interrupted for ventilations at a compression:ventilation ratio of 30:2. After intubation, all patients were treated with continuous chest compressions. Other treatments followed standard advanced cardiac life support guidelines.[8] Some patients were coenrolled in a trial of antiarrhythmic therapy for ventricular fibrillation.[11] These original trials were neutral for differences between interventions, thus avoiding confounding from trial arms.[8,11]

Trial research staff abstracted the following systematically collected data: patient and cardiac arrest characteristics, time-stamped EMS-delivered care (including timing of EMS arrival, initiation of compressions, defibrillator application, first vasopressor administration [and total dose of vasopressin and epinephrine], return of spontaneous circulation, termination of resuscitation, EMS departure time, and hospital arrival time), and hospital care (including length of stay, survival, and survival with favorable neurologic status categorized by the modified Rankin Scale score).[8,9,12]

Selection of Participants

We examined all Continuous or Interrupted Chest Compressions During CPR trial subjects for this analysis. We excluded subjects for whom epinephrine dosing interval was not applicable or could not be calculated, those who received fewer than 2 doses of epinephrine, those with missing data preventing calculation of dosing interval, and those who rearrested in the out-of-hospital setting (the data set does not include data on rearrest time, and we were thus unable to calculate the epinephrine dosing interval in these cases).

The primary outcome was survival with favorable neurologic status at hospital discharge, defined as modified Rankin Scale score less than or equal to 3.[12] Secondary

outcomes included survival to hospital ward admission and survival to hospital discharge.

Methods of Measurement and Primary Data Analysis

We used Microsoft Excel (version 14.5.0; Microsoft, Redmond, WA) and Stata (version 13.1; StataCorp, College Station, TX) for data entry and analysis. We reported categoric variables as counts with percentages and 95% confidence intervals (CIs), continuous variables as medians with interquartile ranges (IQR), and the proportion of cases with missing data.

The independent variable of interest was the average epinephrine dosing interval, calculated as: (end time of EMS-delivered resuscitation–time of first EMS-delivered vasopressor)/total dose of epinephrine (in milligrams). The time before the first EMS-delivered vasopressor was not included in the calculation because this initial phase of resuscitation is focused on alternative priorities such as scene assessment, historical data collection, initiation of high-quality CPR, monitor application, and airway strategies; furthermore, providers with the ability to administer epinephrine may not be on scene initially. The ending time of EMS-delivered resuscitation was determined from the time of return of spontaneous circulation, termination of resuscitation, or arrival at the hospital. We assumed that all epinephrine was administered according to the guideline-recommended dose of 1 mg.[2] The Continuous or Interrupted Chest Compressions During CPR data set does not specify whether the first vasopressin administered was epinephrine or vasopressin; we assumed that epinephrine was the first vasopressin administered for our calculation of epinephrine dosing interval (see sensitivity analysis described below).

We fit logistic regression models to calculate the association between the average epinephrine dosing interval and the primary and secondary outcomes. We classified the average epinephrine dosing interval into categories (in minutes) of less than 3, 3 to less than 4, 4 to less than 5, and greater than or equal to 5, based on the current American Heart Association guideline range, which recommends a dosing interval of 3 to 5 minutes.[2] We adjusted our model for the following covariates: age (continuous), sex, witnessed by bystander, bystander CPR, 911 call to first EMS arrival interval (continuous), initial shockable cardiac rhythm, public location, and study arm (continuous chest compressions versus 30:2). We assessed model calibration for the primary outcome by the Hosmer-Lemeshow goodness-of-fit test. In addition, we tested discrimination of this model for the primary outcome by calculating the area under the receiver operating characteristic (ROC) curve. Multicollinearity was tested by the variance inflation factor. We performed subgroup analyses within the categories of witnessed or unwitnessed arrest, and shockable or nonshockable initial rhythms.

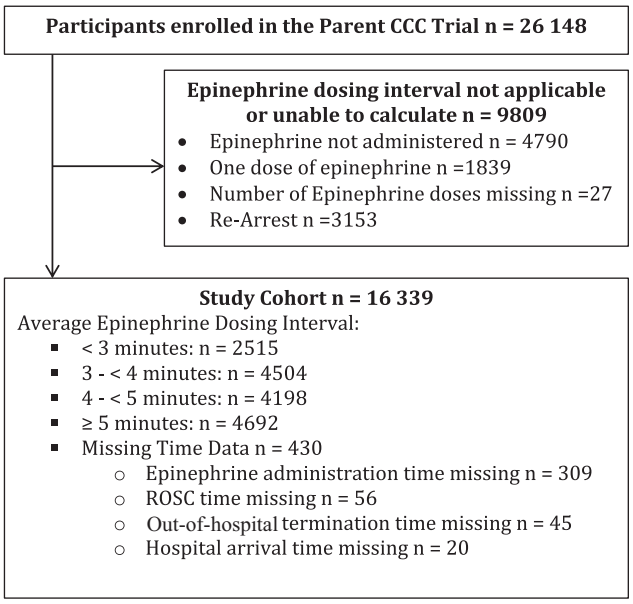

Figure 1. Study flow. Characteristics applied sequentially. *CCC*, Continuous chest compressions; *ROSC*, return of spontaneous circulation.

To demonstrate the association between average epinephrine dosing intervals of 1 to 10 minutes and the probability of survival with favorable neurologic status, we fit an adjusted natural cubic spline curve with 4 knots, adjusting for the same covariates as above. The knots were located at the fifth, 35th, 65th, and 95th percentiles of epinephrine dosing interval.

We performed 7 sensitivity analyses of our study cohort. First, we repeated the primary analysis with the number of epinephrine doses as an adjustment covariate. We did not include this in the primary analysis because the independent variable of interest may affect the number of epinephrine doses administered (ie, if a lower or higher epinephrine dosing interval results in earlier return of spontaneous circulation, this would affect the total number of epinephrine doses). However, as the resuscitation progresses it is possible that paramedics may change the frequency of dosing (either increasing the interval between doses because of an impression of epinephrine ineffectiveness [which would increase the average epinephrine dosing interval] or potentially decreasing the interval between doses because there are fewer competing tasks interfering with regular dosing [which would decrease the average epinephrine dosing interval]).

Second, because EMS protocols and treatments may have varied with treatment location, we incorporated a

Table 1. Patient characteristics, classified by category of epinephrine dosing interval.

	Average Epinephrine Dosing Interval, Minutes									
	<3.0 (n=2,059)		3.0–<4.0 (n=4,136)		4.0–<5.0 (n=4,463)		≥5.0 (n=5,251)		Missing Data in Time (n=430)	
Variable	**n or Median**	**Missing (%)**	**n or Median**	**Missing (%)**	**n or Median**	**Missing (%)**	**n or Median**	**Missing (%)**	**n or Median**	**Missing (%)**
Patient characteristics										
Age (IQR), y	68 (56–81)	1 (<0.1)	68 (56–81)	5 (0.1)	67 (56–80)	3 (0.1)	67 (55–79)	2 (<0.1)	67 (54–79)	0
Male sex (%)	1,287 (62.5)	1 (<0.1)	2,648 (64.0)	1 (<0.1)	2,956 (66.2)	0	3,397 (64.7)	2 (<0.1)	277 (64.4)	0
Initial rhythm (%)		4 (0.2)						3 (0.1)		
Shockable	413 (20.1)		685 (16.6)	2 (<0.1)	842 (18.9)	2 (<0.1)	1,062 (20.2)		96 (22.3)	
Bystander witness (%)	805 (40.2)	57 (2.8)	1,526 (37.8)	95 (2.3)	1,658 (37.9)	90 (2.0)	2,074 (40.3)	108 (2.1)	190 (45.4)	11 (2.6)
Location (%)		5 (0.2)		4 (0.1)		6 (0.1)		2 (<0.1)		3 (0.7)
Public	330 (16.1)		559 (13.5)		526 (11.8)		609 (11.6)		59 (13.8)	
Bystander CPR (%)	960 (47.3)	28 (1.4)	1,912 (46.7)	45 (1.1)	2,086 (47.1)	38 (0.9)	2,226 (42.9)	62 (1.2)	195 (69.4)	149 (34.7)
Study arm (%)		0		0		0		0		119 (27.8)
CCC	1,123 (54.5)		2,200 (53.2)		2,449 (54.9)		2,802 (53.4)		170 (54.7)	
30:2	936 (45.5)		1,936 (46.8)		2,014 (45.1)		2,449 (46.6)		141 (45.3)	
Out-of-hospital treatments										
Total dose of epinephrine (IQR), mg	3.0 (2.0–5.0)	0	4.0 (3.0–5.0)	0	4.0 (3.0–5.0)	0	3.0 (3.0–4.0)	0	3.0 (4.0–5.0)	20 (0.1)
Route of epinephrine (%)										
Intravenous	1,426 (69.3)	0	3,151 (76.2)	0	3,509 (78.6)	0	4,165 (79.3)	0	320 (74.4)	0
Intraosseous	511 (24.8)	0	1,001 (24.2)	0	983 (22.0)	0	1,129 (21.5)	0	99 (23.0)	0
Endotracheal	199 (9.7)	0	110 (2.7)	0	69 (1.6)	0	56 (1.1)	0	12 (2.8)	0
Vasopressin (%)	9 (0.4)	1 (<0.1)	16 (0.4)	0	28 (0.6)	0	194 (3.7)	1 (<0.1)	12 (2.8)	4
911 call to first epinephrine or vasopressin interval (IQR), min	17.7 (14.2–22.6)	0	16.6 (13.2–20.7)	0	16.4 (13.4–20.0)	0	16.3 (13.2–20.0)	0	17.5 (14.0–21.8)	309 (71.9)
EMS arrival to first epinephrine or vasopressin interval (IQR), min	12.0 (8.7–16.3)	0	10.9 (8.1–14.7)	0	10.7 (8.0–14.0)	0	10.7 (8.0–14.1)	0	11.7 (8.0–14.8)	311 (72.3)
911 call to EMS arrival interval (IQR), min	5.6 (3.3–7.1)	0	5.4 (4.1–6.8)	0	5.4 (4.1–6.9)	0	5.3 (4.1–6.7)	0	6.1 (4.8–7.7)	31 (7.2)

911 call to termination or hospital arrival interval (in patients without ROSC) (IQR), min	29.9 (24.5–36.6)	0	31.7 (27.0–38.0)	0	34.0 (29.4–40.0)	0	38.0 (32.8–45.0)	0	40.9 (32.8–51.4)	48 (34.0)
911 call to ROSC interval (IQR), min	22.6 (19.0–27.7)	0	25.6 (21.8–30.5)	0	27.6 (23.7–32.8)	0	31.5 (27.0–37.0)	0	24.8 (20.2–32.4)	38 (40.9)
Out-of-hospital disposition (%)		0		0		0		0		
Termination of resuscitation	820 (39.8)		2,465 (59.6)		2,727 (61.1)		2,653 (50.5)		195 (45.4)	0
Transported to hospital	1,239 (60.2)		1,671 (40.4)		1,736 (38.9)		2,598 (49.5)		235 (54.7)	0
ED arrival status (%)		0		0		0		1 (<0.1)		1 (0.4)
ROSC present	784 (63.3)		704 (42.1)		490 (28.2)		350 (13.5)		93 (39.7)	
Ongoing CPR	455 (36.7)		967 (57.9)		1,246 (71.8)		2,247 (86.5)		141 (60.3)	
Outcomes (%; 95% CI)										
ROSC	908 (44.1; 42.0–46.3)	2 (0.1)	862 (20.9; 19.6–22.1)	3 (0.1)	673 (15.1; 14.1–16.2)	6 (0.1)	656 (12.5; 11.6–13.4)	6 (0.1)	124 (29.0; 22.8–33.6)	3 (0.7)
Survival at hospital admission	713 (32.6; 31.0–36.7)	1 (<0.1)	664 (16.1; 15.0–17.2)	4 (0.1)	516 (11.6; 10.7–12.6)	12 (0.3)	510 (9.7; 8.9–10.6)	3 (0.1)	48 (16.1; 12.1–20.7)	131 (30.5)
Survival at hospital discharge	160 (7.8; 6.6–9.0)	3 (0.1)	134 (3.3; 2.7–3.8)	8 (0.2)	99 (2.2; 1.8–2.7)	6 (0.1)	101 (1.9; 1.6–2.3)	1 (<0.1)	14 (3.3; 1.8–5.4)	0
Survival with favorable neurologic status at hospital discharge	103 (5.0; 4.1–6.0)	4 (0.2)	86 (2.1; 1.7–2.6)	10 (0.2)	64 (1.4; 1.1–1.8)	6 (0.1)	71 (1.4; 1.1–1.7)	2 (<0.1)	11 (2.6; 1.2–4.5)	0

generalized estimating equation logistic regression model with the enrolling region as the clustering variable.

Third, we performed a sensitivity analysis excluding all patients who were treated with vasopressin at any time. The Continuous or Interrupted Chest Compressions During CPR data set records the time of first vasopressor administration (although it does not specify whether epinephrine or vasopressin was used); although it is likely that the majority of patients were treated with epinephrine as the first vasopressor option, it is possible that this was not the case, which would thus invalidate our epinephrine-based calculations.

Fourth, we added the interval between EMS arrival and first vasopressor administration (continuous) as a covariate to the analysis because this value has been associated with outcomes.[4]

Fifth, we excluded patients who arrived at the hospital with ongoing resuscitation because dosing frequency may have changed during extrication and transport, as well as after hospital arrival.

Sixth, we excluded patients whose length of resuscitation after the administration of the first vasopressor was less than 10 minutes. The inclusion of patients with short resuscitation durations may have biased the primary analysis in favor of the short average epinephrine dosing interval because those who achieved very early return of spontaneous circulation would be included in the shorter-interval categories but not in the longer categories (because they would not yet have received the second dose and thus would have been excluded).

Seventh, we repeated the primary analysis within defined subgroups as having epinephrine administered by either the intravenous or intraosseous route.

We limited the primary analysis to cases without rearrest because our data set lacked time data for rearrest or subsequent return of spontaneous circulation episodes. To test the effect of omitting the rearrest cases, we conducted 2 additional sensitivity analyses. We fit a multivariable model including all cardiac arrest cases with and without rearrest, assuming that the resuscitation interval extended from administration of the first vasopressor to first return of spontaneous circulation, or emergency department (ED) arrival or termination of resuscitation for patients who first received a vasopressor after the first return of spontaneous circulation episode (this model assumes the period[s] of rearrest[s] was negligible and represents the shortest possible epinephrine dosing interval). We then fitted a model assuming that the resuscitation interval extended from administration of first vasopressor to ED arrival or termination of resuscitation (this model assumes the period [s] of return of spontaneous circulation was negligible and represents the longest possible epinephrine dosing interval).

RESULTS

Characteristics of Study Subjects

Of 26,148 patients enrolled in the parent trial, we included 15,909 (Figure 1) in the analysis. The median age was 68 years (IQR 56 to 80 years), 35% were women, 13% of arrests occurred in public locations, 46% had bystander CPR, 8.4% had bystander automated external defibrillator application, and 19% had initial shockable rhythms. The median value for the average epinephrine dosing interval was 4.3 minutes (IQR 3.5 to 5.3 minutes). Overall, 1.6% of patients were cotreated with vasopressin.

Main Results

Patient characteristics were similar between average epinephrine dosing interval categories, including age, sex, the proportion with initial shockable rhythms, bystander-witnessed arrests, public-location arrests, and bystander CPR (Table 1). The interval between the 911 call and first EMS arrival, the interval between the 911 call and first vasopressor, and the total dose of epinephrine administered appeared similar between groups. In the group with a less than 3-minute dosing interval, 5.0% (95% CI 4.1% to 6.0%) survived with favorable neurologic status at hospital discharge compared with 2.1% (95% CI 1.7% to 2.6%), 1.4% (95% CI 1.1% to 1.8%), and 1.4% (95% CI 1.1% to 1.7%) for the groups with dosing intervals of 3 to less than 4 minutes, 4 to less than 5 minutes, and greater than or equal to 5 minutes, respectively (Figure 2). When outcomes were examined among patients with return of spontaneous circulation in each group, survival with favorable neurologic status at hospital discharge occurred in 11.3%, 10.0%, 9.5%, and 10.8%, respectively. Patient characteristics and outcomes stratified by 1-minute categories of average epinephrine dosing interval are shown in Table E1 (available online at http://www.annemergmed.com).

The adjusted analyses for the logistic regression models demonstrated that a shorter average epinephrine dosing interval was associated with survival with favorable neurologic status (Table 2). Compared with the reference dosing interval of less than 3 minutes, the dosing interval of 3 to less than 4 minutes had an adjusted odds ratio [AOR] of 0.44 (95% CI 0.32 to 0.60), the interval of 4 to less than 5 minutes had an AOR of 0.26 (95% CI 0.18 to 0.36), and the interval of greater than or equal to 5 minutes had an AOR of 0.21 (95% CI 0.15 to 0.30). Similar relationships were observed with both survival to hospital admission and survival to hospital discharge. The Hosmer-Lemeshow goodness-of-fit test was not significant. Area under the ROC curve was 0.91 (95% CI 0.90 to 0.93). Variance inflation factors in this model were less than 10 (Table E2,

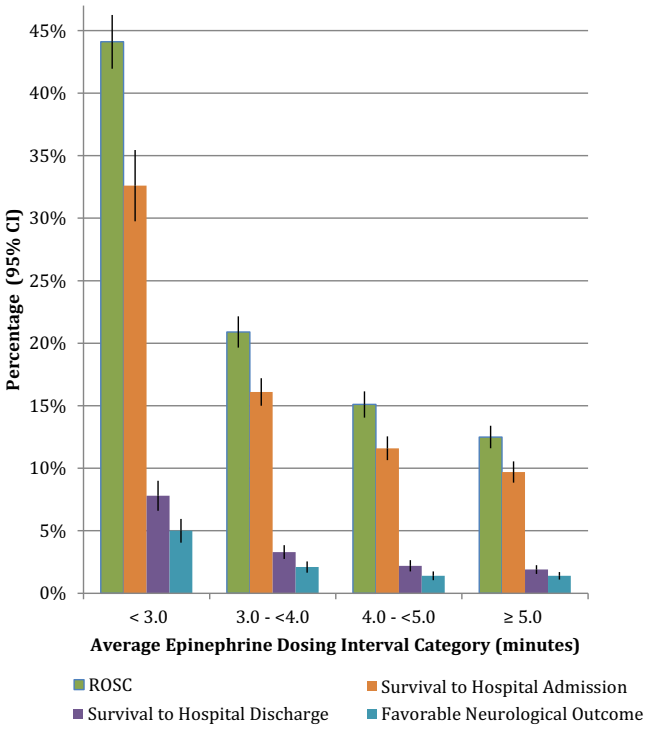

Figure 2. Patient outcomes stratified by average epinephrine dosing interval.

available online at http://www.annemergmed.com). Results were consistent within subgroups of witnessed and unwitnessed arrests, and those with initial shockable and nonshockable rhythms (Table 2).

We fit a covariate-adjusted natural cubic spline curve with 95% CIs to describe the relationship between the average epinephrine dosing interval and the probability of survival with favorable neurologic status (Figure 3).

Sensitivity Analyses

For all 7 sensitivity analyses of our study cohort, results consistently demonstrated an association between a shorter epinephrine dosing interval and improved outcomes (Table E3, available online at http://www.annemergmed.com). For the additional sensitivity analysis including rearrest cases, when we assumed the shortest average epinephrine dosing interval, the median value was 4.0 minutes (IQR 3.0 to 5.2 minutes); there were no major changes in the association between the average epinephrine dosing interval and hospital survival with favorable neurologic status (AOR for the interval 3 to <4 minutes was 0.63 [95% CI 0.48 to 0.81]; for the interval 4 to <5 minutes, 0.32 [95% CI 0.24 to 0.44]; and for the interval ≥5 minutes, 0.37 [95% CI 0.28 to 0.48]). When we assumed the longest average epinephrine dosing interval, the median value was 4.5 minutes (IQR 3.6 to 5.9 minutes); there were no major changes in the association between the average epinephrine dosing interval and hospital survival with favorable neurologic status (AOR for the interval 3 to <4 minutes was 0.42 [95% CI 0.31 to 0.58]; for the interval 4 to <5 minutes, 0.28 [95% CI 0.21 to 0.39]; and for the interval ≥5 minutes, 0.37 [95% CI 0.28 to 0.48]).

LIMITATIONS

This is a secondary analysis, and although we used rigorously collected trial data,[8] results should be considered hypothesis generating. There may have been important

Table 2. Adjusted logistic regression models examining the association of average epinephrine dosing interval with outcomes, within the full cohort and subgroups.

		Full Cohort		Witnessed Status		Initial Cardiac Rhythm	
				Witnessed	Unwitnessed	Shockable	Nonshockable
Outcome	Average Epinephrine Dosing Interval	Crude OR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Survival to hospital admission, min	No. in analysis	15,889	15,366	5,987	9,388	2,895	12,471
	<3.0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
	3.0–<4.0	0.36 (0.32–0.41)	0.36 (0.32–0.41)	0.38 (0.31–0.45)	0.35 (0.29–0.42)	0.38 (0.29–0.49)	0.36 (0.31–0.41)
	4.0–<5.0	0.25 (0.22–0.28)	0.23 (0.20–0.27)	0.23 (0.19–0.28)	0.23 (0.19–0.28)	0.23 (0.17–0.29)	0.23 (0.20–0.28)
	≥5.0	0.20 (0.18–0.23)	0.18 (0.15–0.20)	0.18 (0.14–0.21)	0.18 (0.15–0.22)	0.16 (0.13–0.22)	0.18 (0.16–0.22)
Survival to hospital discharge, min	No. in analysis	15,891	15,369	5,983	9,386	2,896	12,473
	<3.0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
	3.0–<4.0	0.40 (0.31–0.50)	0.42 (0.32–0.54)	0.34 (0.25–0.47)	0.58 (0.38–0.89)	0.50 (0.36–0.69)	0.32 (0.21–0.49)
	4.0–<5.0	0.27 (0.21–0.35)	0.24 (0.18–0.31)	0.23 (0.16–0.32)	0.25 (0.15–0.41)	0.27 (0.19–0.38)	0.19 (0.11–0.31)
	≥5.0	0.23 (0.18–0.30)	0.19 (0.14–0.25)	0.20 (0.14–0.27)	0.17 (0.10–0.28)	0.21 (0.15–0.30)	0.17 (0.10–0.27)
Survival with favorable neurologic status, min	No. in analysis	15,887	15,366	5,982	9,384	2,894	12,472
	<3.0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
	3.0–<4.0	0.40 (0.30–0.54)	0.44 (0.32–0.60)	0.37 (0.26–0.54)	0.64 (0.36–1.15)	0.51 (0.35–0.73)	0.27 (0.14–0.54)
	4.0–<5.0	0.28 (0.20–0.38)	0.26 (0.18–0.36)	0.25 (0.17–0.38)	0.25 (0.13–0.50)	0.27 (0.18–0.39)	0.24 (0.12–0.49)
	≥5.0	0.26 (0.19–0.35)	0.21 (0.15–0.30)	0.21 (0.14–0.31)	0.22 (0.11–0.43)	0.22 (0.15–0.32)	0.21 (0.11–0.42)

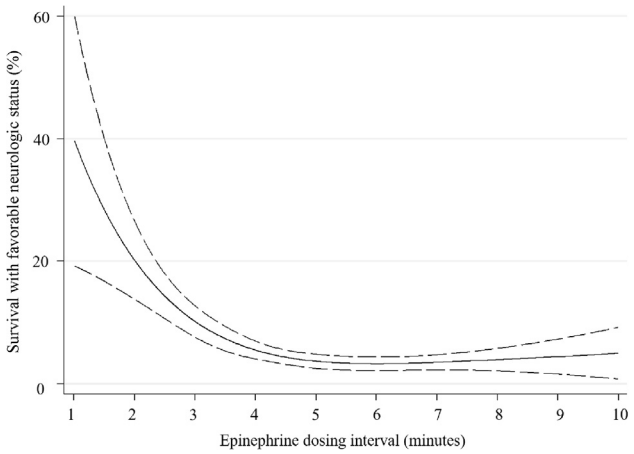

Figure 3. Covariate-adjusted natural cubic spline curve demonstrating the relationship between the average epinephrine dosing interval and the probability of survival with favorable neurologic status.

unmeasured variables that we did not adjust for. We examined the average epinephrine dosing interval as the key variable of interest. We did not have data on the time of administration of individual epinephrine doses, nor the variability of epinephrine dosing intervals within individual resuscitations. It is possible that the dosing interval varied within resuscitations, the effect of which on outcomes is unclear.

Although we controlled for enrolling cluster, this may not have adequately adjusted for unmeasured differences in resuscitation or postarrest quality of care that may have been correlated with regional practices in epinephrine dosing. It is possible that more frequent epinephrine dosing is associated with more overall aggressive or high-quality resuscitation strategies that may lead to better outcomes. However, we found that patient characteristics and resuscitative treatments between average epinephrine dosing interval groups in our study were similar, suggesting a low risk of bias resulting from differing epinephrine dosing strategies between prognostic phenotypes. Overall, 43 patients had noninteger total doses of epinephrine, indicating that providers appeared to occasionally administer nonstandard doses. Although prognostication bias may play a role in all resuscitations, we found that in the category with the poorest outcomes, the longest attempts at resuscitation were used before termination, suggesting that paramedic impression of a poor outcome and premature termination of efforts were not correlated with average epinephrine dosing interval.

DISCUSSION

In this analysis of over 15,000 patients enrolled in the Resuscitation Outcomes Consortium Continuous or Interrupted Chest Compressions During CPR trial, we found that a shorter average epinephrine dosing interval was associated with improved survival and survival with favorable neurologic status at hospital discharge. These findings may have important clinical implications. Current guidelines recommend epinephrine administration at 3- to 5-minute intervals, but these are based solely on expert opinion without supporting evidence. Our study suggests that an increased dosing frequency may improve clinically relevant out-of-hospital cardiac arrest outcomes, although a definitive answer would require a prospective trial.

Our subgroup and sensitivity analyses support the findings of the primary analysis. Although one might expect shorter epinephrine dosing intervals to have a greater influence on patients with nonshockable rhythms, the association between dosing intervals and outcomes appeared independent of presenting rhythm. In addition, although previous data have suggested that the effectiveness of intraosseous medication delivery may be attenuated in comparison with intravenous administration,[13,14] the results of our sensitivity analyses separately examining these 2 routes were very similar.

The recent landmark Paramedic 2 trial compared epinephrine (administered at American Heart Association-recommended dose and dosing intervals) with placebo, with respect to survival at hospital discharge.[15] Epinephrine resulted in a large increase in return of spontaneous circulation and a smaller, but still statistically significant, survival benefit. Although not powered to detect differences in neurologic outcomes, the trial reported no detectable difference in favorable neurologic outcomes, but an increase in survivors with unfavorable outcomes. Our results are congruent in finding that increased dosing frequency was associated with increased return of spontaneous circulation; however, the proportion of neurologic outcomes increased proportionally with the incidence of return of spontaneous circulation, rather than simply yielding non-survivors or unfavorable neurologic outcomes. Patients in our study tended to receive epinephrine earlier (median interval from 911 call to epinephrine 16 minutes) than in the Paramedic 2 trial (>21 minutes), which is associated with survival.[4] The shorter epinephrine dosing interval categories in our analysis also demonstrated shorter intervals until return of spontaneous circulation; it is possible that earlier and more frequent doses at the beginning of the resuscitation yield faster return of spontaneous circulation, which is associated with neurologic outcomes.[16,17] Although the Paramedic 2 trial investigated epinephrine doses of 1 mg every 3 to 5 minutes, other epinephrine strategies—including differing doses, differing interval dosing, or infusions—may yield alternate benefit.

Three previous observational analyses of inhospital cardiac arrest examined the association of average epinephrine dosing interval with outcomes; all reported that longer average dosing intervals were associated with improved outcomes.[5-7] The incongruence of these studies with our results may be multifold. First, inhospital cardiac arrests may have different characteristics. Second, in inhospital cardiac arrests epinephrine was administered in the first 2 to 4 minutes of the arrest, which may have an effect on the optimal dosing interval.[5,7] Two inhospital cardiac arrest analyses reported increased survival with a short dosing interval, but these findings were reversed after adjustment, implying a complex epinephrine-timing relationship.[5,7] One study examined 660 North Carolina out-of-hospital cardiac arrests to estimate the association of several different covariates with return of spontaneous circulation.[18] No meaningful relationship between average epinephrine dosing interval and return of spontaneous circulation was found.

In summary, in this secondary analysis of out-of-hospital cardiac arrest patients receiving epinephrine, a shorter interval between doses of epinephrine was associated with improved survival with favorable neurologic status at hospital discharge.

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Author contributions: BG conceived the study. JC supervised original data collection. All authors designed the investigation. TK performed the statistical analysis. BG drafted the article, and all authors contributed substantially to its revision. BG takes responsibility for the paper as a whole.

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REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292.
2. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132(18 suppl 2):S444-S464.
3. Ornato JP. Optimal vasopressor drug therapy during resuscitation. *Crit Care*. 2008;12:123.
4. Hansen M, Schmicker RH, Newgard CD, et al. Time to epinephrine administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. *Circulation*. 2018;137:2032-2040.
5. Warren SA, Huszti E, Bradley SM, et al. Adrenaline (epinephrine) dosing period and survival after in-hospital cardiac arrest: a retrospective review of prospectively collected data for the American Heart Association's Get With the Guidelines–Resuscitation (National Registry of CPR) Investigator. *Resuscitation*. 2014;85:350-358.
6. Wang CH, Huang CH, Chang WT, et al. The influences of adrenaline dosing frequency and dosage on outcomes of adult in-hospital cardiac arrest: a retrospective cohort study. *Resuscitation*. 2016;103:125-130.
7. Hoyme DB, Patel SS, Samson RA, et al. Epinephrine dosing interval and survival outcomes during pediatric in-hospital cardiac arrest. *Resuscitation*. 2017;117:18-23.
8. Nichol G, Leroux B, Wang H, et al. Trial of Continuous or Interrupted Chest Compressions During CPR. *N Engl J Med*. 2015;373:2203-2214.
9. Morrison LJ, Nichol G, Rea TD, et al. Rationale, development and implementation of the Resuscitation Outcomes Consortium Epistry–Cardiac Arrest. *Resuscitation*. 2008;78:161-169.
10. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344-349.
11. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374:1711-1722.
12. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee. *Resuscitation*. 2015;96:328-340.

13. Daya M, Leroux B, Rea T, et al. Survival after intravenous vs intraosseous amiodarone, lidocaine or placebo in out-of-hospital ventricular fibrillation cardiac arrest. *Circulation*. 2018;138:e777.
14. Kawano T, Grunau B, Scheuermeyer F, et al. Intraosseous vascular access is associated with lower survival and neurological recovery among patients with out-of-hospital cardiac arrest. *Ann Emerg Med*. 2018;71:588-596.
15. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379:711-721.
16. Grunau BE, Reynolds JC, Scheuermeyer FX, et al. Comparing the prognosis of those with initial shockable and non-shockable rhythms with increasing durations of CPR: informing minimum durations of resuscitation. *Resuscitation*. 2016;101:50-56.
17. Reynolds JC, Grunau BE, Rittenberger JC, et al. Association between duration of resuscitation and favorable outcome after out-of-hospital cardiac arrest: implications for prolonging or terminating resuscitation. *Circulation*. 2016;134:2084-2094.
18. Cantrell CL, Hubble MW, Richards ME. Impact of delayed and infrequent administration of vasopressors on return of spontaneous circulation during out-of-hospital cardiac arrest. *Prehosp Emerg Care*. 2013;17:15-22.

IMAGES IN EMERGENCY MEDICINE

(continued from p. 741)

DIAGNOSIS:

Acute ischemic right middle cerebral artery stroke. Computed tomography (CT) angiography (Figures 1 and 2) and magnetic resonance imaging (MRI) (Figure 3) demonstrated a complete acute ischemic right middle cerebral artery infarct as a result of complete occlusive thrombosis of the right internal carotid artery (Figures 4 and 5). Because the patient was outside the treatment window for tissue plasminogen activator, a cerebral angiogram with mechanical thrombectomy of the right internal carotid artery and middle cerebral artery occlusion was performed; no dissection was identified. All evaluation results, including testing involving a hypercoagulability panel, were negative. No definite cause was ascertained. He was discharged after 2 months of inpatient rehabilitation, with some improvement in left extremity function against gravity and improved speech.

Stroke in children is underrecognized and undertreated.[1] Common causes include sickle cell disease, cardiac and rheumatologic conditions, thrombophilia, arteriopathies, malignancy, and inborn errors of metabolism.[2,3] Signs of ischemic stroke are facial or limb weakness, dysarthria, and visual defects. MRI with diffusion-weighted imaging is the criterion standard for diagnosis.[1,4] Management includes administering tissue plasminogen activator if within the treatment window, mechanical revascularization, antithrombotic therapies such as heparin and aspirin, and neuroprotective measures such as seizure control, normotension, normoglycemia, normovolemia, and normothermia.[2,5]

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REFERENCES

1. McKinney SM, Magruder JT, Abramo TJ. An update on pediatric stroke protocol. *Pediatr Emerg Care*. 2018;34:810-815.
2. Felling RJ, Sun LR, Maxwell EC, et al. Pediatric arterial ischemic stroke: epidemiology, risk factors, and management. *Blood Cells Mol Dis*. 2017;67:23-33.
3. Yock-Corrales A, Mackay MT, Mosley I, et al. Acute childhood arterial ischemic and hemorrhagic stroke in the emergency department. *Ann Emerg Med*. 2011;58:156-163.
4. Bernard TJ, Friedman NR, Stence NV, et al. Preparing for a "pediatric stroke alert.". *Pediatr Neurol*. 2016;56:18-24.
5. Rivkin MJ, Bernard TJ, Dowling MM, et al. Guidelines for urgent management of stroke in children. *Pediatr Neurol*. 2016;56:8-17.